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The Staff of the Military Center of Pharmacy and Medical Technology
in Celestynow – Poland

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Druga strona okładki

Our deepest condolences to

Mr Radosław Sikorski

Minister of Foreign Affairs of the Republic of Poland

on the death of his Father

Col Radosław Ziemba, M.D., Ph.D.

Commander of the Military Center for Pharmacy

and Medical Technique in Celestynów

along with the staff and civil personnel of the Center

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Table of Contents

Table of Contents

Ophthalmology

Age-related macular degeneration (AMD): a critical appraisal of diet and dietary supplements as therapeutic modalities

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Summary:

Age-related macular degeneration (AMD) is a vision-threatening ocular disease, affecting the central region of the retina — the macula — and manifesting in the elderly. Its pathogenesis is multifactorial, molecularly complex and only poorly recognized. AMD is a degenerative disease, and the degeneration affects primarily the retinal pigment epithelial (RPE) cells and secondarily the photoreceptors, which leads to disturbances or partial loss of central vision and legal blindness. Principal processes contributing to the development of the disease include: oxidative stress, lipofuscinogenesis, drusogenesis and local inflammation (so-called para-inflammation). A severe complication of clinically recognized dry form AMD (geographic atrophy) is the aggressive neovascularization originating from choriocapillary system (CNV; wet form AMD). At present, there are no therapeutic agents capable of slowing or inhibiting degeneration process in the photoreceptors-RPE complex, therefore preventive rather than therapeutic modalities are under consideration; they include properly adjusted everyday diet and intake of dietary supplements, both rich in antioxidants of which macular pigments (lutein, zeaxanthin, meso-zeaxanthin) are of particular importance. Long-chain unsaturated omega-3 fatty acids (PUFA-ω3) are also recommended to people with already progressing AMD and at an increased risk of the disease development. Despite wide commercial offer of "ophthalmic" antioxidative and PUFA-ω3-rich preparations, no convincing evidence is available to date to support their protective activity in AMD patients. AREDS-2 clinical trials that actually approach completion may likely provide more conclusive answer whether macular pigments (lutein, zeaxanthin) and PUFA-ω3 (EPA, DHA) can really be useful for AMD patients. The aim of this article is twofold: 1. it presents molecular mechanisms underlying the early stages of AMD pathogenesis, which form a platform for the disease development, and 2. it provides a critical appraisal of the prophylactic/therapeutic value of properly profiled diet and the intake of "ophthalmic" dietary supplements rich in macular pigments and omega-3 PUFAs.

Key words: Age-related macular degeneration, AMD, oxidative stress, omega-3 fatty acids, macular pigments, prevention, diet, dietary supplements.

Introduction

This article refers to an earlier article by the same author, entitled *Dry form AMD — do we know how to treat it?*, published in 2011 in issue 5(1) of Magazyn Lekarza Okulisty [1] — a Polish-language journal specialized in ophthalmology and widely distributed among ophthalmologists. There are no drugs specific to this condition; the

therapeutic approach focuses on prophylaxis in the form of properly profiled diet and the intake of dietary supplements. The number of these supplements is constantly growing, and all of them are freely available, i.e. without prescription. The available supplements differ in both qualitative and quantitative composition. A detailed analysis of supplements available at Polish market as described by the author in 2010 in an article entitled *Ophthalmic antioxidant preparations: a survey and supportive arguments for their use in AMD* [2], included 73 products — all of them contained the macular pigment — lutein, some contained also zeaxanthin, and only one contained three macular pigments, namely lutein, zeaxanthin and *meso*-zeaxanthin.

Currently nearly 100 ophthalmic antioxidant preparations are available only at Polish market. This does not include numerous preparations containing polyunsaturated fatty acids of the omega-3 series (PUFA-ω3), discussed by the author in his earlier study entitled *Omega-3 polyunsaturated fatty acids in retina and medical practice — pros and cons* [3]. Ophthalmologists, as well as patients, may have and, according to author's knowledge, indeed have problems with choosing an appropriate preparation. However, resorting to dietary supplement may be perhaps unnecessary if appropriate choice of food products is made for one's everyday diet. The author hopes that this study, confronting the dietary and supplementation aspects of prophylaxis will contribute to appreciation of the role of everyday diet rich in selected products in AMD prophylaxis and acknowledging the value of such diet as not inferior to that of pharmaceutical supplementation.

AMD – origin and development of the pathology

Age-related macular degeneration (AMD) develops inconspicuously over many years. Despite numerous studies conducted worldwide, the pathogenesis of the disease is not fully understood. Due to the plurality of factors, both endogenous (e.g. genetic predispositions) and exogenous (history of exposure to light) or behavioral (e.g. smoking, improper diet), which might predispose, or even contribute to the development of the disease, the critical physiological processes responsible for the vision process (e.g. the visual excitation cascade) move beyond the limits of homeostasis, creating a biochemical platform for the future pathology [4–9]. This involves intensified lipofuscinogenesis in retinal pigment epithelium (RPE) cells, formation of drusen and pseudodrusen — the former occurring under the RPE monolayer (i.e. in the direction of Bruch's membrane), the latter above the RPE monolayer (i.e. towards photoreceptors) and next, a chronic inflammatory process known as para-inflammation. All these phenomena contribute to the development of AMD. Clinically, AMD can be divided into the dry, or atrophic, form (known as geographic atrophy), and wet — exudative, or neovascular form; the latter can be considered a complication of the atrophic form manifesting as choroidal neovascularization (CNV) [1,4,5].

Aging favors the development of AMD, particularly in predisposed individuals (due to concomitant presence of the risk factors listed above); the term "age-related" in the disease name – AMD is fully justified, as the age is the major (albeit individual, i.e. specific to each subject) and unavoidable determinant of various dysfunctions at the cellular and organ level, including these associated with the deficiency of necessary microelements/nutrients or with the loss of function in the aging cells — particularly post-mitotic, i.e. non-regenerable cells. While the lacking microelements/nutrients may be supplied from the outside, thus attempting to compensate for their deficiency in particular cells/tissues, we are unable until now to stop the systemic aging process.

Our bodies contain many non-regenerable (post-mitotic) cells, particularly within the central nervous system. These include the photoreceptors (only the external segments that contain photopigments are subject to regeneration) and retinal pigment epithelium (RPE) cells. In the pathogenesis of AMD, RPE cells are the first cells that become metabolically inefficient and thus undergo degeneration; dysfunction and atrophy of photoreceptors is secondary, as they are unable to function and survive without functionally efficient RPE cells, and therefore also undergo degeneration. The pathological process involves mostly a small region of the retina, known as the macula, where cone photoreceptors, responsible for acute and color vision, are predominant. Therefore, first clinical symptoms of AMD include blurred vision, defects of central vision of

various intensity or gradual loss of color vision, "warping" of perceived images [10,11]. Early form of AMD is often referred to as age-related maculopathy (ARM).

When the eyes are open, photoreceptors are continuously working, absorbing light photons and "recording" the image of the environment. Similarly to TV cameras being turned on, eyes record this image in an automatic fashion, generating the first signal of a complex, multisynaptic vision process. Photoreceptors' outer segments (POS), filled with visual pigment molecules, are characterized by significant functional dynamics; they wear off upon continuous function and, as a consequence, the apical fragments are constantly shed and captured by neighboring RPE cells. At the same time, POS is being rebuilt in order to maintain appropriate size (which is an important parameter determining the efficacy and survival of photoreceptors!). Regeneration proceeds from the perikaryon, i.e. the photoreceptor inner segment (PIS) and requires numerous building blocks, including docosahexaenoic acid (DHA). These building blocks are supplied by the RPE cells and originate partly from the captured POS fragments and partly from circulation (consumed food) [9].

One of the many important roles played by the RPE cells is "digestion" of the absorbed (and continuously being absorbed) photoreceptor material stored in phagolysosomes. Despite the fact that phagocytosis and enzymatic degradation occurring as a result of the activity of numerous lysosomal enzymes are physiological processes that had developed over thousands of years in creatures dwelling on Earth and making use of the visual organ system (retinal processes that govern visual perception in many vertebrates, including humans, are generally very similar), they seem to be of limited efficacy, at least in humans. This claim is supported by systematic accumulation of lipofuscin, known as the age pigment, in RPE cells.

Lipofuscin and the process of its formation, i.e. lipofuscinogenesis, are not the attributes of RPE cells and connections between photoreceptors and RPE, as they are also present in other non-renewable cells, such as neurons, cardiomyocytes or skeletal muscle cells. However, it is in this region of the eye, or more precisely, of the retina, i.e. in the photoreceptors/RPE cells region, where a unique characteristics of lipofuscin accumulated in RPE cells becomes evident: lipofuscin contains retinoids (vitamin A derivatives) originating from the visual cycle, particularly bisretinoids — products of spontaneous fusion of two molecules of all-*trans*-retinal, generated *via* photoreaction (i.e. by absorption of photons) by 11-*cis*-retinal, a cofactor of the visual pigment.

The cis → trans retinal transformation is the crucial first step of visual cycle, initiating further conformational transformations of opsin (i.e. the visual pigment protein) into its active forms (e.g. meta-rhodopsin II), capable of progressing the visual cycle with the final effect consisting in the closure of cGMP-dependent cation channel in the cellular membrane of photoreceptors and quenching the so-called darkness current. In this time, the cellular membrane of photoreceptors is hyperpolarized only to regain the state of being ready to absorb another photon, i.e. the depolarization state; the active pigment, capable of absorbing photons, is a molecule, e.g. rhodopsin, that contains a light sensitive co-factor, 11-*cis*-retinal [5,6].

The all-*trans*-retinal formed following photon absorption is completely dissociated from the visual pigment and undergoes further physiological transformations in the retinoid cycle that takes place in both photoreceptors and RPE cells. However, part of all-*trans*-retinal that does not bind the ABCA4 (ATP-binding cassette [transporter] A4 type, also known as ABCR) transporting the retinoid into the sites with all-*trans*-retinal dehydroghenase activity, "falls out" the cycle and spontaneously dimerizes (using ethanolamine as a "linker") into a highly phototoxic bisretinoid known as A2E. There may be more similar and toxic bisretinoids; however, A2E, which has been studied in more detail, seems to represent an established stress-inducing product. Furano – and peroxy –mtabolites of A2E have significant ability to activate the complement system (an alternative pathway) which represents the innate immunity, capable of efficiently and automatically acting in system's defense, including destruction of "own" cells [5,12].

In addition, the photoreceptor cell membranes contain exceptionally high amounts of polyunsaturated fatty acids (PUFAs), particularly the

most-unsaturated docosahexaenoic acid (DHA). It is this high unsaturation (six double C=C bonds in the hydrocarbon chain) makes DHA particularly susceptible to spontaneous peroxidation and fragmentation into cytotoxic compounds, including 4-hydroxy-2-hexenal (HHE) or 4-hydroxy-7-oxyhept-5-enoic acid (HOHA); the latter may additionally form immunogenic carboxyethylpyrrole-protein (e.g. CEP-albumin) adducts. More details regarding formation of the products of peroxidation of long-chain PUFAs and the properties of carboxyethylpyrrole-protein adducts are available in other articles by the same author [2,5].

Accumulation of lipofuscin deposits in RPE cells is a manifestation of metabolic inefficacy of their lysosomal compartment, characterized by reduced autophagy. The reason for this inefficacy remains unknown, although considering molecular complexity of autophagic processes, the reasons may be multiple, including hypofunction or insufficient quantity/activity of lysosomal enzymes – cathepsins being most predominant in normal conditions. Lipofuscin deposits accumulate with age, and the adverse effect of accumulating oxidative stress that accompanies lipofuscinogenesis is intensified. Local inflammatory reaction that develops at certain moment and is manifested by an atypical process referred to as para-inflammation, as well as drusogenesis (drusens, pseudodrusens), become the driving forces of the developing AMD pathology [4-7, 13].

One should not forget that the supply of oxygen (and microelements/nutrients) *via* the choriocapillary system into the photoreceptors-RPE cells complex is one of the largest in primates. Taking into account the functional specificity of the retina, particularly of photoreceptors (photosensitivity, extensive metabolism, high partial pressure of oxygen being the substrate for the formation of oxygen radicals), one may suspect that retina is particularly well predisposed for formation of reactive oxygen species (ROS) [14].

The nature must have predicted the potentially adverse, propathogenic processes, such as oxidative stress or lipofuscinogenesis, in the retina, as the tissue, and particularly the macular region, very important for acute and color vision in primates, has been equipped with an array of antioxidative defense systems, including specific macular pigments (MPs) – lutein and zeaxanthin and *meso*-zeaxanthin produced from lutein [15].

It should also be mentioned that the classical antioxidative systems present within the body are classified as either enzymatic or non-enzymatic. Enzymatic systems include three basic enzymes: superoxide dysmutase (SOD), catalase and glutathione peroxidase, which are dependent on metal ions, such as zinc, copper, manganium or selenium. The non-enzymatic system consists of carotenoids (including the aforementioned macular pigments), vitamins E and C and glutathione. The enzymatic system is endogenous; however, the metal ions that are required for its proper function are exogenous, i.e. must be supplied with food. As far as the non-enzymatic system is concerned, only glutathione is an endogenous antioxidant. The remaining elements of the system, i.e. carotenoids and vitamins E and C are exogenous factors supplied with food or appropriate dietary supplements. The role of carotenoids is to neutralize singlet oxygen and reactive free radicals. What's interesting, the mechanisms underlying these two activities of carotenoids are different and neutralization of free radicals may, in certain conditions (e.g. those when excessive amounts of radicals are present), change the antioxidative activity of these compounds into prooxidative activity.

Proper functioning of retinal antioxidation defense systems is believed to avert potential early propathogenic changes that may lead to AMD. These propathogenic changes are in fact physiological reactions that become functionally (chemically) impaired due to their intensity and the accompanying overproduction of reactive oxygen species (ROS), crucial transformations of "visual" retinoids and peroxidation and fragmentation of long-chain PUFAs. This may be generally due to indisposition of the aging body – its organs, tissues and cells, and hypofunction of the aforementioned antioxidative defense systems, both enzymatic and non-enzymatic. Since these systems are dependent on the supply of exogenous nutrients, thus their activity is diet-dependent [2,14–17].

A diversified diet, containing vegetables rich in carotenoids, or — more precisely — **oxycarotenoids** or **xanthophylls** (mainly lutein and zeaxanthin; *meso*-zeaxanthin is not of dietary origin, being produced locally from lutein) — **should be the**

first recommendation for patients in whome AMD development is suspected on the basis of generally discrete symptoms, albeit disturbing visual sensations.

Diet

Specific dietary recommendations are crucial in many ailments and diseases. For instance, in diabetic patients, diet is an integral element of therapy, as no therapeutic success can be achieved in these patients without an appropriately profiled diet. Gluten-free diet is necessary in individuals, particularly children, with gluten intolerance. Patients with arterial hypertension should avoid salt, i.e. sodium chloride, in their diet. Excess sodium ions retain water in the body via a kidney-based mechanism; thus the daily dietary content of sodium should be well below 85 mmoles (less than 5 g NaCl) — in practice, one should follow the rule "the less salt, the better". Many examples may be provided, but how about a diet for AMD patients?

Indeed, appropriate dietary recommendations for AMD patients are well justified, although one should expect no miraculous effects of such diets. Individuals who rigorously follow dietary recommendations (abundance of selected vegetables rich in lutein, marine fish rich in PUFA-ω3, etc.) also suffer from AMD. This is the nature of the disease, as it develops inconspicuously over many years and becomes symptomatic after the age of 50, most frequently after the age of 60. Its background is multifactorial, including both environmental/genetic and inflammatory/immune factors; in general opinion, there is no way to avoid it, as reported by the author in numerous studies [1, 2, 4, 5, 18]. Nonetheless, appropriate diet is important in AMD patients.

Considering the threat of AMD or active AMD, one should recommend vegetables that contain high amounts of macular pigments (MPs), i.e. lutein and zeaxanthin [19]. Recommended vegetables include spinach, corn, pumpkin, red grapes (particularly seedless grapes), broccoli etc. (a more detailed list is presented in **Table 1**), as well as egg yolk which contains high amount of zeaxanthin in addition to lutein [15, 20]. It was calculated that the average Western diet content of lutein and zeaxanthin is between 1.3 and 3 mg, with lutein to zeaxanthin ratio of 7:1 [21, 22]. A properly profiled diet may contain more macular pigments, and therefore be more beneficial for individuals with AMD. Macular pigments are guards of metabolic order in the macular region and play a dual role of a filter, as they absorb blue light which is most dangerous for eyes and of a scavenger of free radicals, as they neutralize singlet oxygen and continuously generated free oxygen radicals.

Table 1: The content of lutein and zeaxanthin in widely used vegetables and fruits, given in mol %.

Products	Lutein and zeaxanthin	Lutein	Zeaxanthin
Egg yolk	89	54	35
Corn	86	60	25
Kiwi fruit	54	54	0
Red seedless grapes	53	43	10
Pumpkin	49	49	0
Spinach	47	47	0
Cucumber	42	38	4
Celery	34	3	2
White grapes	31	25	7
Brussels sprouts	29	27	2
Green peas	25	22	3
Broccoli	22	22	0
Mango	18	2	16
Lettuce	15	15	0

Properly selected daily rations of selected vegetables provide the body not only with macular pigments, but also with microelements (including zinc, copper, manganese, selenium, vitamins E and C) required for proper functioning of antioxidative enzymes (superoxide dysmutase, catalase, glutathione peroxidase).

One should not forget other important dietary elements, i.e. unsaturated fatty acids of the omega-3 series, particularly DHA[1], abundantly present in marine fish[2]. Two or three fish-based meals per

[1] DHA is an example of a compound of dual nature, both beneficial and adverse. On one hand, DHA is required for the function of many cells, tissues and organs; on the other hand, due to its unsaturation, it is associated with the risk of adverse phenomena; at the same time, its functional indispensability is associated with structural unsaturation. The pros and cons of DHA were discussed in more detail in [3]. A disadvantage of DHA, as well as of other long-chain polyunsaturated fats, including the omega-3 eicosapentaenoic acid (EPA), omega-6 arachidonic acid (ARA or AA), or docosapentaenoic acid (DPA) is that in the presence of oxygen they easily undergo peroxidation and cleavage leading to propagation of oxidative stress. Despite the dual nature of the omega-3 fatty acids (DHA, EPA, DPA), one should not avoid their presence in food, particularly in the context of AMD prevention. The presence of vitamin E in food/supplement protects long chain polyunsaturated fats from oxidation.

[2] Marine fish contain high amounts of long-chain polyunsaturated fatty acids (PUFAs), including acids of the omega-3 series (PUFA-ω3). Of tested and commonly eaten fish

week (e.g. salmon, herring, mackerel) provide the body with these fatty acids in amounts sufficient not only for needs of the organs of vision, but also of the entire system.

Polyunsaturated fatty acids of the omega-6 series (PUFA-ω6), also essential for human body, are usually consumed in high amounts, as they are present in commonly used vegetable oils – e.g. linoleic acid (C18:2ω6 or C18:2n-6, which is the first acid in the omega-6 series) is abundant in grape seed oil and sunflower oil (63–66%), as well as in corn oil and soybean oil (55–56%); other oils have much lower contents of linoleic acid (rape oil, linen oil, olive oil — 10–21%). In case of PUFA-ω3, the case is more difficult, as EPA and DHA are virtually absent in vegetable oils, while alpha-linolenic acid (ALA; C18:3ω3 or C18:3n-3, being the first acid in the omega-3 series) is present only in moderate amounts in rape oil and soybean oil (7–11%), as well as in large amounts (!) in linen oil (55%)[3]. For the sake of comparison, the overall PUFA-ω3 (ALA, EPA and DHA) content in fish oil (herring oil) is > 28%, while the linoleic acid (ω6) content is slightly above 12%. Cold-pressed linen oil is available in an increasingly broad commercial offer. Although not everyone finds it tasty, linen oil is a recommended addition to the diet, not only of AMD patients. However, one should remember that conversion of ALA into EPA or DHA in human body is very low, and therefore the supply of ALA may not substitute for direct supply of DHA and DPA (which are abundant in marine fish).

species, highest amounts of DHA and EPA (expressed overall in g/100 g of weight) can be found in Atlantic salmon (> 2; farm-raised and wild caught) and herring (mainly Atlantic herring ≈ 2), then in mackerel and tuna (1.2–1.5); the popular canned tuna contains much smaller amounts (0,3–0,8); less DHA + EPA can be found in halibut and cod (0,2–0,6), while a higher content can be found in trout (farm-raised and wild caught) (≈ 1). As far as DHA is concerned, the highest content can be found in salmon, herring and tuna (excluding canned tuna in brine) and trout. Although fish contain particularly high amounts of EPA, DHA and DPA, other natural sources of these acids are human milk, farm-grown marine algae, marine mammals and krill; as mentioned in the article, some vegetable oils, including linen oil, do not contain EPA and DHA, although they may contain large amounts of *alpha*-linolenic acid (PUFA-ω3).

[3] The percentage composition of selected fatty acids in the **linen oil** is as follows: *alpha*-linonenic acid (18:3ω3) – 54.5%, oleic acid (18:1ω9) – 19.7%, linoleic acid (18:2ω6) – 16.2%, palmitic acid (16:0) – 5.1%, stearic acid (18:0) – 3.7%, other acids – 0,8%. The linen oil contains no EPA or DHA. The ω6/ω3 ratio is 0.3. For the sake of comparison, the percentage composition of **fish oil** (herring oil) is as follows: eicosapentaenoic acid (EPA; 20:5ω3) – 17.2%, palmitic acid (16:0) – 13.9%, palmitoleic acid (16:1ω7**)** – 13.1%, linoleic acid (18:2ω6) – 12.4%, oleic acid (*cis*-Δ^9-octadecenoic acid; 18:1ω9) – 11.6%, docosahexaenoic acid (DHA; 22:6ω3) – 9%, myristic acid (tetradecanoic acid; 14:0) – 7.4%, stearic acid (octadecanoic acid; 18:0) – 2.7%, linolenic acid (18:3ω3) – 2.1%, elaidic acid (*trans*-Δ^9-octadecenoic acid; 18:1ω9**)** – 2%, gadoleic acid (*cis*-Δ^{11}-icosenoic acid; 20:1ω9) – 1.5%; ω6/ω3 ratio = 0.4.

Modern diet, particularly the Western diet, is rich in the fatty acids of the omega-6 series, and the ratio of these acids to the omega-3 (ω3) acids may be as high as 20:1, or even higher! The proper ratio should be about 4:1, with a trend towards balanced supply of both types of acids; this leads to the natural need for omega-3 acids supplementation (EPA, DHA, ALA and docosapentaenoic acid — DPA-ω3); in case of AMD, DHA is of the highest importance. Despite its disadvantages (easy peroxidation and fragmentation), DHA is absolutely necessary for regeneration of photoreceptor outer segments worn off in the process of vision as well as to maintain appropriate plasticity/susceptibility of the cell membrane in rods and cones. In addition, EPA and DHA are substrates for production of anti-inflammatory resolvins and maresins (the latter are formed only from DHA) which are very important for the photoreceptors-RPE cells complex. DHA is also a substrate for production of neuroprotectin, which is involved in many protective, anti-inflammatory and cytoprotective mechanisms [8]. More information on the pros and cons of DHA may be found in a recent article by the same author [3].

The advantage of thus-profiled diet (as mentioned above) is that the elements valuable, among others, for intraocular metabolism, are delivered to the organism in natural, purely physiological fashion, which guarantees optimum gastrointestinal absorption and transport to target tissues/cells as long as a diversified and well-balanced diet is maintained. One should remember that these microelements, being so important not only for AMD patients, are absorbed into circulation from the gastrointestinal tract in a diverse manner, as they represent different types of chemical structures and molecular mass ranges. Well-balanced diet containing diverse proteins, carbohydrates and all types of fats (long – and short-chain, saturated and unsaturated) establishes within the stomach and the intestines a natural chemical environment that favors passive or active absorption of microelements supplied with food.

This natural, physiological situation is very much different from situation taking place in the stomach (oftentimes an empty one) after ingestion of dietary supplement tablets/capsules followed by a glass of water! Microelements contained in the

supplements, albeit selected, have no optimum conditions for absorption. This accounts for the superiority of comprehensive natural nutrition over the intake of selected substances contained in dietary supplements, which do not have to be (and, in fact are not) fully absorbed from the gastrointestinal tract. A separate issue relates to the substances being delivered just where they are needed, which is a problem not less important from the standpoint of efficacy and expected results, and providently passed over in silence by the producers or suppliers of dietary supplements.

However, some individuals may, for various reasons, including the fact that preparation of appropriate meal requires time and effort, while swallowing a capsule "solves the problem", may prefer ready-made dietary supplements. Therefore, the dietary supplements must also be included in our considerations.

Dietary supplements and the efficacy of AMD prophylaxis/treatment

From the medical standpoint, the issue as stated in the heading is of primary importance for a wide group of mature population at risk of discomforts associated with the developing or potential AMD. As mentioned before, pathogenesis of the disease is still unknown, which makes it impossible to both early diagnose the developing pathology and to efficiently treat it using appropriate medications.

This does not pertain to the neovascular form of AMD, originating from choroidal neovascularization and considered by many researchers, including the author of this article, to be a serious complication of advanced AMD. This form, or more precisely, the dynamic neovascularization that accompanies AMD, may currently be treated pharmacologically using agents that neutralize the main proangiogenic factor, i.e. the vascular endothelial growth factor (VEGF). Following agents are available: monoclonal anti-VEGF-A antibodies (Avastin – bevacizumab, Lucentis – ranibizumab), the recently registered soluble decoy receptor for the factors of the VEGF-A family, VEGF-B and placenta growth factor – PlGF (Eylea – aflibercept), as well as the less commonly at present used modified pegylated aptamer, an oligonucleotide strongly and selectively binding the VEGF-A_{165} protein, thus inhibiting its activity (Macugen – pegaptanib sodium) – the first registered drug for the treatment of neovascular AMD [23].

However, when starting the treatment of CNV, one should keep in mind, that:

1) the use of anti-VEGF medications will be efficacious only in VEGF-dependent neovascularization (luckily, in a large group of patients CNV is started from a VEGF-dependent process; however, a blockade, particularly a prolonged blockade of this angiogenic pathway may lead to spontaneous switch to another angiogenic pathway, which may depend on PDGF, FGF, CEP, or other factors; also possible is that a non-VEGF-dependent mechanism of neovascularization is activated first – in this case, the CNV process will be refractory to anti-VEGF medications); and

2) fighting neovascularization is a symptomatic treatment , as the AMD pathology continues to develop despite pharmacological inhibition of neovascularization and/or elimination of already formed pathological vessels using verteporfin-based photodynamic therapy (PDT).

How should one therefore manage AMD, particularly the dry (atrophic) form of AMD? There are no appropriate drugs or reliable diagnostic methods for early stages of the disease. What remains is only physician's intuition and knowledge, and prophylactic rather than therapeutic actions. Since the diet has been discussed above, let's focus on dietary supplements.

The dietary supplements or, more precisely, "ophthalmic" supplements, as their trade names often refer, either explicitly or implicitly, to the eye or the retina, include ophthalmic antioxidant preparations (OAPs) and preparations containing PUFA-ω3. Recently, a trend is observed to combine the active ingredients so that one capsule/tablet contains both macular pigments (lutein ± zeaxanthin), microelements, and PUFA-ω3. Thus, the capsules become ever bigger in size, making them hard to swallow without plenty of water.

This, however, is not as important as the qualitative and quantitative composition of the offered products/ingredients. This may be completely arbitrary, including specific substances (such as lutein and zeaxanthin, vitamins, metal salts) and less precisely defined ingredients such as plant extracts with presumed antioxidative

or cytoprotective properties or, as in the case of PUFA-ω3 – extracts from the livers of e.g. shark, cod or other fish, without any quantitative specification with regard to DHA, EPA and other fatty acids possibly included in the extract. Many producers seem to adhere to the motto: "the more, the better", and therefore the dosage of the active ingredients is higher than in competing products: some products contain as much as 20 or more milligrams of lutein per capsule or, besides plant extracts, contain substances which have no chance of arriving at ocular tissues in untransformed, active form (e.g. the tripeptide glutathion) — the goal of all these endeavors is to differentiate the product from other products available at the market and thus promote the purchase.

However, the question whether the therapeutic efficacy of dietary supplements, including OAPs, is an established fact or wishful thinking remains unanswered. What complicates the problem are varied clinical data being published: according to some studies, macular pigments (lutein, zeaxanthin) may have effects protecting against the developing AMD [24–28], while other authors suggest that no such effects can be observed [29–33]. The former suggest that the use of OAPs in AMD (both in prevention and treatment) is justified, while the latter would preclude such conclusion or suggest to think over the decision before pharmaceutical supplementation.

As mentioned earlier, macular pigments are chemical substances present in large quantities in the retina, particularly in the macular region. Exogenous supply of these compounds (e.g. as part of the diet or as dietary supplements) is assumed to lead to the increase in their retinal levels/concentrations. Indeed, the intake of lutein-containing dietary supplements leads to an increase in both the serum lutein level and the macular pigment optical density (MPOD) – both parameters are increased in parallel [34]. The latter value, i.e. the increased MPOD, is ascribed to be associated with the positive effect of supplementation on the improvement of vision; however, there are still no clinical data that would justify this opinion!

Many researchers measure the MPOD – sometimes in addition to clinical evaluation of vision in patients developing AMD, and sometimes as the only measurement ever made. One should keep in mind that reliable MPOD readout is subject to certain limitations stemming from the measurement method, as endogenous lipofuscin also emits light, which might interfere with the measurement. For instance, lipofuscin may be excited by light in the wavelength range of 400-580 nm to emit fluorescent light in the spectral range of 500-800 nm; on the other hand, the macular pigments absorb blue light at wavelengths shorter than 550 nm, with the absorbance peak at 460 nm [35]. In order for the obtained MPOD readout to be reliable, i.e. free of interferences from (auto)fluorescence of lipofuscin, a special methodological approach should be made, such as the use of dual wavelengths to excite the macular pigments, e.g. 488 nm (well absorbed by MPs) and 514 (minimally absorbed by the MPs) [33], and conclusions should be drawn from the differences in measured values. Another factor very important for interpretation of the MPOD results, particularly in AMD patients, is that macular pigments are usually characterized by very slow turnover rates. This means, that in patients taking dietary supplements increased levels of macular pigments in serum and macula (MPOD) would persist for long periods after the dietary supplements, e.g. lutein-rich supplements, are discontinued. Sometimes, such periods may last several months or longer.

In the context of increasing popularity of PUFA-ω3 dietary supplements being recommended to AMD patients, Delyfer *et al.* [37] studied the potential relationship between MPOD and serum PUFA-ω3 levels in 107 healthy volunteers (PIMAVOSA study). The authors confirmed the correlation between MPOD and serum lutein/zeaxanthin, and additionally identified high correlation between MPOD and serum PUFA-ω3 (overall levels). When considering the main 3 acids of the omega-3 series separately, observations regarding correlations between the acid levels and MPOD were as follows: DPA — high correlation, EPA – intermediate correlation, DHA – no statistically significant correlation. Thus, the French authors pointed out another factor that might affect the MPOD value, i.e. the PUFA-ω3, levels/concentrations of which (e.g. in serum) increase after the intake of meals or dietary supplements rich in these acids.

Among recently published data on macular pigments supplementation and its influence on quality of vision in AMD patients, the author would like to take as an example one article, which appeared in PubMed database on August 1, 2012, and was published only in November

issue of Ophthalmology [38] — it presents data on the effect of supplementation with lutein (10 and 20 mg per day) and zeaxanthin (10 mg per day) for 48 weeks on MPOD and best corrected visual acuity (BCVA) in 108 patients with early AMD. The results are similar to those published earlier by other authors, and therefore it is worth to present the conclusions drawn from these results (as the conclusions may as well pertain to the earlier works): *„Among patients with early AMD, supplementation with lutein and zeaxanthin improved macular pigment, which played a causative role in boosting visual function and* ***might prevent*** [highlighted by the author] *the progression of AMD. Future studies are required to evaluate the effect of these carotenoids on the incidence of late AMD".* In other words, lutein and zeaxanthin, as expected, increased the value of MPOD (i.e. increased the pigment levels), while their effect on vision was comparatively small, and the preventive effect with regard to AMD was debatable.

Recent Cochrane review, based on randomized, controlled studies in more than 62,500 subjects also reports the lack of effects of some widely recommended antioxidant supplements [39]. The author's conclusions are as follows: "*There is accumulating evidence that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD. There is no evidence with respect to other antioxidant supplements, such as vitamin C, lutein and zeaxanthin, or any of the commonly marketed multivitamin combinations. Although generally regarded as safe, vitamin supplements may have harmful effects and clear evidence of benefit is needed before they can be recommended.*"

Ophthalmologists are divided in their practical observations in AMD patients receiving OAPs. Many of them ask the well-justified question: Can OAPs cure AMD, delay its progression, or better yet, prevent its development? Considering the marketing activity of OAP manufacturers, as well as the ever-increasing number of commercially available "antioxidant" preparations with varied qualitative and quantitative compositions, one may have serious doubts regarding the actual therapeutic value of OAPs. The most important factors affecting the "aye" or "nay" decision for ophthalmic antioxidant preparations and PUFA-ω3 preparations are presented below.

Dietary supplements vs. drugs

Contrary to drugs, i.e. registered medications with precise and constant composition of active substance(s) and excipient(s) and documented therapeutic potential, dietary supplements may have variable compositions and information leaflets, if included, are often laconic or lacking detail. Self-respectful manufacturers present composition, and even intended use/indications for their products, sometimes referring to published results of research suggesting potentially beneficial effects of the components of these components. And this is pretty much all. Conclusion: **There is no equals sign between a dietary supplement and drug**, although many manufacturers would like their products being treated as drugs.

Dietary supplements are sold freely, and therefore everyone may purchase them and use them, either recommended by the doctor or at one's own discretion, oftentimes prompted by loud, albeit imprecise and sometimes groundless information/messages regarding the efficacy of these supplements presented by the mass media. Dietary supplements must not contain ingredients which, when used in excess (i.e. in a reasonable excess, as nearly everything consumed in appropriate excess might have detrimental effects on health) might have any adverse effects. Dietary supplements should therefore be absolutely safe, as manufacturers want to avoid medical problems resulting from the intake of their product and potentially leading to elimination of such product from the market.

Many physicians, while recommending dietary supplements, including OAPs, to their patients, do not fully believe in therapeutic effects thereof. Some even say that such preparations do no harm while they might actually help (!) etc., so that patients may take them safely hoping they would really help. However, the despaired patients expect the purchased product(s) to have beneficial effects — they trust their physicians and believe, or try to believe, that the product will be efficacious. Patients perceive the paeans presented by the mass media to be reliable information, not marketing tricks, which, unfortunately, is not always true.

Let's assume that a patient purchased a packaging with a month's supply of the dietary supplement

recommended to him/her by his/her physician and that he/she started the treatment. How long should the patient take the recommended product? And, what's more important, when should the patient expect to experience an improvement in vision? There are no satisfactory answers to these well justified (as the patient does not get the products for free — he/she buys them) questions, as the **beneficial effect will surely not be observed after the first month, or even after the first several months of using the dietary supplement(s); in some patients, the effect may be observed after a long-term use that lasts many months, and even years. What's more, there may be no effect at all!**

Patients may feel disappointed with such "supplementation therapy", while the manufacturer of the supplement holds no responsibility whatsoever, as they may always bring up what is already well known, i.e. that the product is a dietary supplement, and not a drug! A question/statement often raised in such cases by the supporters of "supplementation therapy", i.e. what if the supplements had not been taken, is purely rhetorical one. Indeed, there is no answer to this question.

Patients disappointed with their hitherto ineffective therapy, i.e. patients with conditions refractory to the established pharmaceuticals or patients with conditions with no pharmacological treatment available are particularly susceptible to the use of dietary supplements. Cases where no specific drugs are available — as in the case of AMD — favors all kinds of therapeutic speculations and paramedical activities, opening a lucrative area for the manufacturers and suppliers of dietary supplements — appropriately promoted dietary supplements may even be perceived as drugs!

The abundant offer of dietary supplements available at Polish market and targeted at individuals suffering from AMD or at risk of AMD includes nearly 100 products of the OPA type. In a recent study, published in 2010 [2], the author analyzed 73 ophthalmic antioxidant preparations, i.e. all products commercially available in Poland at that time. The call sign of all OAPs is the presence of the macular pigment–lutein; some products contain also another macular pigment, i.e. zeaxanthin (e.g., in alphabetical order, Klarin Perfekt, MaxiVision Total, Nutrof Total, Ocuvite Lutein Forte, Vislea), and one product (Macushield) contains three pigments–lutein, zeaxanthin and *meso*-zeaxanthin in one capsule. The analysis led to the following conclusions:

- All 73 preparations contained lutein in the amounts of 0.125/6–10/50 mg (the range of 6–10 mg was most common), with 7 preparations not stating the precise dose;
- 30 preparations contained also zeaxanthin in the amounts of 0.12–2.4 mg, with no data regarding the dose provided for 3 preparations;
- 1 preparation contained *meso*-zeaxanthin in addition to the two above pigments;
- 52 products contained vitamin E;
- 42 products contained zinc and/or selenium;
- 9 products contained PUFA-ω3;
- 3 products contained glutathione
- 39 products contained vitamin A or β-carotene.

As mentioned above, patients may currently choose from about 100 preparations; however, let us restrict our considerations to the 73 preparations that were analyzed in detail by the author. When purchasing a product, the patient must make a choice, and thus, what factors should the patient be guided by when making this choice? Using the simplest exclusion criteria, such as presence of vitamin A or β-carotene, symbolic dose (< 1 mg) of lutein, lack of details regarding the source/quantity of macular pigments, or the presence of ineffective compounds, such as glutathione, at most 20 out of the total of 73 preparations may be selected. When applying additional criteria (e.g. the seniority and importance of the manufacturer in the drug and/or dietary supplement market), the number of products that could be recommended to patients would not exceed 10. However, for an individual patient who would like to purchase an inexpensive but "good" product, 10 products is simply 9 too many!

The trend to enrich the OAP-type supplements with PUFA-ω3 has already been mentioned. Manufacturers of such "combination" supplements argue that they provide AMD patients with everything they need in a single capsule! Another, more convincing arguments (compared to the "everything you need in one" message, as mentioned above) are arriving from the nearly completed Age-Related Eye Disease Study 2 (AREDS-2), which, contrary to the AREDS-1 (or simply AREDS) study, test the use of macular

pigments and PUFA-ω3 in AMD patients. It should be mentioned that the AREDS study is a multicenter, 5-year clinical study conducted in more than 3,000 patients. The objective of the study was to assess the effect of high doses of antioxidants (these included vitamin C, vitamin E and β-carotene) and zinc on the progression of AMD. As shown by the published reports, the tested AREDS formula did not inhibit vision loss, although it had some beneficial effects reducing the risk of further development of AMD. Authors of the promising article titled *"New approaches and potential treatments for dry age-related macular degeneration"*, published in 2012, make reference to the AREDS study reports of 2001 and the Erratum of 2008 — report as follows: "*the AREDS formula does not prevent GA [geographic atrophy] from forming or progressing*" [40].

AREDS-2 (ClinicalTrials.gov; Identifier NTC 00345176; sponsored by National Eye Institute (NEI) with collaboration from National Heart, Lung, and Blood Institute – NHLBI), is, similarly to AREDS, a 5-to-6-year (2007–December 2012), multicenter (82 clinical centers in the United States), randomized clinical study to evaluate the effect of oral supplementation with macular xanthophylls (lutein, zeaxanthin) and omega-3 polyunsaturated acids (PUFA-ω3) (DHA, EPA) on AMD progression. Below is the list of agents tested in AREDS (AREDS-1) and AREDS-2 studies:

AREDS-1: vitamin C — 500 mg, vitamin E — 400 IU, *beta*-carotene — 15 mg, zinc (as zinc oxide) — 25 and 80 mg, copper (as cupric oxide) — 2 mg;
AREDS-2: lutein — 10 mg, zeaxanthin — 2 mg, vitamin C — 500 mg, vitamin E — 400 IU, copper (as cupric oxide) — 2 mg, EPA – 650 mg, DHA – 350 mg.

Smaller studies (*Secondary Randomization Agents — AREDS-Type Supplement*) were also conducted to examine the effects of zinc (as zinc oxide) at doses of 25 and 80 mg, with particular focus on the lower dose, and elimination of β-carotene form the AREDS formula.

Of note is the lack of *beta*-carotene and zinc in the Primary Randomization Agents of AREDS-2 study. As shown by the *alpha*-tocopherol, beta-carotene cancer prevention study (ATBC), *beta*-carotene contributes to the development of lung cancer in smokers [41]; in addition, *beta*-carotene is a precursor of vitamin A, and the visual cycle retinoids may act as substrates for formation of photocytotoxic bis-retinoids. Beneficial effects of zinc have been known for a long time, and there was no need for another detailed verification of its advantages. However, a question arose with regard to the dose — it would be better if the lower dose (25, not 80 mg) was efficient. As far as the PUFA-ω3 doses used in AREDS-2 study are concerned, the author agrees with the total dose of 1 g, although he is not certain whether 650 mg of EPA and 350 of DHA is a good dose ratio (1.86) for AMD patients. Considering the role of DHA in the photoreceptors–RPE cells complex [3], one might expect a higher dose of DHA (possibly at the cost of a lower amount of EPA).

Combination preparations ("all in one": macular pigments, microelements, PUFA-ω3) may be convenient for patients; however, the manufacturers are well aware that the presence of reasonable amounts of PUFA-ω3 in capsules requires enlarged capsule size, which is not always associated with greater convenience of use. One gram of PUFA-ω3 (as used in AREDS-2) takes up a considerable volume, thus a "combination" capsule containing such an amount should be appropriately large. When trying to adhere to the trend of administering one capsule of a dietary supplement per day, the capsule should contain "daily" doses of all ingredients which would obviously be translated into capsule size.

However, there is one argument that does not support combining PUFA-ω3 with the remaining ingredients in preparations recommended to AMD patients. AMD patients are usually at an advanced age, and PUFA-ω3 are often recommended to them also by physicians of other (non-ophthalmological) specializations. For example, cardiologists and psychiatrists (as well as other physicians, although these two specializations are predominant) nearly routinely recommend PUFA-ω3-rich dietary supplements at daily doses that often exceed 1 g. Facing different trade names of various "cardiologic", "psychiatric" and "ophthalmic" dietary supplements, patients may be unaware that they actually take the same chemical entities! And all these entities are accumulated in the same system! Therefore, it might happen that a patient would take not 1, but 2, and perhaps 3 or more grams of PUFA-ω3 per day while being unaware of this fact! Taking such scenario into consideration, one should not forget preparations

which contain antioxidants and microelements separately from PUFA-ω3, and which could be taken by the patient in line with the overall picture of his ailments and treatment.

It should be mentioned that many national and worldwide medical organizations (including the WHO) recommend daily intake of EPA and DHA in total amounts of 400–600 mg/day, while certain guidelines mention the dose of 1 g/day, and the European Food Safety Authority (EFSA) holds the position that there is no scientifically supported recommended daily dose of PUFA-ω3 for humans. However, EFSA recommends the DHA dose of 100 mg/day in infants, on the premise that DHA contributes to the development and functional maturation of vision system; EFSA also recommends a daily dose of ca. 250 mg (EPA + DHA) to children and adolescents aged 2-18 years[4].

On the other hand, a statement published in 2010 by the French Safe Food Agency (AFSSA, currently MSNA — National Agency for Drugs and Health Products) recommends a daily dose of ca. 500 mg of EPA and DHA combined as a preventive measure in AMD patients. As seen from the presented data, the recommended daily doses of PUFA-ω3 are diverse, cover a wide range of 100–1000 mg and depend on the patient's age and health status.

What's interesting, in case of cardiovascular conditions[5], the recommended dosage of omega-3 fatty acids (EPA + DHA + DPA) may be two-, three-, or even four times higher than the usually recommended maximum doses. When taken to reduce the triglyceride levels in hypertriglyceridemia, the recommended dose of PUFA-ω3 (with or without statin or fibrate) may be up to 3-4 g per day.

Regardless whether macular pigments and PUFA-ω3 are supplied together or as separate preparations, below are the **daily dose** ranges (to be contained in one capsule taken once daily or in two capsules taken twice a day) of the major ingredients of "ophthalmic" dietary supplements which, according to the author of this article, should be beneficial for AMD patients:

- Lutein — 10–12 mg
- Zeaxanthin — 1–2 mg
- Vitamin E — 30–60 mg
- Vitamin C — 60–250 mg
- Zinc — 10–20 mg
- PUFA-ω3 — 500–800 mg (overall, with DHA ≥ EPA)

Optionally: *meso*-zeaxanthin (up to 10 mg), copper, selenium, manganese.

The doses or dose ranges listed above are relative and refer to both the compositions of products available at Polish market and the experimental and clinical data published on the topic. Products containing PUFA-ω3 should necessarily contain vitamin E. The author's opinion is that there is no need to expand the composition of an ophthalmic preparation by ingredients, e.g. vitamins, other than these listed above. The addition of *meso*-zeaxanthin, a macular pigment characterized by potency equal to that of zeaxanthin, may be beneficial for patients. A comment should also be made with regard to the content of lycopene, which is not discussed in this article. Although lycopene is not a macular pigment, it is worth to remember its role, as it is involved in repair of the three oxycarotenoids (lutein, zeaxanthin, *meso*-zeaxanthin) after they react with free radicals. Lycopene is a carotene featuring 11 conjugated double bonds, abundantly present in tomatoes.[6]

With regard to the PUFA-ω3 content and DHA to EPA ratio in supplement preparations, the

[4] By request of the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) performed an analysis and issued a scientific opinion regarding acceptable maximum daily intake of long-chain PUFA-ω3, i.e. EPA, DHA and DPA in humans. A study entitled *"Scientific opinion on the tolerable upper intake level of eicosapentaenoic acid (EPA), docosahexaenoic acid DHA) and docosapentaenoic acid (DPA)"* was published in the recent issue of EFSA Journal [2012; 10(7): 2815]. In final conclusions, one reads: *"The Panel concludes that the available data are not sufficient to establish a tolerable upper intake level for n-3 LCPUFA (DHA, EPA, and DPA, individually or combined) for any population group. The Panel considers that supplemental intakes of EPA and DHA combined at doses up to 5 g/day, and supplemental intakes of EPA alone up to 1.8 g/day, do not raise safety concerns for the adult population. The Panel also considers supplemental intakes of DHA alone up to 1 g/day do not raise safety concerns for the general population. No data are available for DPA when consumed alone. The Panel notes that in the majority of the human studies considered, fish oils, which also contained DPA in generally unknown (but relatively low) amounts, were the source of EPA and DHA."*

[5] According to the European and American Heart Associations (EHA, AHA), all patients with a history of myocardial infarction and patients with stable coronary disease should take PUFA-ω3 at the dose of 1 g per day. According to AHA, supplementation using omega-3 acids should not be associated with rigorous elimination of omega-6 acids (e.g. linoleic acid, C18:2-ω6, which accounts for 85-90% of dietary omega-6 acids) which cannot be synthesized by human body and which, according to numerous opinion-forming sources, including the WHO, should account for 3-10% of daily energy demand. An interesting preparation that meets the AHA recommendations (although its omega-3 acid content is relatively small) is the "EYE Q capsules" preparation by a Swiss company Vifor SA distributed in Poland by Qpharma; the product contains EPA and DHA (marine fish oil) and primrose oil (omega-6).

[6] For more information on lycopene in patients with AMD see Nowak, Wiktorowska-Owczarek, *"AMD, Stargardt's disease, and carotenoids as components of ophthalmic antioxidant preparations used in AMD"* (Mag Lek Okul. 2012; 6(4): 185-98).

author is aware of four products available in Poland, in which the DHA dose is larger than that of EPA. This makes the products worth mentioning — they include:

- Ocuvite Reti-NAT forte (Bausch&Lomb); 1 capsule contains: 900 mg of fish oil, including 540 mg PUFA-ω3 – 420 mg DHA and 120 mg EPA — ratio 3.5; 1 capsule per day (the product has been withdrawn from the market by the manufacturer; perhaps some physicians still retained some supplies);
- Omega 3 (Ophtagen); 1 capsule contains: 500 mg of fish oil, including 250 mg DHA and 85 mg EPA (ratio 2.94), 1-3 capsules per day;
- MaxiVision Total (ASA); 1 capsule contains: 500 mg of fish oil, including 250 mg DHA and 34.6 mg EPA (ratio 7.22), 1 capsule per day; and
- Ocuvite Complete (Bausch&Lomb); 1 capsule contains (according to information on the packaging): 421.5 mg of fish oil, including 175 mg DHA (no information on the content of EPA), 2 capsules per day.[7]

While the two first preparations contain fish oil and no macular pigments (i.e. they are focused on PUFA-ω3), compositions of the two remaining products include also macular pigments, vitamins and minerals. MaxiVision Total — 20% lutein extract (corresponding to 20 mg of lutein), 1 mg of zeaxanthin, vitamins E and C, zinc and selenium; Ocuvite Complete — lutein 5 mg, zeaxanthin 1 mg, vitamins E and C, and zinc.

Ocuvite Reti-NAT forte contains definitely the largest amount of DHA (420 mg compared to 250 mg in MaxiVision and Omega-3 and ca. 175 mg in Ocuvite Complete), while the DHA to EPA ratio in individual supplements is as follows: 7.22 (MaxiVision), 7.19 (Ocuvite Complete), 3.50 (Ocuvite Reti-Nat) and 2.94 (Omega-3). The author is curious with regard to the origin of the fish oil in MaxiVision Total and Ocuvite Complete products, characterized by such high DHA to EPA ratios — no relevant information is provided for Ocuvite Complete, while the information leaflet to MaxiVision Total, which also does not provide this information, mentions that *„The unsaturated omega-3 fatty acids (DHA, EPA) in MaxiVision Total are derived from a high grade fish oil…",* which is perhaps imprecise, but nonetheless reassuring.

As mentioned before in case of properly profiled diet, also pharmaceutical supplementation **may, but does not have to help the AMD patients.** The potential helpful effects might be suggested by the recently published experimental and clinical studies, which were quite numerous in recent years [24–28, 38]. Also the results of the AREDS-2 studies, which should be published starting from 2013[8], should be — or so it seems — suggestive in this matter.

While browsing the published data, there is no missing the fact that results presented in most studies are not definitely convincing (at least, not to the author of the article), although they sometimes meet the threshold of statistical significance. More detailed analysis of these data leads to conclusion that further studies and clinical observations are required to assess the clinical efficacy of dietary supplements in general, and ophthalmic preparations in particular. However, one should not cease being optimistic; optimism should be cherished by both the physicians when recommending appropriate dietary supplements to patients, and patients who would be regularly taking it; otherwise, the supplementation would serve no purpose whatsoever.

As a concluding remark, it should be stated that **when deciding to use dietary supplements, AMD patients should nonetheless remember to adhere to proper diet, including, in addition to selected fruits and vegetables, at least one (or better yet, two) high-fat marine fish meals per week.**

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[7] Ocuvite Complete has only recently been introduced to the Polish market of dietary supplements and probably replaced similar products offered by Bausch&Lomb before its introduction. The product does not feature an accompanying leaflet, and relevant data on its composition are provided on the packaging. According to the information available for the user, the composition of the supplement is as follows (the presented values refer to two capsules recommended as a daily dose): fish oil 843 mg, including 350 mg DHA, vitamin C 180 mg, vitamin E 30 mg, zinc (as zinc sulfate) 15 mg, lutein 10 mg, zeaxanthin 2 mg (macular pigments originate from *Tagetes erecta* flower extract); no EPA content is provided. However, the Polish supplier of the product has made available more detailed data on the content of PUFA-ω3. According to these data, 1 capsule of Ocuvite Complete contains 421.71 mg of fish oil, including: 181.5 mg of DHA-TG (corresponding to 174.4 mg DHA) and 25.3 mg EPA-TG (24.3 mg EPA); thus, the DHA to EPA ratio is 7.19.

[8] On 26 July, 2012, the first report from the AREDS-2 studies, titled: *„The age-related eye disease study 2 (AREDS2): study design and baseline characteristics (AREDS2 Report number 1)" – Ophthalmology* 2012 Nov; 119(11): 2282-9, presenting the study design and basic characteristics of the project was published as an e-pub in PubMed database.

References:

1. Nowak JZ: [Dry form AMD – do we know how to treat it?]. Mag Lek Okul. 2011; 5: 44–8.
2. Nowak JZ: [Ophthalmic antioxidant preparations: a survey and supportive arguments for their use in AMD]. Mag Lek Okul. 2010; 4: 185–98.
3. Nowak JZ: [Omega-3 polyunsaturated fatty acids in retina and medical practice – pros and cons]. Mag Lek Okul. 2009; 3: 208–20.
4. Nowak JZ: Age-related macular degeneration (AMD): pathogenesis and therapy. Pharmacol Rep. 2006; 58: 353–63.
5. Nowak JZ: [In search of biomarkers for age-related macular degeneration (AMD)]. Mag Lek Okul. 2009; 3: 132–43.
6. Nowak JZ: [Role of lipofuscin in pathogenesis of age-related macular degeneration (AMD)]. Magazyn Okulistyczny. 2005, 2: 103–14.
7. Nowak JZ: [Drusens, basal deposits, inflammation and age-related macular degeneration (AMD)]. Magazyn Okulistyczny. 2005; 2: 174–86.
8. Nowak JZ: [Inflammation: acute, chronic and para-inflammation – new ideas, new drugs]. Mag Lek Okul. 2011; 5: 194–211.
9. Bhutto I, Lutty G: Understanding age-related macular degeneration (AMD): relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. Mol Aspects Med. (2012); 33: 295-317.
10. Fine SL, Berger JW, Maguire MG, Ho AC: Age-related macular degeneration. N Engl J Med. 2000; 342: 483–92.
11. McConnell V, Silvestri G: Age-related macular degeneration. Ulster Med J. 2005; 74: 82–92.
12. Klaska I, Nowak JZ: [The role of complement in physiology and pathology]. Post Hig Med Dosw (Online). 2007; 61: 167–77.
13. Anderson DH, Radeke MJ, Gallo NB, Chapin EA, Johnson PT, Curletti CR et al.: The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis revisited. Prog Retin Eye Res. 2010; 29: 95–112.
14. Wiktorowska-Owczarek A, Nowak JZ: [AMD and oxidative stress. 1. The analysis of factors influencing the generation of reactive oxygen species in the retina]. Mag Lek Okul. 2008; 2: 200–4.
15. Wiktorowska-Owczarek A, Nowak JZ: [Lutein and zeaxanthin – two carotenoids serving the protection against age-related macular degeneration (AMD)]. Okulistyka. 2004; 7: 29–34.
16. Wiktorowska-Owczarek A, Nowak JZ: [AMD and oxidative stress. 2. The analysis of components of pharmaceutical preparations used in prophylaxis of AMD]. Mag Lek Okul. 2008; 2: 205–12.
17. Wiktorowska-Owczarek A, Nowak JZ: [Pathogenesis and prophylaxis of AMD: focus on oxidative stress and antioxidants]. Postepy Hig Med Dosw (online). 2010; 64: 333–43.
18. Nowak JZ: [Age-related macular degeneration and immunological system: how much immunology is in AMD?]. Mag Lek Okul. 2009; 3: 102–14.
19. Khoo HE, Prasad KN, Kong KW, Jiang Y, Ismail A: Carotenoids and their isomers: color pigments in fruits and vegetables. Molecules. 2011; 16: 1710–38.
20. Sommerburg O, Keunen JE, Bird AC, van Kuijk FJ: Fruits and vegetables that are sources for lutein and zeaxanthin: the macular pigment in human eyes. Br J Ophthalmol. 1998; 82: 907–10.
21. Nebeling LC, Forman MR, Graubard BI, Snyder RA: Changes in carotenoid intake in the United States: the 1987 and 1992 National Health Interview Surveys. J Am Diet Assoc. 1997; 97: 991–6.
22. Nebeling LC, Forman MR, Graubard BI, Snyder RA: The impact of lifestyle characteristics on carotenoid intake in the United States: the 1987 National Health Interview Survey. Am J Public Health. 1997; 87: 268–71.
23. Nowak JZ, Koszela K: [Eylea™ (VEGF-Trap-Eye) – New „antiVEGF" drug: therapeutic applications and significance for the Avastin-Lucentis dilemma]. Mag Lek Okul. 2011; 5: 324–36.
24. Loane E, Kelliher C, Beatty S, Nolan JM: The rationale and evidence base for a protective role of macular pigment in age-related maculopathy. Br J Ophthalmol. 2008; 92: 1163–8.
25. Bone RA, Landrum JT, Mayne ST, Gomez CM, Tibor SE, Twaroska EE: Macular pigment in donor eyes with and without AMD: a case-control study. Invest Ophthalmol Vis Sci. 2001; 42: 235–40.
26. Bernstein PS, Zhao DY, Wintch SW, Ermakov IV, McClane RW, Gellermann W: Resonance Raman measurement of macular carotenoids in normal subjects and in age-related macular degeneration patients. Ophthalmology. 2002; 109: 1780–7.
27. Obana A, Hiramitsu T, Gohto Y, Ohira A, Mizuno S, Hirano T et al.: Macular carotenoid levels of normal subjects and age-related maculopathy patients in a Japanese population. Ophthalmology. 2008; 115: 147–57.
28. Sabour-Pickett S, Nolan JM, Loughman J, Beatty S: A review of the evidence germane to the putative protective role of the macular carotenoids for age-related macular degeneration. Mol Nutr Food Res. 2011; 55: 1-17.
29. Sabour-Pickett S, Nolan JM, Loughman J, Beatty S: A review of the evidence germane to the putative protective role of the macular carotenoids for age-related macular degeneration. Mol Nutr Food Res. 2012; 56: 270–86.
30. Kanis MJ, Berendschot TT, van Norren D: Influence of macular pigment and melanin on inci-

dent early AMD in a white population. Graefes Arch Clin Exp Ophthalmol. 2007; 245: 767–73.

31. Jahn C, Wüstemeyer H, Brinkmann C, Trautmann S, Mössner A, Wolf S: Macular pigment density in age-related maculopathy. Graefes Arch Clin Exp Ophthalmol. 2005; 243: 222–7.
32. Berendschot TT, Willemse-Assink JJ, Bastiaanse M, de Jong PT, van Norren D: Macular pigment and melanin in age-related maculopathy in a general population. Invest Ophthalmol Vis Sci. 2002; 43: 1928–32.
33. LaRowe TL, Mares JA, Snodderly DM, Klein ML, Wooten BR, Chappell R; CAREDS Macular Pigment Study Group: Macular pigment density and age-related maculopathy in the Carotenoids in Age-Related Eye Disease Study. An ancillary study of the women's health initiative. Ophthalmology. 2008; 115: 876–83.
34. Dietzel M, Zeimer M, Heimes B, Claes B, Pauleikhoff D, Hense HW: Determinants of macular pigment optical density and its relation to age-related maculopathy: results from the Muenster Aging and Retina Study (MARS). Invest Ophthalmol Vis Sci. 2011; 52: 3452–7.
35. Burke JD, Curran-Celentano J, Wenzel AJ: Diet and serum carotenoid concentrations affect macular pigment optical density in adults 45 years and older. J Nutr. 2005; 135: 1208–14.
36. Trieschmann M, Heimes B, Hense HW, Pauleikhoff D: Macular pigment optical density measurement in autofluorescence imaging: comparison of one – and two-wavelength methods. Graefes Arch Clin Exp Ophthalmol. 2006; 244: 1565–74.
37. Trieschmann M, Beatty S, Nolan JM, Hense HW, Heimes B, Austermann U et al.: Changes in macular pigment optical density and serum concentrations of its constituent carotenoids following supplemental lutein and zeaxanthin: the LUNA study. Exp Eye Res. 2007; 84: 718–28.
38. Delyfer MN, Buaud B, Korobelnik JF, Rougier MB, Schalch W, Etheve S et al.: Association of macular pigment density with plasma ω-3 fatty acids: the PIMAVOSA study. Invest Ophthalmol Vis Sci. 2012; 53: 1204–10.
39. Ma L, Yan SF, Huang YM, Lu XR, Qian F, Pang HL et al.: Effect of Lutein and Zeaxanthin on Macular Pigment and Visual Function in Patients with Early Age-Related Macular Degeneration. Ophthalmology. 2012; 119: 2290-7.
40. Evans JR, Lawrenson JG: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Cochrane Database Syst Rev. 2012; 6: CD000253.
41. Damico FM, Gasparin F, Scolari MR, Pedral LS, Takahashi BS: New approaches and potential treatments for dry age-related macular degeneration. Arq Bras Oftalmol. 2012; 75: 71–6.
42. Albanes D, Heinonen OP, Taylor PR, Virtamo J, Edwards BK, Rautalahti M et al.: Alpha-Tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. J Natl Cancer Inst. 1996; 88: 1560–70.

Physiology

Assessment of the energy expenditure of soldiers of the Representative Battalion of the Polish Army during three days of drill training as part of preparations for the celebration of the National Independence Day of November 11th

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Summary:

Introduction: The main mission of the Representative Battalion of the Polish Army consists of stately representation of the Polish Army during state celebrations, various state and military holidays or patriotic and religious events, as well as performing representative tasks at the Presidential Residence or during official visits hosted by the Prime Minister.
Aim of the work: The objective of this study was to assess the energy expenditure of soldiers during a three-day grill training as part of preparations for the celebration of the National Independence Day of November 11th.
Methods: The measurements were made on the basis of systolic heart rate as recorded by Polar Sport Tester 810 pulse meters. The energy expenditure was calculated from the relationship between the systolic heart rate and oxygen consumption.
Result: The mean energy expenditure of tested soldiers was 4.93±1.59 kcal/min.
Conclusion: Energy expenditure of soldiers during 7 hours of effective drill training as part of preparations for the celebration of the National Independence Day of November 11th was different and allowed the workload to be classified as light to very heavy.

Key words: energy expenditure, Representative Battalion of the Polish Army, military service.

Introduction

Current history of the representative units of the Polish Army dates back to 1944. In that year, on September 14th, the first post-war Warsaw Garrison Headquarters was established in the Praga district. The headquarters fulfilled representative and garrison tasks which were later taken over by the Warsaw Garrison Command.

As a result of organizational changes in the structure of units under the Warsaw Garrison Command, the Capital City of Warsaw Garrison Headquarters, including representative subunits, was disbanded as of December 31st, 2000. The representative tasks were taken over by the Representative Battalion of the Polish Army. The new unit became operative as of January 1st, 2001. The newly formed unit consisted of three Representative Companies of the Polish Army, the Polish Armed Forces Representative Band, a salute platoon, a protection company and staff. Starting from January 1st, 2009, the

Battalion comprises also a Cavalry Squadron of Polish Armed Forces as a mounted representative subunit.

The main mission of the battalion consists of stately representation of the Polish Army during state celebrations, various state and military holidays or patriotic and religious events, as well as performing representative tasks at the Presidential Residence or during official visits hosted by the Prime Minister [1].

Every year, soldiers of the battalion provide ceremonial setting to ca. 1200 events, mainly state, military, or patriotic and religious celebrations both home and abroad, as well as perform the guard of honour duties at the Tomb of the Unknown Soldier and the Presidential Palace. Representative Battalion soldiers are well-known for their mastery of parade drill, presented to much acclaim during state and military holidays, band festivals or other events.

The objective of this study was to assess the energy expenditure of soldiers during a three-day drill training as part of preparations for the celebration of the National Independence Day of November 11th.

Material and methods

The study was conducted in 22 soldiers serving in the Representative Battalion of the Polish Army The energy expenditure was measured over three days of intense drill training taking up 8 hours per day. The measurements were made on the basis of systolic heart rate as recorded by Polar Sport Tester 810 pulse meters. The energy expenditure was calculated from the relationship between the systolic heart rate and oxygen consumption. The energy expenditure was measured in soldiers performing different ceremonial tasks under weather conditions consisting of the air temperature of 7–9 °C and drizzle precipitation.

Results

The average age of the tested soldiers was 25.3±2.5y, ranging from 22 to 31 years. Mean height of the soldiers was 182.7±3.7 cm (176-191 cm), while mean body weight was 87.9±7.5 kg (67-101 kg).

Table 1: Energy expenditure during preparations to the National Independence Day of November 11th.

Subject no.	Energy expenditure kcal/min	Heart rate		
		Minimum	Maximum	Mean
1	3.013	80	180	104
2	3.105	52	142	80
3	3.122	59	121	84
4	3.454	60	144	86
5	3.665	53	132	84
6	3.689	69	145	87
7	3.830	55	177	118
8	3.852	57	161	89
9	3.872	45	225	91
10	3.938	47	161	118
11	4.036	83	163	111
12	4.676	69	148	94
13	5.191	68	159	96
14	5.359	63	160	97
15	5.510	65	158	98
16	5.848	68	159	102
17	5.924	70	208	102
18	6.647	81	161	105
19	6.551	64	222	102
20	6.928	83	173	107
21	7.465	79	227	111
22	8.711	86	176	114
Mean:	**4.93±1.59**	**66.1±12.1**	**168.2±29.1**	**99.1±11.4**

The energy expenditure during preparations to the National Independence Day of November 11th is presented in Table 1.

Mean energy expenditure in subjects was 4.93±1.59 kcal/min. Depending on the ceremonial activity being trained, the energy expenditure ranged from 3.013 kcal to 8.711 kcal/min. According to Christensen's classification of workload, the measured mean energy expenditure associated with the activities performed by the soldiers of the Representative Battalion of the Polish Army as part of preparations to the celebration of the National Independence Day of November 11th allows the workload to be classified as light [2]. Also indicative of light workload is the mean systolic heart rate of 99.1±11.4 bpm [3]. During the three-day concentration, the training sessions were held for 8 hours/day, with the effective drill training time of 7 hours. Mean energy expenditure of soldiers

during a 7-hour training was 2068.9±671.2 kcal, with actual values ranging from 1265.5 to 3658.6 kcal depending on the activity performed. Although according to the classification of workload depending on the energy expenditure per labour shift, can be classified as heavy on the basis of mean energy expenditure [4], the actual values of energy expenditure were diverse and depended on the type of ceremonial activities performed. As shown by the obtained results, work performed by some soldiers was classified as light, while energy expenditure of others was typical for heavy, or even very heavy workloads. The results of earlier studies of the energy burden of soldiers of the Representative Company of the Polish Army suggested that the daily energy expenditure was 4,648 kcal, which classified the work performed by the soldiers as very heavy [5].

Conclusion

The energy burden of the soldiers of the Representative Battalion of the Polish Army during the drill training held as part of preparation for the celebration of the National Independence Day of November 11th was varied and allowed the workload to be classified as light to very heavy.

References:

1. www.brepr.wp.mil.pl
2. Christensen C.G., Frey H.M., Foenstelinen E. A.: A critical evaluation of energy expenditure estimates based on individual O2 consumption/heart rate curves and average daily heart rate. Am. J. Clin. Nutr. 1983, 37, 468-472
3. Klonowicz S.: Wybrane zagadnienia fizjologii pracy w: J. Rosner Ergonomia. Zagadnienia przystosowania pracy do człowieka. Warszawa, 1974, 139.
4. Bugajska J.: Ocena obciążenia pracą fizyczną dynamiczną na stanowisku pracy. Pakiet edukacyjny „Nauka o pracy – bezpieczeństwo, higiena, ergonomia". CIOP, www.cop.pl
5. Kłos A., Szymański A.: Ocena wydatku energetycznego młodych mężczyzn pełniących służbę wojskową w Kompanii Reprezentacyjnej WP, Lekarz Wojskowy 1996, 9-10, 522-525

Epidemiology

Assessment of microbial quality of drinks not included in the hospital diet as consumed by patients during hospitalization and the assessment of microbial contamination of hospital air

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Summary:

Introduction: According to epidemiological data from different countries, the incidence of nutrition-related poisonings and infections is constant, and even growing in some regions. Currently, there are no standards defining acceptable levels of airborne microorganisms in indoor air (hospital facilities) in Poland
Material and methods: 100 juice samples collected from previously opened packagings between March 2007 and December 2009 in the Voivodship Specialist Hospital in Krakow were subjected to microbial examination. Open juice packagings were kept for 48 hours at room temperature in patient rooms at the hospital wards. Ninety-one air quality measurements were also conducted at different locations in the hospital to monitor microbial infections. The control group consisted of 50 juice samples stored in home conditions.
Conclusions: Significant transgression of the acceptable air contamination limits in hospital rooms, together with the transgressed limits of microbial contamination in juices suggest that the juices might be a potential source of nosocomial infections. Opened juices should not be stored at room temperature for periods longer than 24 h.

Key words: microbial contamination, juices, air, nosocomial infections.

Introduction

According to epidemiological data from different countries, the incidence of nutrition-related intoxications and infections is constant, and even growing in some regions. In the past, juices were excluded from food safety studies due to their low pH values resulting from the presence of organic acids with antibacterial properties. However, recent studies suggested a possibility of food poisoning induced by contaminated juices [1-3].

Intestinal infections occurring in different groups of patients during hospitalization may

be not only due to patient-to-patient transmission, but also to the consumption of food of poor microbial quality. The threat may originate mainly from products brought to patients by visitors [1]. It is common for the visitors to bring drinks in large packagings, both carton and plastic bottles. Patients, particularly children and the elderly, have difficulties using such packagings. This also pertains to patients who cannot move easily after procedures they underwent. With water consumption recommendations suggesting that a single serving should not exceed ca. 100 mL (in adults), depletion of a 1.5 L, or sometimes even a 2 L takes a significant amount of time [4]. This poses a significant threat of microbial infection with bacteria, fungi and molds present in the hospital environment [5].

Currently, there are no standards defining acceptable levels of airborne microorganisms in indoor air (hospital facilities) in Poland *The Ordinance of the Minister of Health of 26 June 2012 on detailed requirements for the facilities and equipments in entities engaged in medical activities, being the executive act for the Act of 15 April 2011 on medical activities (Journal of Laws of 2011, No. 112 item 654)* contains only one paragraph regarding air quality. Paragraph 37 of Section 6 of the Ordinance, titled *System requirements reads that In operating, theaters, isolation wards and immunocompromised patient rooms, ventilation systems should be used that ensure air quality parameters suited to the function of these facilities.* There are no numerical values indicating air quality assessments [6,7].

French standard NF S 90-351: 2003 classifies the facilities into 4 infection risk zones. The standard's guidelines classify corridors, elevators, staircases, waiting rooms, physician's offices accessible to outpatients, rehabilitation rooms, pregnancy wards, facilities for patients requiring long or medium hospitalization periods, mental health care facilities, central sterilization facilities (washing zones), drugstores, laundries and toilets as zone 2 facilities. According to the authors of the guidelines, zone 2 is a medium risk level zone [8]. Of highest interest to microbiologists is the quality of air in operating rooms [9-11]. Studies in residential facilities may provide basis to comparisons of conditions in the areas where patients are staying.

The study of hazardous factors published by J.L. Górny in 2004, which included standards, recommendations and proposed acceptable level fully illustrates the vastness of public health issues which have to be considered, including issues regarding patients staying at healthcare facilities [15].

No studies of the contaminating effect of hospital air on food brought to patients' rooms and consumed by patients were found in the available literature. Thus, fruit juices were selected for analysis, as they are the drinks that are most commonly consumed by both children and adults staying in hospital facilities (unpublished data from own observations).

The objective of the study was to evaluate the microbial risks for hospitalized patients in relation to juices brought to the hospital by visitors.

Material and methods

The study took place in one of the Voivodship Specialist Hospitals in Krakow. Selection of juices followed an analysis of consumption patterns in patients staying in patient rooms and surveys regarding the frequency of drink consumption (unpublished data from own observations). A total of 100 juice samples were collected for microbial analysis from previously opened carton, glass or plastic packagings between March 2007 and December 2009. Opened juices were stored in patient rooms for 48 hours at room temperature. Ninety-one air quality measurements were also conducted at different locations in the hospital to monitor microbial infections.

The control group consisted of 50 juice samples stored in home conditions. Microbial quantitative analysis of juices was performed by the Koch's plate dilution method. Bacterial counts were performed after 72 h of incubation at 37°C.

Air samples were collected for microbial analyses using a MAS-100 Microbial Air Monitoring System by MERCK. The system automatically sampled a pre-defined volume of air into the instrument head containing a sterile single-use Petri dish with agar medium suitable for tested microbial groups. Following solid selective media were used for quantitative determinations of microorganisms:

1) Total bacterial count — Columbia agar medium.
2) Staphylococci — Chapman ager medium.
3) Gram-negative rods — MacConkey agar.
4) Fungi — Sabourand agar medium.

Petri dishes with air samples and selective culture media were incubated in appropriate conditions.

The results of analyses were compared to relevant standards and literature data.

Results and discussion

Microbial contamination of foods (including drinks) may be due to both improper pasteurization process, and to contamination with pathogenic bacteria after pasteurization. As mentioned before, large-size juice packagings purchased by visitors are commonly found in patient rooms. They are usually stored at patients' beds. Microbial purity of these juices may be doubtful, particularly after a prolonged time of storage at room temperature. Food safety monitoring procedures might reduce hospitalization costs as well as to potentially allow to avoid e.g. nosocomial infectious diarrhea, which is a factor that prolongs hospitalization of children [16,17].

Of all biological risk factors, bacteria and molds are characterized by the furthest range of allergic and toxic effects. They are also emitted with dust into the air, which might lead to chronic organ diseases, such as respiratory or gastrointestinal diseases [18].

Microbial evaluation of juice samples collected at hospitals revealed the total bacterial count standard limits being exceeded in 56% of samples. Fungal count standard limits were exceeded in 23% of samples. Evaluation of control samples revealed the total bacterial count standard limits being exceeded in 21 cases (42%), with the remaining samples being within limits. Fungal count standard limits were exceeded in 5 (10%) control samples (Table 1).

In 26 cases, juices standing at patients' bedsides were not contaminated with either bacteria or fungi. Statistical analysis revealed that compared

Table 1: Number of pathogenic bacteria and fungi in juices.

Sampling site	Pathogenic bacteria (Columbia agar medium)			Pathogenic fungi (Sabourand agar medium)		
	None	0 < ..< Normal	Above normal	None	0 < ..< Normal	Above normal
Hospital N=100						
n (%)	28 (28)	16 (16)	56 (56)	64 (64)	13 (13)	23 (23)
X±SD	-	70.92±44.6*	151,467.5 ±307,313.8*	-	55.5±54.8*	261,929.7 ±345,018.2*
Median	-	71.25	9,875	-	45	72,000
Minimum	-	10	280	-	1	600
Maximum	-	155	1,724,000	-	158	1,280,000
Control — private houses N=50						
n (%)	23 (46)	6 (12)	21 (42)	39 (78)	6 (12)	5 (10)
X±SD	-	89.2±56.9**	44,438.6 ±191,496.2**	-	35.0±52.8**	318,572.6 ±537,984.4**
Median	-	85	2,023	-	13	146
Minimum	-	10	350	-	2	2,733
Maximum	-	155	880,000	-	140	1,250,000

n – number of samples, X±SD - arithmetic mean ± standard deviation; * ,** statistically significant differences between groups.
PN-A-79034 Non-carbonated soft drinks. Bacterial counts determined after 72 h of incubation not larger than 200 per 1 mL.
Mold content per 1 mL: unacceptable.
Yeast counts not larger than 200 per 1 mL [19].

to juices stored in home conditions, juices opened by patients in hospital wards significantly more often contained pathogenic bacteria and fungi ($p<0.05$). However, the latter were also observed in ranges exceeding the normal limits in home conditions ($p<0.05$).

All objects surrounding the patients may be potential sources of nosocomial pathogens. Patients themselves are most responsible for contamination of hospital surfaces. This is particularly true in children who show significant mobility and willingness to explore their surroundings typical for their age [20].

Staphylococcal count limits were exceeded in 87% of 91 air quality measurements. Total bacterial counts were exceeded in 63% of samples, while fungal counts were exceeded in 16% of samples (Table 2).

Both internal and external factors have significant impact on airborne microbial counts. Most commonly, microorganisms migrate on dust particles. Air dustiness is several times higher in large urban areas than in green regions. Seasonal changes and precipitations may periodically reduce this difference [22,23].

The degree of microbial air contamination depends on various factors. Literature reports report the role of facility population, sanitary and hygienic conditions and intensity of air exchange. The type of airborne microorganisms also depends on the type of the surrounding environment [24].

One of the possible approaches is to reduce patients' exposure to airborne microbial pathogens. An efficient way to obtain air characterized by low microbial levels in hospital facilities is the use of state of the art ventilation and air conditioning systems. In many hospitals, there is virtually no collaboration or communication between epidemiology physicians and nurses and the technical staff.

This is largely due to the lack of appropriate knowledge and care for proper exploitation of ventilation/air conditioning system in hospital administration, technical and medical staff [25,26].

Table 2: Prevalence of microbial contamination of air in hospital facilities.

Sampling site	Number of measurements n (%)	Prevalence of microbial contamination of air		
		Number of measurements – bacteria (Columbia agar medium) n (%)	Number of measurements – fungi (Sabourand agar medium) n (%)	Number of measurements – pathogenic staphylococci (Chapman agar medium) n (%)
Patient room 1 table	12 (100%)	9 (75%)	2 (17%)	11 (92%)
Patient room 2 floor	13 (100%)	8 (62%)	3 (23%)	11 (85%)
Patient room neighbouring the toilet	13 (100%)	9 (69%)	0 (0%)	9 (69%)
Corridor near the toilet	12 (100%)	9 (75%)	4 (33%)	12 (100%)
Corridor near patient rooms	19 (100%)	12 (63%)	3 (16%)	15 (79%)
Corridor at main entrance	22 (100%)	19 (86%)	3 (14%)	21 (95%)
Total	**91 (100%)**	**57 (63%)**	**15 (16%)**	**79 (87%)**

n – number of samples
Acceptable microbial contamination of air in service facilities (accd. to B. Krzysztofik)
Acceptable microbial counts per 1 m^3 of air
Patient room
MPA total bacterial count – 1,000
Number of microorganisms causing hemolysis in blood-containing agar (e.g. pathogenic staphylococci) – 50
Total fungal count – 200 [21]

Bacterial cultures

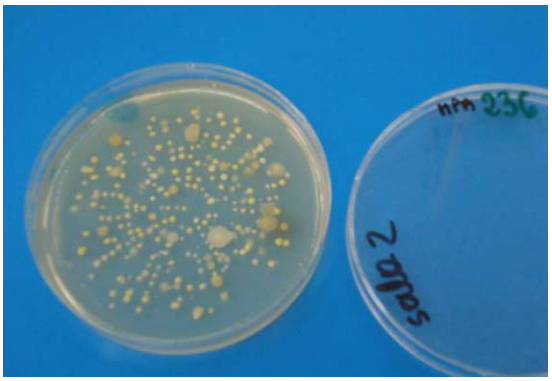

Figure 1: Total number of bacteria in the hospital air (Columbia agar medium).

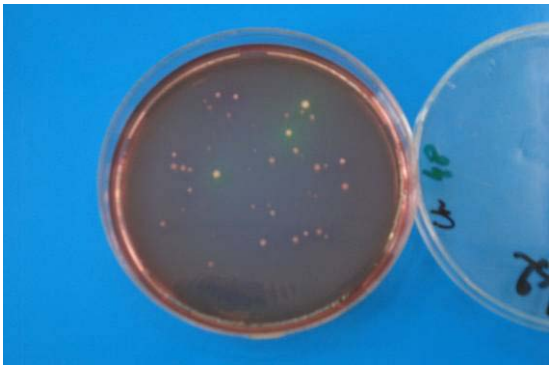

Figure 2: Total number of staphylococci in the hospital air (Chapman agar medium).

Figure 3: Total number of fungi in a juice sample (Sabourand agar medium).

Conclusions

Transgression of acceptable limits of air purity in hospital rooms, as well as of the microbial contamination of juices, is alarming.

Significant transgression of the acceptable air contamination limits in hospital rooms, together with the transgressed limits of microbial contamination in juices suggest that the juices might be a potential source of nosocomial infections.

Opened juices should not be stored at room temperature for periods longer than 24 h.

References:

1. Windyga B, Ścieżyńska H, Grochowska A et al.: Ocena zagrożeń zdrowotnych wynikająca z zanieczyszczenia żywności drobnoustrojami chorobotwórczymi. Bromat Chem Toksykol Supl, 2003; 36: 281-284.
2. Visser H, Verhoef L, Schop W et al.: Outbreak investigation in two groups of coach passengers with gastroenteritis returning from Germany to the Netherlands in February 2009. Euro Surveill, 2010; 15(28).pii: 19615.
3. Noel H, Hofhuis A, De Jonge R et al.: Consumption of fresh fruit juice: how a healthy food practice caused a national outbreak of Salmonella Panama gastroenteritis. Foodborne Pathog Dis, 2010; 7(4): 375-381.
4. Jarosz M, Bułhak-Jachymczyk B: Normy żywienia człowieka. Podstawy prewencji otyłości i chorób niezakaźnych. PZWL Warsaw, 2008.
5. Charkowska A: Czystość mikrobiologiczna i pyłowa środowiska szpitalnego (cz. II). Chłodnict Klimatyz, 2006; 2: 28 (http://archiwum.chlodnictwoiklimatyzacja. pl/artykuly/2006_02/28.htm Accessed on: 20.11.2012).
6. Ordinance of the Minister of Health of 26 June 2012 on detailed requirements for the facilities and equipments in entities engaged in medical activities.
7. Act of 15 April 2011 on medical activities. Journal of. Laws 2011 no. 112 item 654.
8. NF S 90-531 standard for healthcare centers in France (http://www.armstrong.pl/assets/global/commclgeu/flash/healthcare-01-2011/pl/pdf/PL_NORMA%20NF%20S%2090-351%20DLA%20PLACOWEK%20SLUZBY%20ZDROWIA%20WE%20FRANCJI.pdf Accesed on: 20.11.2012)
9. Charkowska A: Jakość i czystość powietrza wewnętrznego w salach operacyjnych w szpitalach. Educational Meeting at the Chief Sanitary Inspectorate, Warsaw 8.12.2011 r. (http://www.gis.gov.pl/ckfinder/userfiles/files/Departament%20Higieny%20%C5%9Arodowiska/Wydzia%C5%82%20ds%20Nadzoru%20Sanitarnego/Nadz%C3%B3r%20Zapobiegawczy/Anna%20Charkowska%20-%20Wyk%C5%82ad%20szpitale%202011%20cz%C4%99%C5%9B%C4%87%201.pdf Accessed on: 20.11.2012).

10. Gregorowicz-Warpas D, Pałubicka A, Wolski A, Kaiser K: Czyste powietrze w salach operacyjnych. Materiały szkoleniowe dla pielęgniarek epidemiologicznych. Zesz. IV, Wrocław 2005.
11. Napoli C, Marcotrigiano V, Montagna MT: Air sampling procedures to evaluate microbial contamination: a comparison between active and passive methods in operating theatres. BMC Public Health, 2012; 12:594 doi: 10.1186/1471-2458-12-594.
12. Rokitka H, Krajewska-Kułak E, Szepietowski J et al.: Analiza występowania grzybów w pomieszczeniach bloku operacyjnego. Mikol Lek, 2006; 13(4): 301-305.
13. Krajewska-Kułak E, Łukaszuk C, Gniadek A et al.: Zanieczyszczenie powietrza w pomieszczeniach mieszkalnych, ze szczególnym uwzględnieniem roli grzybów. Mikol Lek, 2011; 18(3): 135-139.
14. Krogulski A: Metody oznaczania ogólnej liczby bakterii w powietrzu atmosferycznym i wewnątrz pomieszczeń. Roczn PZH, 2006; 57(1): 1-7.
15. Górny RL: Biologiczne czynniki szkodliwe: normy, zalecenia i propozycje wartości dopuszczalnych. Podstawy i Metody Środów Pracy, 2004; 3(41): 17-39.
16. Abushelaibi AA, Sofos NJ, Samelis J et al.: Survival and growth of Salmonella in reconstituted infant cereal hydrated with water, milk or apple juice and stored at 4° C, 15° C and 25° C. Food Microbiol, 2003; 20: 17-25.
17. Neuhoff–Murawska J, Socha P, Socha J: Soki: zalety i zagrożenia w żywieniu dzieci i młodzieży. Stand Med, 2007; 4: 91-99.
18. Sadowski T, Czuba Z, Król W: Mikrobiologiczna ocena produktów żywnościowych w magazynach szpitalnych. Zdr Publ, 2006; 116(3): 512-514.
19. Napoje bezalkoholowe niegazowane wraz ze zmianami. PN-A-79034/A1: 1997 — z wyłączeniem p. 5.1.
20. Krzysztofik B: Mikrobiologia powietrza. Wyd. Politechniki Warszawskiej, Warszawa 1992.
21. Czyżanowska J, Bulanda M: Czynniki ryzyka zakażeń szpitalnych u dzieci. Pediatr Pol, 2007; 11: 873-878.
22. Krogulski A: Lokalizacja szpitali a czystość mikrobiologiczna powietrza w pomieszczeniach. Roczn PZH, 2008; 59: 97-102.
23. Krogulski A: Czystość mikrobiologiczna powietrza sal operacyjnych – wybrane aspekty. Roczn PZH, 2006; 57: 277-282.
24. WHO Guidelines for indoor dampness and mould. Executive Summary. WHO, Copenhagen Danmark, 2009.
25. Łukaszuk C, Krajewska–Kułak E, Wrońska I et al.: Badania powietrza w oddziałach onkologicznych w Białymstoku i Lublinie. Onkol Pol, 2002; 5(3-4): 147-152.
26. Krogulski A., Szczotko M.: Czystość mikrobiologiczna powietrza w szpitalach. Sale operacyjne klimatyzowane. Roczn PZH, 2010; 61(4): 425-429.

Pharmacology & Pharmacy

Cholesterol oxyethyleneation products as modifiers of the absorption base in anti-inflammatory ointments

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Summary:

Introduction: The assumption behind the study was to attempt modification of pharmacopoeial anhydrous absorption base, i.e. hydrophilic vaseline, by the addition of novel cholesterol oxyethyleneation products. Novel base with variant compositions was proposed as a carrier for ketoprofen – a medicinal substance with analgesic, anti-inflammatory and antipyretic activity.
Material and methods: 5 model ointments were prepared with the absorption base consisting of hydrophilic vaseline modified with cholesterol oxyethyleneation products. Extensometric method was used to test spreadness of the preparations, gravimetric method to determine the rate of volatile components loss, while viscosity parameters were determined with cone-plate digital rheometer. The test for ketoprofen pharmaceutical availability was performed with spectrophotometric method.
Results: Modification of the absorption base (hydrophilic vaseline) by introduction of novel cholesterol oxyethyleneation products increased the extensibility parameters of all prepared ointments. Viscosity tests showed that all hydrophilic vaseline-based ointments with variant compositions were tixothropic and rheologically unstable. Introduction of cholesterol derivatives into the formulae of hydrophilic vaseline-based ointments reduces their structural viscosity values. Comparison of the areas under the curves of the release of ketoprofen lysinate showed that the active substance was best released from ointments with cholesterol oxyethylenates with the lowest n umber of segments (n_{TE}), regardless of the type of the catalyst used to produce these oxyethylenates (M-Ch-10 Na and M-Ch-10 Ca).
Conclusions: As shown by the conducted studies, the use of novel oxyethylate-containing products affects optimization of the rheological parameters of the ointments and the efficacy of the release of ketoprofen lysinate into a model recipient fluid.

Key words: ointments, skin inflammation, hydrophilic vaseline, cholesterol oxyethyleneation products.

Introduction

The objective of rheological studies in drug formulation technology is to determine correlations between structure-related physicochemical properties of the drugs and the usability of these drugs [1,2,3]. Rheological parameters of topical pharmaceuticals, such as ointments, creams, gels, or pastes, are determined by components included in the base [4]. Appropriate selection of these components impacts

pharmaceutical availability of medicinal substances, and thus the efficacy of treatment.

The assumption behind the study was to attempt modification of pharmacopoeial anhydrous absorption base, i.e. hydrophilic vaseline, by the addition of novel cholesterol oxyethyleneation products manufactured by the Surface Active Agents Production Plant ICSO Blachownia in Kędzierzyn-Koźle [5,6,7]. The novel base with variant compositions was proposed as a carrier for ketoprofen — a medicinal substance with analgesic, anti-inflammatory and antipyretic activity [8].

The main indications for local application of ketoprofen include muscle and joint pains, inflammatory conditions caused by injuries such as joint dislocations, sprains or sports injuries, and tendonitis [9]. Local administration of ketoprofen determines its activity in pathological tissues and minimizes the risks of adverse events reported for oral use [10].

Objectives

The goal of the study was to assess the effects of cholesterol oxyethyleneation products on rheological parameters of hydrophilic vaseline-based ointments and the efficacy of the release of a non-steroidal anti-inflammatory drug available as lysinate salt into the external compartment.

Reagents and equipment

Reagents:
- hydrophilic vaseline (Coel);
- ketoprofen lysinate (Sigma);
- cholesterol oxyethyleneation products containing the following numbers of oxyethylenic segments (n_{TE}); 10, 20, 30, 40 (products manufacture using a sodium catalyst) and 10 for calcium catalyst (Surface Active Agents Production Plant ICSO Blachownia in Kędzierzyn-Koźle);
- distilled water.

Instrumentation:
- MR 200 formulation mixer (Alpina);
- water bath MLL 147/6 AJL (Electronic Krakow, Poland);
- Cone/plate DV-III digital rheometer, version 3.0 (Brookfield);
- bath thermostat PGW E1 (Medingen);
- extensometer, pH-meter N5170E with ERH-131 electrode (Hydromet Gliwice, Poland);
- drug release apparatus Erweka DT 600 (Erweka), apparatus accd. to Mutimer et al.;
- Visking Dialysis Tubing C/100 membrane, wall thickness 74 μm and pore diameter 75 μm (Serva Electrophoresis GmbH);
- spectrophotometer Nicolet Evolution 300, version 1.0 (Spectro-Lab);
- technical balance (Radwag, Precision Mechanics Plant in Radom, Poland), analytical balance (Radwag, Precision Mechanics Plant in Radom, Poland).

Experimental method

Development of model formulae

5 model ointments were prepared with the absorption base consisting of hydrophilic vaseline modified with cholesterol oxyethyleneation products. The formula of the ointments is presented in Table 1.

Table 1: Formula of the ointments with the absorption base consisting of hydrophilic vaseline modified with cholesterol oxyethyleneation products.

Ingredient	Quantity (g)
Ketoprofen lysinate	2.5
Hydrophilic vaseline	76.5
Cholesterol oxyethyleneation product*	1.0
Distilled water	20.0

* Oxyethyleneation products used included products prepared using a sodium catalyst had the following numbers of oxyethylenic segments: n_{TE}=10 (M-Ch-10 Na ointment), n_{TE}=20 (M-Ch-20 ointment), n_{TE}=30 (M-Ch-30 Na ointment), n_{TE}=40 (M-Ch-40 Na ointment) and the product of n_{TE}=10, prepared using a calcium catalyst (M-Ch-10 Ca ointment).

For comparison, an ointment containing no cholesterol oxyethyleneation products was also prepared (M-0 ointment). The formula of the ointments is presented in Table 2.

Table 2: The formula of the ointments with hydrophilic vaseline base.

Ingredient	Quantity (g)
Ketoprofen lysinate	2.5
Hydrophilic vaseline	77.5
Distilled water	20.0

Ointment extensibility test
The test was conducted at 25 °C using the extensometric method.

Determination of ointment viscosity parameters
Ointment viscosity tests were conducted at 32 °C±0.1 °C using a cone/plate digital rheometer coupled with a bath thermostat [12].

Determination of the kinetics of the loss of volatile ointment components
Plates with the diameter of d=9cm and total surface area of P=63.59 cm2 were covered with uniform ointment layers. Thus prepared samples were placed in a dryer-balance at 32±0.1 °C for 2.5 and the percentage weight loss readings were taken every 15 minutes.

Determination of the kinetics of the release of lysinate from the ointment
The test was conducted using the technique used for transdermal therapeutic systems according to Ph.Eur. 6 requirements [13].

A 5 g ointment sample was placed in a dialysis container with the mass exchange surface P=19.625 cm^2 (apparatus accd. to Mutimer *et al.*). Next, the ointment surface was covered by an appropriately prepared Visking dialysis membrane. Before the test, the dialysis membrane was exposed to distilled water over 24 h. The entire system was closed with the lid and tightened with nuts. Thus prepared dialysis container was placed in a thermostated vessel (32°±0.1 °C), containing 0.25 dm^3 of distilled water as a recipient liquid. The solution above the container was put in continuous rotational motion using a stirrer rotating at 100 rpm. The mass exchange rate was measured by spectrophotometric analysis of ketoprofen lysinate released from the ointment. Measurements were made at nine time points over 6 hours (samples collected at 40-minute intervals). The amount of the released ketoprofen lysinate was determined at λ=260 nm using the following equation: A= 0.4249·c+ 0.0677 (r=0.9991), where: A is absorbance and c is the concentration of the pharmaceutical substance.

Results and Discussion

Results of extensometric tests

Extensometric tests (measurements of extensibility) allowed to assess products' capacity to increase its surface area under the pressure force. Figure 1 presents an example extensibility curve (relationship between the extended ointment surface area and the force load applied).

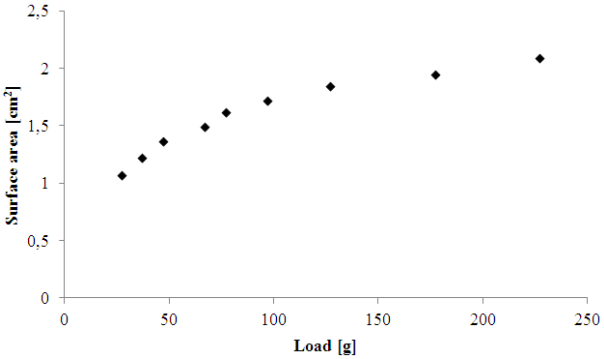

Figure 1: The relationship between the applied load and the observed increase in M-Ch-30 Na ointment surface area.

Figure 2 compares the extensibilities of all tested ointments under the highest load applied during the test (227 g).

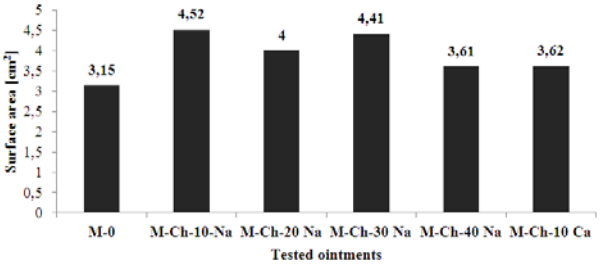

Figure 2: Comparison of extensibilities of all tested ointments under the highest load applied during the extensometric test.

Extensibility is the measure of product's capacity to increase its surface area under increasing pressure force. Products of high extensibility are easily distributed over the administration site. This affects the quality of application. Administration of ointments on inflamed tissues should not increase the pain sensation. Good extensibility of the ointment increases the rate of release of the active substance at the site of administration. Diffusion of the active substance into the external compartment may occur over a large ointment surface area that has been spread using a low pressure force.

Modification of the absorption base (hydrophilic vaseline) by introduction of novel cholesterol oxyethyleneation products increased the extensibility parameters of all prepared ointments (Fig. 2). In case of ointments prepared using novel ointments, and in case of the highest loads applied during the extensometric tests, the surface areas of extended ointments ranged from: 3.61 to 4.52 c.u. In case of the ointment with unmodified formula (M-0), the value was 3.15 c.u.

Viscosity test results

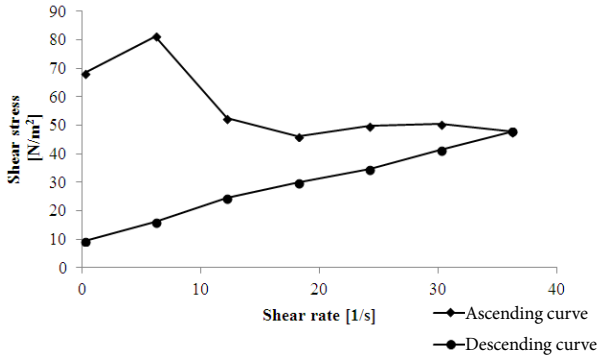

Figure 3: Hysteresis loop for the M-0 ointment.

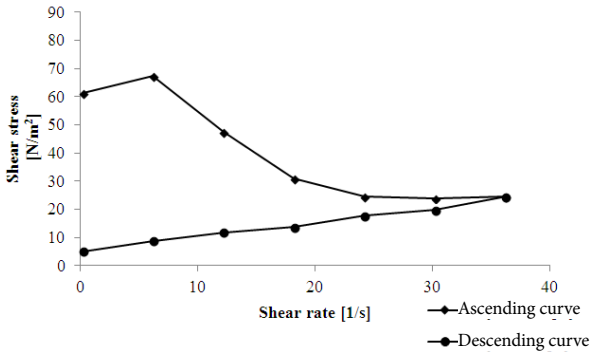

Figure 4: Hysteresis loop for the M-Ch-10 Na ointment.

Viscosity tests showed that all hydrophilic vaseline-based ointments with variant compositions were tixothropic and rheologically unstable, as confirmed by the hysteresis loop test [14]. Measurements of shear stress depending on shear rate were performed by increasing the shear rate from zero to a pre-defined maximum value and than back to zero immediately after reaching the maximum point. Figures 3 and 4 present example hysteresis loops obtained for the M-0 ointment and for an ointment containing a cholesterol oxyethyleneation product (M-Ch-10 Na).

Positive tixotrophy was observed for all prepared products. Upon isothermal flow of the fluid that has previously been in stasis for a prolonged time, the shear stress was reversibly reduced over time in these systems.

Structural viscosity of the tested ointments was compared at the ascending hysteresis loop curve fragments for three arbitrarily selected shear rates of 12.2, 24.2 and 30.2 1/s. The results are listed in Table 3.

Introduction of cholesterol derivatives into the formulae of hydrophilic vaseline-based ointments reduces their structural viscosity values, as observed at all three shear rates tested in the study. Based on the Einstein-Smoluchowski equation: $D=kT/6\pi r\eta$, (where: D — diffusivity of the medicinal substance, k — Boltzmann constant, T — temperature in Kelvins, r — observed radius of the molecule of the medicinal substance, η — viscosity) [15], one may expect that the reduction in viscosity parameters would enhance diffusibility of the medicinal substance (ketoprofen lysinate) from the ointment into the external compartment, which is associated with increased anti-inflammatory efficacy of the product.

Table 3: Structural viscosity parameters for the model ointments.

Ointment	Shear rate 12.2 1/s		Shear rate 24.2 1/s		Shear rate 30.2 1/s	
	Shear stress [N/m2]	Viscosity [mPa·s]	Shear stress [N/m²]	Viscosity [mPa·s]	Shear stress [N/m²]	Viscosity [mPa·s]
M-0	52.5	4286	49.7	2054	50.5	1672
M-Ch-10 Na	47.5	3895	24.5	1010	23.9	789.9
M-Ch-20 Na	42.3	3471	30.4	1257	30.2	994
M-Ch-30 Na	44.1	3618	28.2	1167	29.6	980.8
M-Ch-40 Na	52.1	4269	39.2	1618	42.9	1422
M-Ch-10 Ca	51.1	4188	40.0	1651	38.8	1284

Water loss kinetics test results

The measurements of water loss kinetics constitute a supplement to the rheological tests (extensibility, structural viscosity). The ointment's tendency to lose water affects its structural viscosity following application on the skin, and thus, the kinetics of the release of the active substance. From this standpoint, slight viscosity changes are preferred over time. The measurements of the water loss kinetics may also be used to assess the rheological stability of the product as part of stability tests. Slight changes in the ointment mass occurring over time

affect the stability of its physicochemical parameters upon storage.

Figure 5 presents an example curve of ointment water loss.

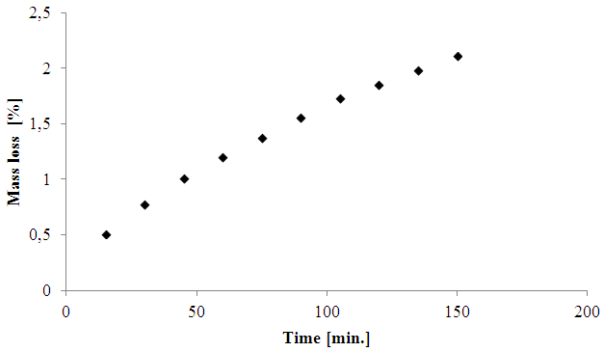

Figure 5: Kinetics of water loss for the M-Ch-10 Ca ointment.

Table 4: Parameters of the regression equation of the type y=ax+b describing the kinetics of the loss of water from the ointment

Ointment	Regression equation coefficients		Correlation coefficient r	Surface area [c.u.]
	a	b		
M-0	0.1653	0.4036	0.9916	1895.5
M-Ch-10 Na	0.1721	0.4951	0.9912	1983.6
M-Ch-20 Na	0.1560	0.4693	0.9871	1800.8
M-Ch-30 Na	0.1875	0.4776	0.9945	2152.8
M-Ch-40 Na	0.1760	0.4549	0.9921	2021.6
M-Ch-10 Ca	0.1744	0.4520	0.9927	2003.4

The relationship between the loss in the mass of the tested ointments [%] and time [min.] was described at the significance level of p=0.05 by a regression equation of the type y=ax+b. Parameters a and be were used to calculate the surface areas P under the water loss curves, expressed in conventional units [c.u.], using an integration method. The obtained values are listed in Table 4.

It was shown that introduction of cholesterol oxyethyleneation products into the ointment formula did not significantly affect the loss of water from the products. Surface areas under the curves of the loss of water from the ointment containing different cholesterol derivatives ranged from 1800.8 to 2152.8 c.u. In case of the ointment with unmodified formula (M-0), the value was 1895.5 c.u. (Table 4). As shown by the calculations, the tested ointments would be characterized by comparable changes in viscosity parameters during application on the tissue affected by inflammation. The diffusibility of ketoprofen lysinate would be at similar levels throughout the contact with the application site, as follows from th e Einstein-Smoluchowski equation (D=kT/6πrη).

Results of determination of the kinetics of the release of lysinate from the ointment

Figure 6 presents an example of the relationship between the quantity of the released ketoprofen lysinate (in mg per cm2 of the dialysis membrane) as a function of the square root of time.

The obtained relationships were described by correlation equations of the types y=ax+b and lg(y)=a·lgx+b (a logarithmic form of the exponential

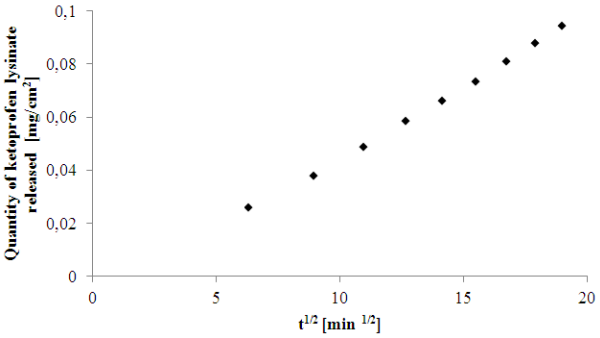

Figure 6: Kinetics of the release of ketoprofen lysinate from the M-Ch-30 Na ointment.

Table 5: Regression equations describing the kinetics of the release of ketoprofen lysinate from model ointments

Ointment	Regression equation type	Regression equation coefficients		Correlation coefficient r	Surface area [c.u.]
		a	b		
M-0	y=ax+b lg(y)=a·lgx+b	4.1365·10-3 0.6435	-2,0335·10-2 -1.8417	0.9731 0.9651	0.4044
M-Ch-10 Na	y=ax+b lg(y)=a·lgx+b	5.160·10-3 1.0252	-0.0451·10-2 -2.3003	0.9746 0.9668	0.9088
M-Ch-20 Na	y=ax+b lg(y)=a·lgx+b	5.1299·10-3 1.6352	-2.2820·10-2 -3.2015	0.9940 0.9971	0.5319
M-Ch-30 Na	y=ax+b lg(y)=a·lgx+b	5.4611·10-3 1.1811	-1.0226·10-2 -2.5368	0.9991 0.9998	0.7442
M-Ch-40 Na	y=ax+b lg(y)=a·lgx+b	6.0644·10-3 1.5758	-2.7472·10-2 -3.0646	0.9881 0.9975	0.6225
M-Ch-10 Ca	y=ax+b lg(y)=a·lgx+b	5.5206·10-3 1.4582	-2.3623·10-2 -2.9553	0.9846 0.9909	0.9746

equation y=axb). Regression equations and areas under the curves of ketoprofen lysinate release expressed in conventional units are listed in Table 5.

As shown by the high correlation coefficient for the linear equation y=ax+b at p=0.05, the process of release of ketoprofen lysinate from the ointment follows a zero-order kinetics. The exact kinetic equations based on the analysis of the diffusion process are usually complex and have the form of a sum of exponential functions [16].

The areas under the curves of release of the active substance from cholesterol derivatives-containing ointments are larger than the area obtained for the ointment obtained from hydrophilic vaseline only. For the cholesterol derivatives-containing ointments, the values ranged from 0.5319 to 0.9476, while for the M-0 ointment, the value was 0.4044 c.u.

Comparison of the areas under the curves of the release of ketoprofen lysinate showed that the active substance was best released from ointments with cholesterol oxyethylenates with the lowest n umber of segments (n_{TE}), regardless of the type of the catalyst used to produce these oxyethylenates (M-Ch-10 Na and M-Ch-10 Ca). More than a twofold increase in the efficacy of release of ketoprofen lysinate was achieved from ointments containing cholesterol derivatives including n_{TE}=10 oxyethylenic fragments.

Conclusions

Novel formulae for the ointment base, obtained after introducing oxyethyleneated cholesterol derivatives into hydrophilic vaseline may comprise a potential vehiculum for anti-inflammatory ointments. Regardless of their chemical structure (the number of oxyethylenic fragments) and the type of catalyst used in the synthesis of the oxyethyleneate, its presence in the ointment contributes to the favourable change in rheological parameters (increased surface area of extended ointment under pressure force, reduced structural viscosity with a negligible effect on the effect of the water loss). Introduction of cholesterol derivatives into the hydrophilic vaseline-based ointments enhances the efficacy of the release of ketoprofen lysinate from the ointment. The highest areas under the release curved were obtained for products containing cholesterol derivatives featuring n=10 oxyethylenic fragments.

References:

1. Górecki M: Reologia farmaceutyczna - perspektywy rozwoju. Farm Pol, 1996; 52(16): 739-743.
2. Górecki M, Zalewska A: Reometryczna analiza farmaceutycznych układów rozproszonych. Farm Pol, 2000; 56(15): 748-752.
3. Górecki M, Zalewska A: Reologia farmaceutyczna w analizowaniu układów nienewtonowskich. Farm Pol, 2001; 57(9): 417-419.
4. Lee ChH, Moturi V, Lee Y: Thixotropic property in pharmaceutical formulations. J Control Release, 2009; 136 (2): 88-98.
5. Zgoda MM, Nachajski M, Kołodziejczyk M, Woskowicz M, Lukosek M.: Właściwości solubilizacyjne i litogenolityczne wodnych roztworów niejonowych związków powierzchniowo aktywnych produktów oksyetylenowania cholesterolu. Polim Med, 2007; 37(4): 39-57.
6. Kołodziejczyk M., Zgoda MM: Oksyetylenowany cholesterol jako składnik modelowych płynów akceptorowych w ocenie dostępności farmaceutycznej liofilowych środków leczniczych. Farm Pol, 2007; 63(8): 342-348.
7. Kołodziejczyk M, Zgoda MM: Ocena właściwości fizykochemicznych produktów oksyetylenowania cholesterolu w aspekcie micelarnej solubilizacji liofilowych środków leczniczych. Pol J Cosmetol, 2006; 9(4): 250-263.
8. Korzeniowska K, Jankowski J, Jabłecka A: Niesteroidowe leki przeciwzapalne. Farm Współcz, 2010; 3: 192-197.
9. Sarzi-Puttini P, Atzeni F, Lanata L, Bagnasco M, Colombo M, Fischer F, D'Imporzano M: Pain and ketoprofen: What is its role in clinical practice. Reumatismo, 2010; 62(3): 172-178.
10. Coaccioli S: Ketoprofen 2,5% gel: a clinical overview. Eur Rev Med Pharmacol Sci, 2011; 15(8): 943-949.
11. Samczewska G, Zgoda MM: Solubilizacyjne właściwości wodnych roztworów siarczanu neomycyny. Pol J Cosmetol, 2002; 1: 49-63.
12. Kołodziejska J: Parametry reologiczne past do zębów a dostępność farmaceutyczna jonu fluorkowego. Bromat Chem Toksykol, 2004; 36 (1): 77-83.
13. Zgoda MM., Ogiński M: Przydatność wybranych membran dializacyjnych do oceny warunkach in vitro procesu wymiany masy na granicy faz z preparatu typu hydrożel. Pol J Cosmetol, 1999; 3: 197-208.
14. Tamburic S: The aging of polimer- stabilized creams: the rheological viewpoint. C&T, 2000; 115(10): 43-49.
15. Poradnik fizykochemiczny, Wydawnictwo Naukowo-Techniczne, Warszawa 1974.
16. Bodek KH: Badania porównawcze kinetyki uwalniania diklofenaku z hydrożelu mikrokrystalicznego chitozanu i hydrofilowej maści farmakopealnej. Farm Pol, 2000; 56 (15): 753-762.

Ophthalmology

Non-steroidal anti-inflammatory drugs (NSAIDs) in ophthalmology: pharmacological and clinical characteristics

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Summary:

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of inflammation and pain of different origins. Although NSAIDs differ in their structures, their mechanism of action is similar. The therapeutic target of NSAIDs is cyclooxygenase (COX), occurring as two isoenzymes: COX-1 (a constitutive enzyme) and COX-2 (an inducible enzyme, expressed in the course of the inflammatory process). Being a component of prostaglandin H synthase (PGHS), COX catalyzes the first step of transformations of arachidonic acids into prostaglandins (of the D, E and F series), prostacyclin (PGI2) and thromboxanes — all products characterized by diverse biological activities; some of them having pro-inflammatory action, some being involved in pain mediation. The registered NSAIDs are a numerous family of drugs, with vast majority available as products for systemic use (*per os, per rectum*, intramuscular or intravenous injections) and external use (ointments); only a few products are intended for intraconjunctival administration (ophthalmic products). Active substances used in ophthalmic NSAIDs include indomethacin (the active substance in the first ophthalmic drug), suprofen (currently not used), flurbiprofen, pranoprofen, ketorolac, diclofenac, bromfenac and nepafenac. Ophthalmic NSAIDs currently available in Poland include: Indocollyre (indomethacin; at present rarely used drug), Dicloabak, Difadol 0,1% and Naclof (all containing diclofenac), Yellox (bromfenac) and Nevanac (nepafenac); the two latter compounds have only recently become available in Poland. Therapeutic indications may differ slightly between individual drugs, but generally they include prevention and treatment of cystoid macular edema after cataract surgery, inhibition of intra-operative miosis during cataract surgery, reduction of pain and photophobia after refractive surgery, and, in addition, treatment of allergic conjunctivitis (mainly ketorolac-containing products). This article provides a critical review of NSAIDs used in medical therapy with particular focus on ophthalmic preparations.

Key words: Non-steroidal anti-inflammatory drugs, NSAID, ophthalmic preparations, therapeutic indications.

Introduction

Non-steroidal anti-inflammatory drugs (NSAID) are popular medications commonly prescribed by physicians and well known to patients. Many of such drugs are available without prescription, which contributes to the massive use of such products as aspirin, ibuprofen and paracetamol — a drug closely related to the NSAID family,

particularly to reduce or relieve pain and fever, as well as to improve certain less precisely defined ailments that reduce the comfort and quality of life.

The progenitor of the NSAID family is acetylsalicylic acid — aspirin, a drug with a history of more than 100 years and enormous worldwide popularity. Aspirin was introduced into the drug market in 1899 and has been extensively used ever since, although many other analgesic, antipyretic and anti-inflammatory drugs have also became available in that period. The word *aspirin* contains the stem *spir*, referring to the Latin term ***Spir**ea ulmaria*, i.e. meadowsweet (modern name is *Filipendula ulmaria*) — a plant from which the glycoside salicin, characterized by analgesic activity, was initially obtained. Salicin generates analgesic salicylic acid which is transformed by acetylation into acetylsalicylic acid (ASA), i.e. aspirin. The first letter of the word *aspirin*, i.e. the letter *a* (preceding the stem, i.e. *spir*) stood for acetylation, while the suffix *in* was commonly added to the drug names at that time.

Aspirin's mechanism of action was elucidated in early 1970s, when Sir John R. Vane — an English pharmacologist and physician, together whith two Swedish researchers, Sune K. Bergstrom, Bengt I. Samuelsson — discovered a cyclooxygenase-dependent pathway of transformations of arachidonic acid into prostaglandins (for which they were later awarded the Nobel Prize in physiology and medicine in 1982) [1]. The researchers demonstrated that aspirin causes acetylation of cyclooxygenase and inhibits the synthesis of prostaglandins — endogenous mediators of inflammatory reactions, pain sensation and pathologically elevated body temperature. These observations turned out to have far reaching consequences, as they became the point of departure for the research of other compounds that would inhibit cyclooxygenase activity, with hopes that at least some of these compounds would become more efficient and safer than salicylates (including aspirin), expressing mainly anti-inflammatory and analgesic activity. This initiated the era of NSAIDs — ones of the most common drugs in today's medical therapy, used mainly in the relief of pains of various origins and diverse inflammatory conditions.

The mechanism of action of NSAIDs

All NSAIDs exert their activity in the process of conversion of arachidonic acid (AA) into prostaglandin H–PGH_2 [2]. This step is catalyzed by prostaglandin H synthase (PGHS), having a dual enzymatic activity of cyclooxygenase and peroxidase. The AA → PGH_2 conversion consists of a sequence of two reactions: first, cyclization of AA into an unstable 15-hydroxyperoxide (PGG_2) followed by double oxidation in positions 9-11 by means of the cyclooxygenase component and next, reduction of the 15-hydroxyperoxide group in PGG_2 molecule, leading to an equally unstable PGH_2; this step is achieved by means of the peroxidase activity of PGHS [1]. Prostaglandin H_2 is a substrate for specific syntha-ses, tissue-dependent isomerases that catalyze its transformations into various endogenous regulators, such as prostaglandins of the D (PGD_2), E (PGE_2), and F (PGF_2) series, prostacyclin (PGI_2) and thromboxanes (TXA_2 and TBX_2) — all products characterized by diverse biological activities, with some of them having pro-inflammatory action (Fig. 1).

One should keep in mind that arachidonic acid (AA) is a substrate for many other important, biologically active molecules, to mention only the **pro-inflammatory** leukotrienes (resulting from AA molecules undergoing transformation by the activity of lipoxygenase [LOX]) or **anti-inflammatory**

[1] Conversion of arachidonic acid (AA) into prostaglandin H_2 (PGH_2) consists of two reactions: the first reaction involves an oxygen molecule being incorporated into the AA molecule and the resultant structure undergoing cyclization into an unstable prostaglandin G_2 (PGG_2), while the other reaction involves reduction of PGG_2 to its 15-hydroxy analog, i.e. PGH_2. These reactions are catalyzed by prostaglandin H synthase — a bifunctional enzyme exerting both cyclooxygenase and peroxidase activities. Some textbooks suggest that the cyclooxygenation is achieved by the activity of cyclooxygenase (COX) while peroxidation is achieved by hydroperoxidase (HPOX); however, PGHS is most commonly identified as COX. Cyclooxygenase was described in 1976, and its amino acid sequence was determined 12 years later. The spatial structure of COX was elucidated as late as in years 1994–1996 — by that time, it was already known that two isoforms of the enzyme, COX-1 and COX-2, existed, the latter one being inducible by inflammatory stimuli (including pro-inflammatory cytokines such as IL-1β or TNFα). Following cell activation, COX-2 gene activity reaches its peak value within a dozen or so minutes, and is later reduced to non-determinable levels within one hour. The activity of COX-2 increases about 1 hour after the inflammatory stimulus and is maintained at a high level for several hours after that. The increased activity of COX-2 leads to rapid formation of prostaglandins within the pericellular space and development of an inflammatory reaction. The main difference in the spatial structure of the two isoforms COX-1 and COX-2 is that the COX-2 molecule has a wider cyclooxygenase activity channel and features a side pocket associated with the presence of valine instead of isoleucine at position 523 of the COX-2 molecule. Molecules of selective COX-2 antagonists blocking the channels containing the active sites of the enzyme anchor their side chains in said pocket.

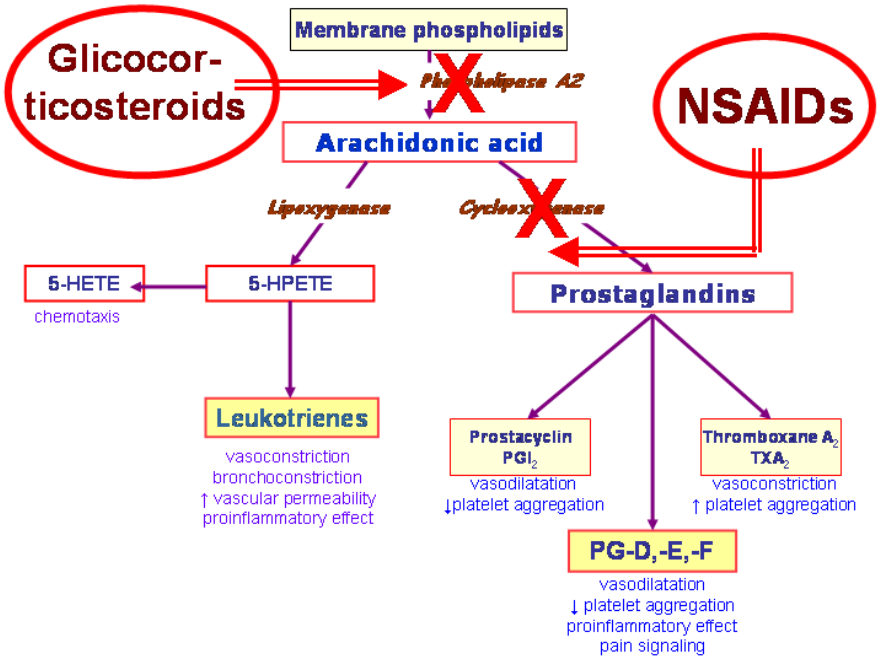


Figure 1: Metabolizm of arachidonic acid (AA) with the aid of cyclooxygenases (COX) and lipoxygenases (LOX) and sites of actions of non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticosteroids in comparison.

NSAIDs inhibit COX activity (the COX-1 and COX-2 isoenzymes); depending on the drug the inhibitory effect on COX-1 and COX-2 is varied (COX-1 > COX-2, COX-2 > COX-1). Glucocorticosteroids inhibit phospholipase A2 – PLA2 (this enzyme releases AA from the pool of membrane phospholipids, which makes the free AA a substrate for COX and LOX).
The PLA2-related effect of glucocorticosteroids refers to rapid nongenomic action, which in fact involves an indirect mechanism via lipocortin-1 and EGF receptor-driven signaling pathway. However, the main anti-inflammatory and immunosuppressive effects of glucocorticosteroids, as well as their unwanted effects, result from the specific glucocorticosteroid receptor-mediated genomic mechanisms involving trans-suppression or inhibition of the expression of genes encoding pro-inflammatory mediators (main therapeutic effect), and trans-activation, i.e. stimulation of the expression of genes encoding various proteins with varied biological activity (most of the effects are unwanted).

lipoxins (resulting from AA molecules undergoing transformation by the activity of acetyl-COX-2, i.e. the enzyme acetylated with aspirin, ASA-COX2) [3]. One should also remember that AA is a constant ingredient of membrane phospholipids and, in order to become a substrate for COX, LOX and ASA-COX2 it must be extracted from the phospholipid pool into its free form, which is achieved by means of a specific phospholipase A_2 (PLA_2) enzyme [4]. This step is the stage for anti-inflammatory activity of glucocorticosteroids, where endogenous cortisol and its synthetic analogs, all of them used in medicine, inhibit the PLA_2 activity, blocking the supply of the AA substrate for the synthesis of pro-inflammatory mediators, both COX-dependent (mostly prostaglandins) and LOX-dependent (leukotrienes) (Fig. 1). It should be highli-ghted that the main anti-inflammatory effects of glucocorticosteroids are achieved by means of a receptor-dependent genomic mechanism as a result of inhibition of the expression of genes encoding inflammatory mediators (transsuppression), while the adverse effects of this class of drugs are due to activation of the transactivation mechanism.

The findings of the Nobel Prize winners as mentioned in Introduction did not differentiate between individual COX isoforms, as the second isoenzyme, known as COX-2, was identified only as late as in early 1990s [6]. Experiments in dog tissues revealed the existence of a third COX isoform, COX-3, characterized by particular sensitivity to paracetamol. However, as soon became evident, such paracetamol-sensitive COX-3 isoform is absent from human body, and the human equivalent of dog COX-3 gene, present in some tissues, particularly the tissues of the central nervous system (CNS) is an alternatively spliced variant of COX-1, without preferential sensitivity to paracetamol, encoding a protein with the amino acid sequence different from that of COX and exerting no COX-like activity. Thus, contribution of COX-3 to the mechanism of action of the popular drug paracetamol in humans, as proposed by some authors, is not substantiated, as confirmed by Kis [7] and the recent detailed analyses conducted by Hinz and Brune's group [8] [2].

[2] The exact mechanism of action of paracetamol is unknown, despite the long history of its use in pharmacology. Discovered more than 100 years ago and extensively used in medicine for more than half a century, paracetamol

Both COX-1 and COX-2 catalyze the conversion of arachidonic acid (AA) to prostaglandins and thromboxanes, and the difference between them, besides the fact of both isoforms being encoded by separate genes (located at chromosomes 9 and 11, respectively) and besides the structural differences (MW 70 kDa and 70-72 kDa; number of amino acid residues: 599 and 604; 60% homology) consists in the fact that COX-1 is mainly a constitutive enzyme, i.e. an enzyme that is present and active all time, while COX-2 is mainly an inducible enzyme, becoming active in certain circumstances, e.g. in the course of inflammation. Therapeutic NSAIDs have different affinities towards COX-1 and COX-2, which is due both to the structural differences between the drug molecules, and to the structural and conformational differences between the molecules of both enzymes. Active sites of COX molecules (i.e. substrate binding sites and catalytic domains) are slightly different in both isoenzymes — they are contained in hydrophobic substrate channels at the core of the enzyme molecule. In COX-2, the substrate channel is larger — more spacious and more flexible; thus, COX-2 inhibitors may enter the channel of the COX-2 molecule (where they are able to exert their effects), while being too large to enter the COX-1 channel to block the catalytic center.

This fact translates into the biological activity profiles of the NSAIDs, particularly in the context of their adverse effects. This relates obviously to the systemic drugs, not local drugs as ophthalmic NSAIDs, as the side effects if extensive or long-term therapies with the drugs of this group are mostly gastrointestinal (including serious ulceration effects → onset or complications of gastric or duodenal ulcers, including hemorrhage and perforation) or cardiovascular (thrombotic complications in patients with cardiovascular disorders and atherosclerosis). The list of the adverse effects of NSAIDs is longer, albeit it seems to be not of such importance for topical treatment; therefore, these considerations will not be pursued in this article, and interested readers may find relevant information in the recently published article by the same author, titled *New NSAIDs and modern forms of anti-inflammatory drugs* (Puls Medycyny — educational issue, 2012).

NSAIDs — Characteristics and classification

There is a huge number of NSAIDs available at the market — they include both the original and generic products in formulations suitable e.g. for oral (tablets, capsules), intramuscular and intravenous (liquids for injection), or rectal (suppositories) administrations, as well as ophthalmic preparations (eye drops).

According to the latest edition of the Polish-language edited guide-book on drugs currently available in Poland: *Leki Współczesnej Terapii* [*Medications in Modern Therapy*] (20th ed., Medical Tribune 2010), the most numerous NSAID products contain ibuprofen — 77 simple and 12 combination products or diclofenac — 66 simple and 3 combination products; less numerous

(synonymous term: acetaminophen) was and remains one of the most common analgesic and antipyretic drugs worldwide, available without prescription both as a single-agent product or combined with other agents. The anti-inflammatory effect of paracetamol is assessed as poor or non-existing, and therefore, the drug has never been considered a member of the NSAID family; what's interesting, however, it has always been and remains discussed together with this class of drugs. Some authors define paracetamol as an atypical NSAID. In recent decades, the prevalent opinion was that paracetamol exerted its analgesic and antipyretic effect via a central mechanism, and that paracetamol's effect on the activity of COX-1 and COX-2, and thus on the synthesis of prostaglandins, is insignificant. Paracetamol was shown not to inhibit the synthesis of prostaglandins in a tissue/cell homogenate, while exerting such effect in functionally efficient cells (see the comprehensive discussion on the topic in the article by Graham and Scott, 2005 [9]). Graham and Scott argued that the analgesic effect of paracetamol might be centrally-mediated by activation of descending serotonergic pathways; however, the authors add that the principal stage for the action of the drug might be the inhibition of prostaglandin synthesis. The authors further ponder on the possibility of formation of reactive metabolites at the molecular level as a result of activation of the peroxidase function of COX-2. Such metabolites would lead to degradation/inactivation of glutathione — a co-factor of enzymes involved in the synthesis of PGE, and thus to inhibition of the synthesis of PGE_2. The concept of paracetamol action involving only the central-mediated, COX-dependent mechanisms does not stand the time test [7]; what is, therefore, the mechanism of paracetamol's action? The beneficial clinical effects of the drug are beyond all doubt, albeit the knowledge regarding the mechanism of its action is still incomplete. Contribution from the central serotonergic, or even cannabinoid system, is suggested in the effects of paracetamol. The role of cerebral vessel endothelium behind the beneficial therapeutic effects of paracetamol within the CNS is also suggested. Studies conducted in recent years revealed that paracetamol has an inhibitory effect on the activity of both COX-1 and COX-2 in peripheral tissues, although to a different degree — a stronger effect was observed always in relation to COX-2, particularly in vascular endothelial cells. Articles published in years 2006-2012 and discussing the results of the extensive studies conducted by Hinz and Brune reveal that paracetamol is a preferential inhibitor of the COX-2 isoenzyme, although its effect is largely dependent on the environmental redox status. The opinion held by the German authors is important enough to require verification in other centers worldwide, as it is not only the mechanism of paracetamol's therapeutic effect is just concerned, but also the increasingly often-reported cases of intoxication with this drug, particularly of pronounced hepatotoxicity resulting from overdosage (intake of more than >4 g/day), which is not difficult to achieve as numerous paracetamol-containing products are available everywhere and prescription-free.

are products containing ketoprofen — 26 simple products and 1 combination product. Many of these drugs are available without prescription. These products are outnumbered only by medications containing paracetamol. i.e. an analgesic and antipyretic drug. It is available in 92 products, including 39 simple and as much as 53 combination products, all available without prescription.

NSAIDs are a structurally heterogeneous family of drugs, spanning from simple chemical structures like aspirin to complex, often polycyclic structures of relatively high molecular weights. Such a numerous and diverse family of medications with similar therapeutic indications and a wide spectrum of potentially adverse events requires some order being introduced by means of classification that would take into consideration different properties of NSAIDs as regards their chemical structures and biological activity. However, there is no uniform and worldwide classification of NSAIDs. Later on in the article, two most popular classifications will be presented, based on either the chemical structure of drugs, or their affinity to individual cyclooxygenase subtypes. [3] Both classifications are important, since understanding of the chemical structure and biological role of COX isoenzymes allows the assessment of particular drugs in functional terms, i.e. from the standpoint of both therapeutic, and potential adverse effects thereof.

NSAIDs are classified by their chemical structures into four groups of carboxylic acids, enolic acids, naphtyl ketone derivatives and coxibs.

Carboxylic acids include the derivatives of:
- **salicylic acid** — various salicylates and acetylsalicylic acid (aspirin);
- **acetic acid** — e.g. *bromfena*c, *diclofenac*, *ketorola*c, *nepafenac*, sulindac;
- **propionic acid** — *flurbiprofen*, *suprofen, pranoprofen, flurbiprofen,* ibuprofen, ketoprofen, tiaprofenic acid, naproxene;
- **anthranilic acid** — flufenamic acid, mefenamic acid, meclofenamic acid, niflumic acid;
- **indole** — *indomethacin*, acemetacin

Enolic acids include:
- Pyrrazolone derivatives, e.g. aminophenazone, phenylbutazone, metamizole (pyralgin), oxyphenbutazone;
- Oxicams, e.g. meloxicam, pyroxicam;

Naphtyl ketones — e.g. nabumetone.

Coxibs — celecoxib (available in Poland under trade name Celebrex), the only coxib currently used in therapy. Other coxibs, available in the drug market until recently, such as valdecoxib (Bextra by Pfizer; removed in 2005), and lumiracoxib, etoricoxib shared the fate of the first coxib recalled from the market in 2004, i.e. rofecoxib (Vioxx by Merck) due to their potential cardiovascular adverse effects.

When discussing this classification, one should also mention drugs related to NSAIDs, having the analgesic and antipyretic activity and devoid of anti-inflammatory effects, such as paracetamol (acetaminophen) and phenacetin (not longer in the pharmacopoeia, previously known as the ingredient in popular APC — aspirin/phenacetin/caffeine — tablets), which are the derivatives of 4-aminophenol.

The widely used classification of NSAIDs based on their affinity to individual COX isoenzymes was proposed by Vane *et al.*; it divides all NSAIDs into 4 groups:

1) Drugs that completely inhibit COX-1 and COX-2 with low selectivity but a pronounced preference towards COX-1; e.g.. aspirin (ASA), *diclofenac*, ibuprofen, *indomethacin*, naproxen, piroxicam, as well as *bromfenac*, *flurbiprofen*, *ketorolac*, *nepafena*c, *suprofen pranoprofen, fenoprofen*.
2) Drugs that inhibit COX-2 with a selectivity that is 5–50 times higher compared to COX-1, e.g. celecoxib, meloxicam, nimesulide.

[3] As on case of other drugs, NSAIDs may also be classified in sequential generations; such classification highlights certain structural innovations or upgrades, which are the effects of researchers' strive for drugs characterized by better safety (in terms of the adverse events profiles) or better bioavailability and pharmacodynamic parameters. The classification of NSAIDs into three generations is mentioned by some studies on the topic; however, such classification may not replace either of the two classifications mentioned above. The generation-based classification is as follows:

1st generation — drugs that preferentially inhibit COX-1 (COX-1>COX-2) — Vane et al. group 1 drugs.

2nd generation — drugs relatively selective towards COX-2 (COX-2>COX-1), e.g. etodolac, meloxicam, nabumetone, nimesulide.

3rd generation — coxibs (selective drugs) characterized by >200 times higher affinity towards COX-2 compared to COX-1.

3) Drugs that inhibit COX-2 with a selectivity that is >50 times higher compared to COX-1, e.g. refecoxib (Vioxx, withdrawn from market).
4) Drugs that are weak inhibitors of both COX isoforms: 5-aminosalicylic acid (known as mesalazine or mesalamine), sodium salicylate, sulfosalazine.

The active substances listed above in italics are available in both non-ophthalmic and ophthalmic products. With regard to the first, i.e. structural classification, of note is the fact that ophthalmic NSAIDs are listed in two groups: acetic acid derivatives, or, more precisely, heteroaryl — and/or phenylacetic acid derivatives (most of the listed compounds, including indomethacin that contains indole moiety) and arylpropionic acid derivatives (flurbiprofen as sodium salt dihydrate). With regard to the second classification, based on the effects against COX-1 and COX-2, all ophthalmic preparations are in Group 1, encompassing inhi-bitors of both isoenzymes, with preference towards COX-1.

Ophthalmic NSAIDs

Compared to all available NSAIDs, ophthalmic preparations are a small group of products — currently, only six such products are available at Polish market (according to the latest ophthalmic drugs guide-book: Pharmindex-Okulistyka [Ophthalmology] 2012): **Indocollyre** contains indomethacin, **Dicloabak**, **Difadol 0,1%** and **Naclof** contain the same active substance — diclofenac, while the other two ophthalmic drugs, Nevanac and Yellox contain nepafenac and bromfenac, respectively.

Other ophthalmic preparations are available outside Poland, including **Acular**, **Acular-LS**, **Acular-PF**, and **Acuvail** (all containing ketorolac), as well as **Ocufen** and **Ocuflur** containing flu-rbiprofen; the suprofen—containing product **Profenal** is not used as a medicinal product any more [10-12]. In the past, one other compound, **fenoprofen**, was tested in ophthalmic preclinical and clinical trials; however, these did not lead to the drug being registered.

Table 1 presents ophthalmic NSAIDs currently available in Poland, as well as other compounds of this class available elsewhere in the world.

Indomethacin was the first member of the family of ophthalmic NSAIDs, introduced in the early 1980s — it was widely used in ophthalmological practice (and is still available in the European market), but it has never been registered by FDA to be sold within the US. Another non-steroidal compounds included flurbiprofen, suprofen, diclofenac and ketorolac; the therapeutic potential of these compounds in ophthalmology was described by Abelson and Sloan in 1994 [13]. At that time, the first two of these drugs were used mostly for prevention of miosis during ocular procedures, diclofenac was used in the treatment of post-operative inflammation following cataract removal, and ketorolac was used to treat itching occurring in the course of seasonal allergic conjunctivitis (SAC). Another ophthalmic NSAIDs contained fenacs — nepafenac and

Table 1: Ophthalmic NSAIDs currently available in Poland and other compounds of this class available elsewhere in the world.

Ophthalmic NSAIDs

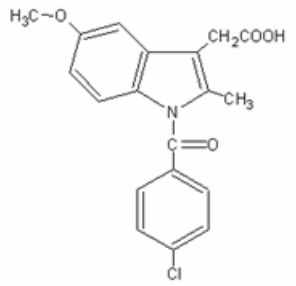
Bromfenak	**Yellox**	0,09% eyedrops; 0.9 mg/ml	Croma/B&L
Diclofenak	**Dicloabak** **Difadol 0,1%** **Naclof**	0.1% eyedrops; 1 mg/ml	Thea Polfa W-wa Novartis
Indomethacine	**Indocollyre**	0.1% eyedrops; 1 mg/ml	Chauvin B&L
Nepafenak	**Nevanac**	0.1% eyedrops; 1 mg/ml	Alcon
Flurbiprofen	**Ocufen** **Ocuflur**	0.03% eyedrops; 0.3 mg/ml	Allergan
Ketorolac	**Acular** **Acular LS** **Acuvail**	0.4-0.5% eyedrops; 4-5 mg/ml tromethamine salt; racemate	Allergan
Suprofen	**Profenal**	1% eyedrops; 10 mg/ml	Alcon

bromfenac which, together with their extensively studied and clinically effective (not only in ophthalmology) progenitor, diclofenac, are currently the most common drugs in this category.

A detailed characteristics of ophthalmic NSAIDs is presented below. The first part discusses drugs currently available in Poland (Indocollyre, Dicloabak, Difadol 0,1%, Naclof, Nevanac, Yellox), while the second part discusses other ophthalmic NSAIDs — both drugs used in the past (Profenal, fenoprofen) and currently used in other countries Acular/Acular-LS/Acular-PF/Acuvail and Ocufen/Ocuflur, Niflan).

Indomethacin

1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid [$C_{19}H_{16}ClNO_4$; MW 357.80 g/mol] — an indole derivative of acetic acid (Fig. 2).



INDOMETHACIN

Figure 2: Chemical structure of indomethacin.

In the early 1960s, Hart and Boardman were the first to demonstrate that indomethacin (code no. MK 615) efficiently reduced joint edemas in patients with active rheumatoid arthritis [14]. Two years later (1965), indomethacin was approved for marketing by the US FDA and became the first non-steroidal anti-inflammatory drug available. The mechanism of indomethacin's action, i.e. inhibition of prostaglandin synthesis — was described by Ferreira, Moncada and Vane in 1971 [15]. Indomethacin was also the first ophthalmic NSAID available, and a review of early initial clinical observations regarding its efficacy in patients with post-operative cystoid macular edema following lens extraction and retinal detachment surgery was published in 1984 [16].

Indocollyre (Chauvin/Bausch&Lomb) 0.1% ophthalmic drops (1 mg indomethacin/mL), bottle of 5 mL.

Indications and dosage[4] (according to Pharmindex-Okulistyka [Ophthalmology], 2012):
the drug is intended for use during ophthalmic procedures and in post-operative settings to counteract miosis, as well as an anti-inflammatory agent after cataract removal procedures or surgeries of the anterior ocular segment and an analgesic following photorefractive keratectomy on first days following the procedure.

The dosage depends on the objective of treatment:
- prevention of miosis during surgical procedures: 4 drops on the day before the procedure and 4 drops 3 h before the procedure;
- prevention of inflammatory conditions due to cataract surgeries or surgeries in the anterior ocular segment: 1 drop 4-6x/day, starting 24 hours before the procedure and continued until complete resolution of the symptoms of inflammation;
- treatment of pain after photorefractive keratectomy: 1 drop 4x/day on first days after the surgery.

Currently, Indocollyre is used less and less commonly, as newer ophthalmic NSAIDs, discussed below, have been introduced.

Earlier, eye drops with trade names of Indoptol and Chibro-Amuno contained 10-fold higher concentrations of indomethacin (1%; 10 mg/mL); however, solubility and pH-dependent stability are significant problems in the case of this agent. Indomethacin itself is practically insoluble in water (while being soluble in alcohol) and was used in ophthalmic preparations (eye drops) only as sodium or tromethamine salts. Indomethacin undergoes decomposition in alkaline solution, while being only slightly soluble in acidic solutions, precipitating when the pH value drops below 6. The drug, formulated as ophthalmic suspension buffered at pH of 5.6, was stable in the presence of polyvinyl alcohol (PVA) or hydroxypropylmethylcellulose (HPMC). Therefore, the later formulation of the drug (0.1% solution) contained Poloxamer-407 as a solvent. Indomethacin's penetration of the cornea increases significantly (compared to ophthalmic solutions) when the drug has the form of oil-based suspension, and particularly emulsion (the difference being

[4] All ophthalmic NSAIDs are intended for intraconjunctival administration — this information shall not be mentioned again when describing the use of individual products.

nearly 4-fold), which, at relatively low pH, assumes the non-ionized and lipophilic form. Low pH of the aqueous phase (<4) would, however, have its consequences, as intraconjunctival instillation of acidic drug would lead to reduction in the pH of the lachrymal fluid, and thus to increased lachrymation, which would in turn result in the drug being washed out the conjunctival sac faster, thus reducing its bioavailability. Restoration of physiological pH of the lachrymal fluid would in turn reduce the ocular permeability due to indomethacin's ionization. Thus, the circle is closed, creating no chances for better *in vivo* absorption of indomethacin after using the seemingly beneficial emulsion-based formulation.

Indomethacin has a high COX inhibition potential, which is the basis for its strong anti-inflammatory effect; therefore, many researchers attempted to find an ophthalmic formulation of the drug that would warrant better bioavailability of the drug inside the eye. In years 2003-2004, ocular inserts and sclerotic implants containing indomethacin and appropriate blends of low-and high-molecular polyvinyl alcohol (PVA) to increase the time of release and effect of the drug were produced and tested, but without satisfactory results [17]. However, new formulations of indomethacin-based ophthalmic preparations are still produced and tested in the clinic. For example, recent direct comparison in rabbits of two preparations containing HPMC (e.g. Indom™, Alfa-Intes) and hydroxypropyl-β-cyclodextrin (Indocollirio™, Bausch&Lomb) showed the former drug, i.e. indomethacin-HPMC formulation, has "good ocular distribution reaching relevant indomethacin levels in the back of the eye, suggesting that this formulation may be very useful for clinicians to manage retinal conditions" [18]. Furthermore, very recent report by Weber *et al.* [19] showed that indomethacin 0.1% eye drops displayed equal or better clinical efficacy than ketorolac 0.5% eye drops in the management of ocular inflammation after cataract surgery in patients.

Considerations on the acceptable formulation for an ophthalmic preparation containing indomethacin will be completed with the mention of acemethacin, which is the ester of indomethacin and glycolic acid. Acemethacin, present in the drug Rantudil (Forte and Retard; Bayer), is a prodrug converted into indomethacin in the body. Acemethacin has considerably better pharmacokinetic properties and a more favorable adverse effects profile compared to indomethacin. It is possible that acemethacin might be a better alternative to indomethacin in ophthalmic preparations, however, the author is unaware of relevant studies and, as of yet, Indocollyre remains the inly indomethacin-containing drug at ophthalmologist's disposal.

Diclofenac

2-(2-(2,6-dichlorophenylamino)phenylacetic acid [$C_{14}H_{11}Cl_2NO_2$; MW 296.15 g/mol] — a derivative of phenylacetic (arylacetic) acid (Fig. 3).

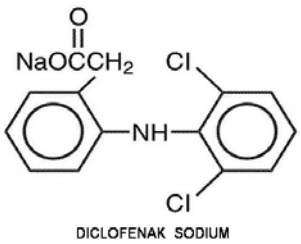


Figure 3: Chemical structure of sodium diclofenac.

The name of the active substance is derived from the initial fragments/letters of terms contained in its chemical name: 2-(2,6-**dichlo**ranilino)**phen**ylacetic **ac**id → dichlophenac). Currently, products available at the pharmaceutical market contain diclofenac as diclofenac sodium or diclo-fenac potassium, depending on the country and/or manufacturer. The compound was developed in 1973 in the laboratories of Ciba-Geigy pha-rmaceutical corporation (which, following the merger with Sandoz, in 1996, has been active at the market to date under the name of Novartis corporation). The product Voltaren received marketing authorization in 1979 in the United Kingdom, and later on in other countries. Diclofenac-containing products are available worldwide under numerous trade names, offering a wide assortment of prescription-only (mainly) and over-the counter (some) products to be applied by nearly all application route available. Main therapeutic indications include the treatment of various pains and inflammatory conditions (including the leading ailments such as rheumatoid arthritis and osteoarthritis) and painful menstruation. Although diclofenac is well tolerated when used either in a single or in several doses (acute administration) or in prolonged or long-term administration, it has side effects in at least 20% of patients, requiring treatment discontinuation only in several percent of patients. The adverse effects include mostly symptoms typical for all NSAIDs, including gastrointestinal intolerance symptoms.

Ophthalmic diclofenac preparations include:
Dicloabak (Thea; bottle of 10 mL), **Difadol 0.1%** (Polfa Warsaw; bottle of 5 ml), **Naclof** (Novartis; bottle of 5 mL) — all products contain diclofenac sodium (0.1% ophthalmic drops;1 mg/mL).
Dicloabak does contain no preservatives (it is distributed in a multi-dose bottle with 0.2 μm filter membrane to protect contamination upon use); the remaining two products, i.e. **Difadol 0.1%** and **Naclof** contain the preservative — benzalkonium chloride.
Other substances present in the aforementioned drugs: Dicloabak — castor oil, tromethamine (also known as tromethamol or Tris, i.e. tris (hydroxymethyl) aminomethane), boric acid; Difadol 0.1% — polysorbate-80, boric acid, borax; Naclof — polyoxyethylenated castor oil-35, tromethamine, boric acid, sorbic acid (2 mg/mL), sodium edetate (1 mg/mL) — composition identical to that of Voltaren Ophthalmic.

Indications (accd. to Pharmindex — Okulistyka, 2012):

Dicloabak — inhibition of miosis during cataract surgeries prevention of inflammation in the surgeries of cataract and anterior ocular segment; relief of ocular pain due to photorefractive keratectomy within 24 hours after the procedure.

Difadol 0.1% — inflammation following cataract surgery or other surgical procedures; fighting symptoms of eye pain and photophobia, inhibition of miosis in the course of cataract surgery, prevention of cystoid macular edema following cataract surgery with lens implantation.

Naclof — post-operative inflammatory conditions after removal of cataract and other surgical procedures, prevention of cystoid macular edema following cataract surgery with lens implantation, post-traumatic inflammation in injuries without perforation of the eyeball; inhibition of miosis, fighting symptoms of eye pain and photophobia.

Although the three aforementioned products slightly differ in formal therapeutic indications, there are no rational premises capable of shaking an opinion that the three compounds can be used interchangeably, as they are practically identical.

Dosage (accd. to Pharmindex — Okulistyka, 2012):

Dicloabac:
- Inhibition of miosis during cataract surgery and prevention of inflammation in cataract surgeries and the surgeries of the anterior ocular segment: before surgery — 1 drop up to 5x within 3 h before the surgery; after surgery — 1 drop 3x immediately after surgery, and next 1 drop 3-5x/day, for as long as required.
- Fighting ocular pain in photorefractive keratectomy within the first 24 h after the surgery: before surgery — 2 drops within 1 h before surgery; after surgery — 2 drops within 1 h after the surgery followed by 4 drops within 24 h after the surgery.

Difadol 0,1%:
- Ocular surgery and complications: before a surgical procedure — 1 drop 5x within 3 h; after surgical procedure — 1 drop 3x during the surgery and then 1 drop 3-5x per day, for as long as required.
- Pain and photophobia: 1 drop every 4-6 h.
- Prevention of pain associated with surgical procedures — 1-2 drops within 1 h before the procedure, 1-2 drops within 15 min. after the procedure and then 1 drop every 4-6 hours over the following 3 days.

Naclof:
- Ocular surgery and complications: before a surgical procedure — 1 drop 5x within 3 h; after surgical procedure — 1 drop 3x during the day after the surgery and 1 drop 3-5x per day over the following days, for as long as required.
- Pain and photophobia: 1 drop every 4-6 h.
- Pain resulting from surgical procedures — 1-2 drops within 1 h before the surgery, 1-2 drops within 15 min after the surgery and 1 every 4-6 h over 3 days after the surgery.

As in the case of therapeutic indications of the aforementioned drugs, which should be identical due to the similarity of products, also the dosage of individual products in particular situations should be identical. Diverse summaries of therapeutic indications and dosage results in introduction of unnecessary confusion, implying that the products are used for different purposes, which is not true.

As mentioned above, diclofenac is the original product by Ciba-Geigy (currently Novartis),

registered under the trade name Voltaren, used in numerous products containing this active substance for different uses. Voltaren Ophthalmic or Voltaren Ophthalmic Solution is an ophthalmic product very popular in the US, while its equivalent in Poland (and other countries, including the Central/Eastern European countries) is Naclof. The dosage of the American product is as follows: cataract removal — 24 h after the surgery — 1 drop of the solution 4x a day for a 2-week post-operative period; refractive surgery — 1 drop of the drug one hour before the procedure and 1 drop 15 minutes after the surgery, followed by 1 drop 4x a day for 3 days. The differences in the recommended dosage of Voltaren 0.1% ophthalmic solution and its sibling product Naclof remain the manufacturer's secret.

Nepafenac

2-amino-3-benzoylbenzeneacetamide or 2-amino-3-benzoylphenylacetamide (nepafenac or amfenacamide; pro-drug) [$C_{15}H_{14}N_2O_2$; MW 254,28 g/mol] → 2-amino-3-benzoylbenzeneacetic or 2-amino-3-benzoylphenylacetic acid (amfenac; the active agent) [$C_{15}H_{13}NO_3$; MW 255.27 g/mol] — a derivative of phenylacetic (arylacetic) acid (Fig. 4).

Nevanac (Nepafenac ophthalmic suspension; Alcon):

- is a 0.1% suspension containing nepafenac (1 mg/mL) as the active ingredient; in addition, the product composition includes a preservative — benzalkonium chloride (0.05 mg/mL = 0.005%) and ingredients considered to be inactive, e.g. mannitol, carbomer 974P, tyloxapol (a non-ionic surfactant), disodium edetate. The pH of the solution is 7.4 and the osmolarity is 305 mOsmol/kg. Following intraconjunctival administration, nepafenac quickly penetrates through the cornea and is hydrolyzed into the active form of amfenac, reaching the peak concentration in the aqueous humor after 1 hour [20].

Indications (accd. to Pharmindex-Okulistyka, 2012):
prevention and treatment of post-operative pain and inflammation associated with surgical cataract removal; reduction of the risk of post-opera-tive macular edema associated with surgical cata-ract removal in diabetic patients.

Dosage:

- Prevention and treatment of post-operative pain and inflammation associated with surgical cataract removal — 1 drop 3x/day. The product is first applied on the day before the procedure, continued on the day of the procedure and for up to a 21-day post-operative period, or up to as much as 60 days in diabetic patients, as recommended by the physician. Additional drop of the drug should be administered 30-120 minutes before the procedure.
- Reduction of the risk of post-operative macular edema associated with surgical cataract removal in diabetic patients — 1 drop 3x/day starting from the day before the surgical cataract removal, continued on the day of the procedure and for up to a 21-day post-operative period, or up to as much as 60 days in diabetic patients, as recommended by the physician; additional drop of the drug should be administered 30-120 minutes before the procedure.

As mentioned above, nepafenac is a prodrug[5], or a precursor for the formation of the active substance, amfenac. Intraocular hydrolases catalyze the conversion of nepafenac to amfenac — a potent COX-1 and COX-2 inhibitor. Therefore, the condition for making nepafenac active is its penetration into the ocular structures, which occurs following intraconjunctival instillation. The first structure to be reached by nepafenac is the cornea, followed by aqueous humor in the anterior, and then in the posterior chamber. Prodrug's penetration and transformation into amfenac is fast — peak concentrations of amfenac in the aqueous humor are observed 1 h after instillation.

[5] Traditionally, the term "prodrug", introduced in 1958 by Albert, refers to compounds that have no biological activity (or low biological activity) and undergo enzymatic or chemical transformations (e.g. hydrolysis) inside the system, producing drugs that exert specific pharmacological actions [24, 25]. The process of secretion/formation of the active substance from the prodrug occurs before, during or after its absorption. In case of some prodrugs, the secretion/formation of the active substance occurs only after the prodrug reaches the planned target site. Prodrugs are estimated to account for about 5-7% of all drugs currently used in medicine. The development of prodrugs has a three objectives: a pharmaceutical, a pharmacokinetic and a pharmacodynamic one. The pharmaceutical objective pertains to e.g. reduction of problems associated with formulation technology, improvement of solubility or stability; the pharmacokinetic objective focuses on e.g. improvement of absorption, reduction of the metabolism of the drug before it reaches the target site(s), increase in the rate of penetration through biological barriers or optimization of the duration of the therapeutic effect; the pharmacodynamic objective focuses on e.g. reduction of toxicity, improvement of the therapeutic index or activation of the prodrug into the active compound. In case of Nevanac, the pharmacokinetic and pharmacodynamic aspects are of highest importance.

Compared to the cornea, higher concentrations of the drug are reached in the ciliary body and the retina (the rate of conversion of nepafenac to amfenac expressed in pM/min/mg of human tissue was 0.26 for cornea and 0.39 for the iris/ciliary body complex; at higher concentrations of the substrate (nepafenac), the respective values were 107 and 454, while the value for the retina/uvea complex was 135 [21]. Applying the drug three times a day guarantees the achievement and maintenance of amfenac levels that effectively inhibit the COX activity and prostaglandin production within the ocular structures.

Many years before ophthalmic nepafenac (Nevanac), amfenac sodium (AHR-5850) was registered under the trade name Fenazox in Japan (1986) for systemic use in patients with rheumatic diseases. Several analogs of amfenac (or 2-amino-3-benzoylbenzeneacetic acid) were synthesized to improve its biological activity profile, i.e. increase the therapeutic index and reduce the adverse effects; these analogs included the amide derivative — 2-amino-3-benzoylbenzeneacetamide (or nepafenac). However, it turned out that nepafenac's effect on COX was very weak, but its metabolite formed in the body, amfenac, had a stronger *in vivo* inhibitory activity against PGHS, with IC50 values (in μM) against COX-1 being 0.25 for amfenac and 64.3 for nepafenac (in parallel studies, the IC50 for diclofenac was 0.12 μM); amfenac's IC50 against COX-2 was 0.15 [22]. It should be mentioned that amfenac, with its analgesic effect stronger that that of phenylbutazone and aspirin in animals, was considered as a potential oral analgesic at the dose of 100 mg in humans, with rapid onset and many hours' duration of therapeutic action [23].

Thus, amfenac (sodium) was the original drug, while nepafenac was developed as an improved version — a precursor of amfenac sodium (AHR-5850). In early 1980s, amfenac was tested in detailed toxicological and comparative studies (with indomethacin, acemethacin, diclofenac and ketoprofen) in rodents, which served as the basis for the assessment of safety and dosage in humans.

Bromfenac

2-[2-amino-3-(4-bromobenzoyl)phenyl]acetic acid [$C_{15}H_{12}BrNO_3$; MW 334.16 g/mol] — a derivative of phenylacetic (arylacetic) acid (Fig. 4).

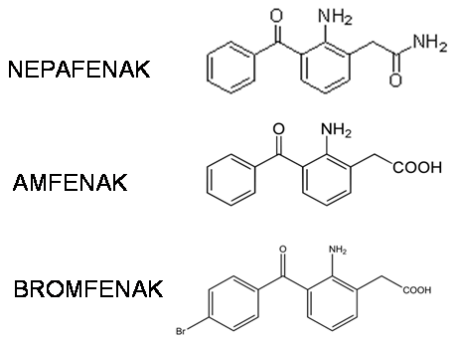


Figure 4: Chemical structure of nepafenac, amfenac and bromfenac.

As a result of action of tissue hydrolases, nepafenac (with minor effect on cyclooxygenase – COX) is converted to the biologically active amfenac, a strong inhibitor of COX-1 and COX-2 activity. It is interesting to note that bromfenac differs from amfenac structure with the presence of a bromine atom at the 4th position in benzene ring. Like amfenac, bromfenac is a strong inhibitor of COX activity.

The history of bromfenac is short but interesting and didactic, and therefore deserves being mentioned. Before the compound became an active substance in ophthalmic products, it was originally an ingredient of oral drugs. It was available in oral drugs for a short but dramatic period. In July 1997, US FDA registered a drug named Duract by Wyeth-Ayerst (capsules containing 25 mg of bromfenac) for short-term (lasting up to 10 days) treatment of various pain conditions (headaches, muscles, teeth, menstrual pains, post-traumatic pains) and reduction of inflammation symptoms. Due to its strong analgesic effect, Duract (*Bromfenac-Oral*), used in the regimen of 1 capsule or 2 capsules taken with meals every 6-8 h, with total daily dose not exceeding 150 mg — was to offer an alternative to the abused opiate analgesics in cases of severe pains. Duract grew on popularity and quickly made it to the top of the list of the new painkillers; according to IMS America, nearly 1.3 million prescriptions were issued in the US within less than one year [The Associated Press, Washington, February 11, 1998]. Contrary to numerous well-known adverse effects of opiate treatments, short-term use of Duract was expected to be safe, and the side effects stated by the manufacturer included only less important symptoms such as stomach upset as the most common ailment, possible abdominal pains and headaches, nausea and vomiting; less common effects dizziness, somnolence and blurred vision. In the meantime, US FDA pointed out that jaundice, hepatitis, and even severe hepatic insufficiency requiring liver transplant were observed in some Duract (*Bromfenac-Oral*) recipients, particularly in patients taking the drug form more than 10 days. In consequence, Duract (Bromfenac-Oral) was withdrawn from the pharmaceutical market by FDA's decision dated 22 June, 1998, due to the risk of severe hepatic complications, after only 11 months on the market.

However, bromfenac was not completely abandoned — after two years of absence, it reappeared in the pharmaceutical market — this time as an ophthalmic drug: *bromfenac ophthalmic solution*.

Yellox (Croma Pharma/Bausch&Lomb)
- 0,09% ophthalmic drops (0.9 mg of bromfenac/mL; bottle of 5 mL; active substance — bromfenac sodium as sesquihydrate ($C_{15}H_{11}BrNNaO_3$ x 1½ H_2O). In addition, the product contains a preservative — benzalkonium chloride (0.05 mg/mL = 0.005%), and ingredients considered to be inactive, e.g.boric acid, sodium edetate (0.2 mg/mL), emulsifier — polysorbate-80 (1.5 mg/mL), povidone (20 mg/mL). The pH of the solution is 8.3 and the osmolarity is 300 mOsmol/kg [26, 27].

The chemical structure of bromfenac is nearly identical to that of amfenac (the active compound formed of nepafenac), the only difference being a bromine atom at C-4 carbon, hence the name of the compound. The presence of bromine has beneficial effects on the properties of the molecule: it enhances its lipophilicity and facilitates penetration through cell membranes of various eye tissues, contributing to elongation of drug's inhibitory effect on the activity of COX enzymes, particularly of the COX-2 isoform.

Therapeutic indications
(accd. to Pharmindex–Okulistyka, 2012):
treatment of post-operative inflammation of the eye following cataract removal in adults.

Dosage: 1 drop 2x a day, starting on the day after the cataract surgery; the drug should be used for the first two weeks of the post-operative period. The treatment duration should not exceed 2 weeks, as there are no safety data available regarding longer-term treatment.

Following instillation onto the eye surface, Yellox reaches its peak concentration in the aqueous humor after 2.5-3 h; this concentration is then maintained for 12 h.

Yellox is a safe medication, with adverse effects observed in 2-7% patients including conjunctival hyperemia, pain, burning, or itching sensation and/or vision disorders, iritis (generally mild and usually transient, principally with no effect on the course and the success of the treatment) [26, 27].

According to Cho *et al.* [27], bromfenac's *in vitro* inhibitory effect on COX-2 was stronger than that of diclofenac (3.7x), amfenac (6.5x) and ketorolac (18x); however, it must be emphasized that these values were obtained in *in vitro* studies and do not necessarily reflect the relationships observed *in vivo*; they are only suggestive of bromfenac's therapeutic benefits over the listed products.

Although **Yellox** has only recently become available in Polish pharmaceutical market, it had been registered as bromfenac sodium ophthalmic solution 0.1% and under the trade name of Bronuck (Senju Pharmaceutical Co., Osaka, Japan) in Japan in May 2000, with the recommendations for use in the treatment of post-operative inflammation, blepharitis, conjunctivitis and scleritis.

Five years later (March 2005), bromfenac was registered by the US FDA under the trade name of Xibrom, in the form of 0.09% solution of bromfenac sesquihydrate, with the recommendations for use in the treatment/prevention of post-operative inflammation in patients after cataract removal. Recommended dosage is 1 drop into the affected eye(s), 2x a day 24 h after the procedure, continued for 2 weeks. In October 2010, US FDA approved a new formula named Bromday, to be used once daily as opposed to Xibrom and Yellox, which require a twice-daily administration. European registration of Yellox (May 2011) was initiated in 2009 by an application submitted to EMEA by Austrian company Croma-Pharma GmbH, which had obtained the relevant license from the Japanese company Senju in 2005. Based on the agreement between Croma Pharmaceuticals and Bausch&Lomb, both companies distribute the drug in the countries of the Central and Eastern Europe.

Other ophthalmic NSAIDs

Active substances of drugs listed below are phenylalkanoic (propionic) acid derivatives which are, by their nature,well soluble in water and thus easier used in ophthalmic products. These include suprofen, flurbiprofen, ketorolac and pranoprofen.

Suprofen

(RS)-α-methyl-2-[4-(2-thienylcarbonyl]propionic acid [$C_{14}H_{12}O_3S$; MW 260.31 g/mol] — a derivative of arylpropionic acid.

Before suprofen was marketed as ophthalmic preparation, it had been available at pharmaceutical market under the trade name of Suprol (200 mg modified release tablets/capsules). However, the manufacture and distribution of the drug was discontinued due to potential toxic effects manifested as acute lumbar pain syndrome and reversible renal insufficiency, most commonly manifested as urate nephropathy. Thus, the only product available at the market is the ophthalmic product Profenal.

Profenal (Alcon) — 1% Ophthalmic Solution contains 10 mg of suprofen per 1 mL and, additionally, thiomerosal (0.005%; 0.05 mg/mL), caffeine (2%; 20 mg/mL) and other, less important ingredients.

Profenal was approved for medical marketing by the US FDA in 1987 as a drug to inhibit intraoperative miosis. According to manufacturer's instructions, the drug was to be administered according to the following schedule: 2 drops (equivalent to 1 mg of suprofen) into one eye 5x on the day before surgery, and then 3x on the day of the procedure (the total dose received by the patient during the two days is ca. 25 times smaller that a single oral dose of 200 mg).

Profenal was available as an ophthalmic product at least until 2007; afterwards, its production was discontinued.

Flurbiprofen

(RS)-α-methyl-2-fluorobiphenyl-4-yl)propionic acid [$C_{15}H_{13}FO_2$; MW 244.26 g/mol] — a derivative of arylpropionic acid.

Flurbiprofen is present in products with different trade names, (e.g. Rubifen, Ansaid, Flurwood, Froben) and is used to treat inflammation and pain in the joints. It is also present in popular throat lozenges Strepsils Intensive. In the available preparations, flurbiprofen is present as a racemic mixture (a mixture of levorotational and dextrorotational forms: R,S, ±). What's interesting, contrary to the levorotational isomer, i.e. S(+)-flurbiprofen, the dextrorotational form, i.e. R(–)-flurbiprofen, has no anti-inflammatory activity and does not inhibit either COX-1, or COX-2. The dextrorotational isomer, known as tarenflurbir, was recently tested under an advanced clinical study program as a potential drug named Flurizan (by Myriad Genetics) to be used in Alzheimer's disease; however, having completed phase III studies in nearly 2,000 patients, the manufacturer announced suspension of further registration process. Tarenflurbir is currently tested in clinical studies in patients with metastatic prostate cancer.

Ocufen/Ocuflur (Allergan) are ophthalmic preparations containing RS(±)-flurbiprofen at concentration of 0.03% (0.3 mg/mL); in addition, the product contains 0.005% of thimerosal as a preservative, 1.4% of polyvinyl alcohol (PVA) and a number of less crucial components, used mostly to stabilize the solution. After being approved by the US FDA as an agent against intraoperative miosis, Ocufen (*flurbiprofen sodium ophthalmic solution, USP, 0.03%*) entered the medical market in the US in January 1987; in some European countries, as well as in India, it is available under the trade name Ocuflur. Ocuflur available in Belgium is indicated, except for the indication mentioned above, in the treatment of inflammation following surgical intervention, laser trabeculoplasty and in prevention of cystoid macular edema after cataract surgery. Comparative clinical studies in patients with post-operative inflammation following cataract surgery performed by Diestelhorst *et al.* [28] showed that the anti-inflammatory effect of 0.03% flurbiprofen was weaker than that of 0.1% diclofenac and 1% indomethacin, which led to reduced interest in the drug. Today, flurbiprofen, although still commercially available in many countries, does not measure up to competition from other, newer products and is a drug that is relatively rarely used in clinical setting.

Ketorolac

(RS,+/–)-5-benzoyl-2,3-dihydro-1H-pyrrolysine-1-carboxylic acid [C15H13NO3; MW 255.27 g/mol] — a derivative of arylacetic acid

Ketorolac, present as tromethaminium salt in products with different trade names (e.g. Toradol, Acular, Minolac), as well as in Sprix Nasal Spray, is an NSAID used for short-term treatment of moderate to severe pain.

Acular, **Acular LS**, **Acular PF**, **Acuvail** are ophthalmic products by Allergan. Acular and Acular LS contain respectively 0.5% and 0.4% solution of ketorolac with tromethamine (NH_2-$C[CH_2OH]_3$); in addition, both products include benzalkonium chloride 0.006%

(0.06 mg/mL) and octoxynol-40 (chemically inert detergent, also known as Triton X-100). Acular PF contains a 0,5% solution of ketorolac/tromethamine, without preservatives, i.e. benzalkonium chloride and octoxynol-40; it is available as single use 0.4 mL vials (12 vials per pack). Acuvail (registered by US FDA in July 2009 r.) contains a 0.45% solution of ketorolac/tromethamine without preservatives and with the addition of carboxymethyl cellulose (CMC) which enhances the adhesion of drops to the conjunctiva and cornea [29, 30].

Acular (0.5% Ophthalmic Solution) was approved by the US FDA to be used after cataract surgeries: 1 drop 4 times per day starting 24 h after the procedure for 2 weeks. The official indications of the drug include also the treatment of itching that accompanies allergic conjunctivitis. Acular LS is officially registered for use in reduction of ocular pain and burning after cataract surgeries, while the newest product, Acuvail, is used in the treatment of pain and inflammation after cataract removal. The drug may also be used to relieve ocular itching due to allergic conjunctivitis (dosage: 1 drop — 0.25 mg of the drug 4 times a day) and to treat post-operative inflammation in patients undergoing surgeries for cataract (1 drop 4 times a day starting from the second day after the procedure for 2 weeks). According to the manufacturer, the strength of the anti-inflammatory effect of ketorolac is comparable to that of 0.1% diclofenac.

Pranoprofen

α-methyl-5H-[1]benzopyrano[2,3-b]pyridine-7-acetic acid or α-methyl-2-(5H-chromeno[2,3-b] pyridin-7-yl)propanoic acid [$C_{15}H_{13}NO_3$; MW 255,27 g/mol] — a derivative of arylpropionic acid.

Pranoprofen (an original product of Yoshitomi Pharmaceuticals, Osaka, Japan) is characterized by a strong anti-inflammatory and analgesic and a weaker antipyretic action. It was taken by cooperating pharmaceutical companies Yoshitomi and Senju (Osaka) to produce ophthalmic drug under the name Niflan.

Niflan (Senju, Osaka; the drug known outside Japan under various names: Oftalar, Pranofen, Pranoflog, Pranox) — 0.1% eye drops (1 mg pranoprofen/mL). The drug was registered in Japan in 1988 and is available until now in some Asian and European countries (Japan, China, Belgium, Italy, Portugal, Spain and Turkey). The drug does not possess US FDA registration and is not used in the US. In clinical studies before registration, pranoprofen was shown to produce irritation of conjunctiva, the effect being eventually eliminated using a combination of components in future drug formula of which boric acid appeared to be a crucial component (it is worth of mention that boric acid occurs in formulas of many ophthalmic NSAIDs); other components include: polysorbat-80 and benzalkonium chloride (0.007% = 0.07 mg/mL) and disodium edetate [31].

Therapeutic indications for Niflan include inflammation following eye surgery, blepharitis, conjunctivitis and keratitis. Dosage: 1-2 drops 4x during the day for a period necessary for complete resolution of the symptoms of inflammation.

Fenoprofen

α-methyl-2-(3-phenoxyphenyl)propionic acid [$C_{15}H_{14}O_3$; MW 242,27 g/mol] — a derivative of arylpropionic acid.

As mentioned before, fenoprofen ophthalmic drops were tested in preclinical and clinical studies as an ophthalmic anti-inflammatory and analgesic agent. Eye drops containing 1% solution of fenoprofen as hydrated sodium salt were tested mostly for prevention of uveitis. Although the efficacy of ophthalmic fenoprofen was comparable to that of 1% dexamethazone in a rabbit uveitis model [32], the obtained results were not very encouraging and the studies showed no progress. No positive results were also obtained in the clinical trials of 1% fenoprofen sodium solution in patients with aphakic eyes and chronic cystoid macular edema [33]. In consequence, fenoprofen was not introduced as an ophthalmic drug, although its dihydrate calcified form is registered in the US under the trade name of Nalfon (fenoprofen calcium capsules, USP; 200 mg and 400 mg capsules; Pedinol Pharmacal, Inc.) for use in e.g. rheumatoid arthritis, osteoarthritis or acute gout episodes.

Conclusion

Polish ophthalmologists have currently six NSAID products at their disposal. Three products contain diclofenac and, from medical standpoint, are practically identical (although it should be mentioned that one of these products contains no preservative) and can be used interchangeably. One medication contains indomethacin — an active substance that has been known in medical practice for the longest time. The list is completed by two relatively new fenacs: nepafenac and bromfenac. In the Pharmindex–Okulistyka [Ophthalmology] 2012 handbook, the latter two drugs contained in Nevanac and Yellox products are announced in the part titled *New registrations*, although, to be exact, both were some time ago the pioneer drugs in the worldwide market of ophthalmic preparations.

However, in Poland, Nevanac (nepafenac) and Yellox (bromfenac) are new drugs, and therefore most commonly referred to in current discussions, although the remaining compounds (mainly diclofenac products) are still extensively used in worldwide practice.

However, let us focus on these two products that are new to the Polish market. Nevanac contains the active substance amfenac administered as a precursor compound, nepafenac. Yellox contains the active substance bromfenac, which differs from amfenac by a bromine atom in the benzene ring. In other words, bromfenac is a brominated amfenac. The difference may seem small, but is a significant one in practical terms. Similarly to other halogens, i.e. fluorine, chlorine or iodine, the non-metal bromine modified the properties of the structure it is bound to — for example, halogenated structures usually penetrate cell membranes better. In consequence, bromfenac, when administered intraconjunctivally, would easier/faster penetrate into the eye than amfenac, which would affect the concentrations achieved by both compounds in ocular structures and fluids (cornea, aqueous humor, iris/ciliary body, uvea). Thus, bromfenac would faster reach higher concentrations at target site (of potential or ongoing inflammation) compared to amfenac. However, it is not amfenac that is the ingredient of the Nevanac drug — it is nepafenac, which is an amide derivative of amfenac, converted to amfenac in ocular tissues by means of ubiquitous hydrolase enzymes. Nepafenac is, by comparison, a poor PGHS inhibitor (IC_{50} = 64 μM against COX-1), but it penetrates into ocular tissues faster than amfenac; there it is transformed into amfenac, which is a highly active PGHS inhibitor (IC_{50} = 0.25 μM — COX-1 and 0.15 μM — COX-2) [22].

To sum up these considerations, one might say that the use of a prodrug formula in Nevanac functionally balances out the presence of bromine atom in the structure of bromfenac (Yellox). Is therefore the therapeutic efficacy of Yellox (aqueous solution) and Nevanac (suspension) clinically comparable? Theoretically, yes, although ophthalmologists should remember that every patient is a non-fully-predictable individual who does not have to respond in the same manner even to very similar drugs. This is due to the fact that drugs contain not only active substances, but also excipients which might have multidirectional, non-specific effects. With regard to the latter, both Nevanac and Yellox contain benzalkonium chloride (0.05%) and disodium edetate preservatives, but differ in all other excipients: Nevanac contains mannitol, carbomer 974P, and tyloxapol, while Yellox contains boric acid, polysorbate 80, and povidone. In addition, both compounds have different pH values: 7.4 vs. 8.3 and slightly different (albeit comparable) osmolarity: 305 vs. 300 mOsmol/kg.

With reference to the discussion on nepafenac and bromfenac, one should also ask whether the diclofenac products (Dicloabac, Difadol 0.1%, Naclof) are therapeutically different from Yellox and Nevanac? There is no definitive answer to this question. In the author's opinion, the newer fenacs have advantages over the older ones, but the treatment success is determined by patient's response, both in the terms of therapeutic activity and adverse events. The planned duration of therapy and frequency of application may also provide a hint when making therapeutic decisions, as both these parameters prefer safer drugs, i.e., in this case, the newer products. However, it must also be stressed that the therapeutic, i.e. anti-inflammatory and analgesic effects will be achieved with **all** currently available ophthalmic NSAIDs. Short-term treatments are not as rigorous as long-term ones; the armory of drugs available for use over several or a dozen or so days is thus very wide.

Literature contains comparative data from parallel group studies evaluating clinical efficacy of various ophthalmic NSAIDs in various ophthalmic conditions (including prevention and treatment of postoperative inflammation after cataract surgery). These included comparisons of diclofenac 0,1% — flurbiprofen 0.03% — indomethacin 1% [28], ketorolac 0.45% — bromfenac 0.09% — nepafenac 0.1% [34], as well as other sets of drugs, including glucocorticosteroids, tested in humans [35-37] and in animal models [38].

There are numerous works of this type, however, they were not included in this survey for various reasons, including clinical picture being blurred due to the lack of clear differences between drugs or the results originating from small patient groups which might suggest random character of the clinical picture. In order for an analysis of such factual material to be reasonable and justified, it should compare possibly the largest number of published/available studies, including the goals of the overall treatment and the treatment with individual drugs. This, obviously, would be out of the scope of this study.

I want to conclude this article with a known opinion shared by the physicians with regard to pharmacological therapy: Oftentimes, therapeutic efficacy of drugs within a particular group is generally similar, and the fact, whether a particular drug is more or less suitable for a particular patient, is determined by the adverse (side) effects of that drug. This is also the case for systemic drugs. No patient suffering from inflammatory or painful conditions of joints, muscles and tendons and chronically receiving NSAIDs would question the therapeutic efficacy of drugs containing diclofenac or meloxicam, although when faced with the risk of adverse effects, e.g. gastrointestinal effects, the latter product may be a more reasonable choice (though, on the other hand, the range of available diclofenac-based drugs includes newer and safer formulas characterized by modified active substance release profiles, biphasic activity and combinations of diclofenac with agents that protect gastric mucosa).

Now returning to ophthalmic NSAIDs — looking forward and taking into consideration the development in the systemic NSAIDs, one may expect that completely novel structures with anti-inflammatory and analgesic potential and potential intraconjunctival application should emerge, or that previously-known compounds would be "revitalized" in the therapeutic sense, enhancing the range of available therapies.

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References:

Besides the bibliography listed below, information used in this review is based on registration data for individual drugs (FDA, EMEA), information provided by manufacturers in product information leaflets and other data published in pharmacological handbooks specialized in ophthalmic drugs, including Pharmindex – Okulistyka, 2012; Leksykon – Vademecum Okulisty, 2011; Leki po Dyplomie — Okulistyka, 2010/2011, and Leki Współczesnej Terapii, 20th Ed., 2010.

1. Vane JR: Inhibition of prostaglandin synthesis as a mechanism of action of aspirin-like drugs. Nature (New Biology). 1971; 231: 232-5.
2. Botting RM: Vane's discovery of the mechanism of action of aspirin changed our understanding of its clinical pharmacology. Pharmacol Rep. 2010; 62: 518-25.
3. Ryan A, Godson C: Lipoxins: regulators of resolution. Curr Opin Pharmacol. 2010; 10: 166-72.
4. Nowak JZ: [Anti-inflammatory pro-resolving derivatives of omega-3 and omega-6 polyunsaturated fatty AIDS]. Post Hig Med Dosw (Online). 2010; 64: 115-32.
5. Barnes PJ: Glucocorticosteroids: current and future directions. Br J Pharmacol. 2011; 163: 29-43.
6. Fu JY, Masferrer JL, Seibert K, Raz A, Needleman P: The induction and suppression of prostaglandin H2 synthase (cyclooxygenase) in human monocytes. J Biol Chem. 1990; 265:16737-40.
7. Kis B, Snipes JA, Busija DW: Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties. J Pharmacol Exp Ther. 2005; 315: 1-7.
8. Hinz B, Brune K: Paracetamol and cyclooxygenase inhibition: is there a cause for concern? Ann Rheum Dis. 2012; 71: 20-5.
9. Graham GG, Scott KF: Mechanism of action of paracetamol. Am J Ther. 2005; 12: 46-55.

10. Schalanus R: Topical nonsteroidal anti-inflammatory therapy in ophthalmology. Ophthalmological. 2003; 217: 89-98.
11. Kim SJ, Flach SJ, Jampol LM: Nonsteroidal anti-inflammatory drugs in ophthalmology. Surv Ophthalmol. 2010; 55: 108-33.
12. Colin J: The role of NSAIDs in the management of postoperative ophthalmic inflammation. Drugs. 2007; 67: 1291-308.
13. Abelson MB, Sloan J: Nonsteroidal anti-inflammatory drugs. Current ophthalmic therapy. J Fla Med Assoc. 1994; 81: 261-3.
14. Hart FD, Boardman PL: Indomethacin: a new non-steroid anti-inflammatory agent. Br Med J. 1963; 2: 965-70.
15. Ferreira SH, Moncada S, Vane JR: Indomethacin and aspirin abolish prostaglandin release from the spleen. Nat New Biol. 1971; 231: 237-9.
16. Miyake K: Indomethacin in the treatment of postoperative cystoid macular edema. Surv Ophthalmol. 1984; 28 (Suppl.): 554-68.
17. Ahuja M, Dhake AS, Sharma SK, Majumdar DK: Topical ocular delivery of NSAIDs. AAPS J. 2008; 10: 229-41.
18. Bucolo C, Melilli B, Piazza C, Zurria M, Drago F: Ocular pharmacokinetics profile of different indomethacin topical formulations. J Ocul Pharmacol Ther. 2011; 27: 571-6.
19. Weber M, Kodjikian L, Kruse FE, Zagorski Z, Allaire CM: Efficacy and safety of indomethacin 0.1% eye drops compared with ketorolac 0.5% eye drops in the management of ocular inflammation after cataract surgery. Acta Ophthalmol. 2012; doi: 10.1111/j.1755-3768.2012.02520.x.
20. Lindstrom R, Kim T: Ocular permeation and inhibition of retinal inflammation: an examination of data and expert opinion on the clinical utility of nepafenac. Curr Med Res Opin. 2006; 22: 397-404.
21. Ke TL, Graff G, Spellman JM, Yanni JM: Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation: II. In vitro bioactivation and permeation of external ocular barriers. Inflammation. 2000; 24: 371-84.
22. Gamache DA, Graff G, Brady MT, Spellman JM, Yanni JM: Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation: I. Assessement of anti-inflammatory efficacy. Inflammation. 2000; 24: 357-70.
23. Jain AK, Hunley CC, Kuebel J, McMahon FG, Ryan JJ: Analgesic efficacy of amfenac, aspirin and placebo after extraction of impacted teeth. Pharmacotherapy. 1986; 6: 236-40.
24. Rautio J, Laine K, Gynther M, Savolainen J: Prodrug approaches for CNS delivery. The AAPS J. 2008; 10: 92-102.
25. Olejniczak AB, Zawilska JB: [Future therapies – prodrugs]. Farm Pol. 2012; 68: 350-7.
26. Jones J, Francis P: Ophthalmic utility of topical bromfenac, a twice-daily nonsteroidal anti-inflammatory agent. Expert Opin Pharmacother. 2009; 10: 2379-85.
27. Cho H, Wolf KJ, Wolf EJ: Management of ocular inflammation and pain following cataract surgery: focus on bromfenac ophthalmic solution. Clin Ophthalmol. 2009; 3: 199-210.
28. Diestelhorsta M, Schidl B, Konen W, Mester U, Raj PS: Efficacy and tolerance of diclofenac sodium 0.1%, flurbiprofen 0.03%, and indomethacin 1.0% In controlling postoperative inflammation. J Cataract Refract Surg. 1996; 22 Suppl 1: 788-93.
29. McCormack PL: Ketorolac 0.45% ophthalmic solution. Drugs Aging. 2011; 28: 583-9.
30. Yilmaz T, Cordero-Coma M, Gallagher MJ: Ketorolac therapy for the prevention of acute pseudophakic cystoid macular edema: a systematic review. Eye (Lond). 2012; 26: 252-8.
31. United States Patent Number 4,607,038 – Ophthalmic Pranoprofen Compositions (Ogata K, Yamamoto Y, Ozaki Y): Date of Patent: 1986 Aug 19.
32. Harris LS, Kahanowicz Y, Hughes J: Ocular anti-inflammatory effects of fenoprofen. Arch Ophthalmol. 1974; 92: 506-8.
33. Burnett J, Tessler H, Isenberg S, Tso MO: Double-masked trial of fenoprofen sodium: treatment of chronic aphakic cystoid macular edema. Ophthalmic Surg. 1983; 14: 150-2.
34. Bucci FA, Waterbury LD: Prostaglandin E2 inhibition of ketorolac 0.45%, bromfenac 0.09%, and nepafenac 0.1% in patients undergoing phacoemusification. Adv Ther. 2011; 28: 1089-95.
35. Sivaprasad S, Bunce C, Crosby-Nwaobi R: Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. The Cochrane Library 2012, Issue 2.
36. Brennan KM, Brown RM, Roberts CW: A comparison of topical non-steroidal anti-inflammatory drugs to steroids for control of post cataract inflammation. Insight. 1993; 18: 8-9.
37. Roberts CW, Brennan KM: A comparison of topical diclofenac with prednisolone for postcataract inflammation. Arch Ophthalmol. 1995; 113: 725-7.
38. Stroobants A, Fabre K, Maudgal PC: Effect of non-steroidal anti-inflammatory drugs (NSAID) on the rabbit corneal epithelium studied by scanning electron microscopy. Bull Soc belge Ophthalmol. 2000; 276: 73-81.

Additional reference:

39. Nowak JZ, Dzielska-Olczak M: [New NSAIDs and modern forms of anti-inflammatory drugs]. Puls Medycyny. 2012 (educational issue).

Emergency Medicine

The role of paramedics in British emergency aid system

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Summary:

The article presents the role of paramedics in the United Kingdom's emergency aid system, including differences in the British programs of training of technicians and paramedics with particular focus on paramedic qualification degrees. In addition, the article presents the United Kingdom's pre-hospital care system in cases of serious disorders and injuries

Key words: emergency calls, technician, paramedic, training programs, United Kingdom paramedic qualification degrees, pre-hospital care.

Paramedics in the United Kingdom's emergency aid system

The Emergency Medical Service (EMS) is a standalone organizational unit of the United Kingdom's emergency aid system. First aid provided by two-person field teams consisting of medical technicians and paramedics. The team is highly trained in emergency aid and authorized to:

- administer certain drugs, assess and monitor vital parameters, including heart rate and function, respiratory rate;
- use specialist medical equipment, such as semiautomatic external defibrillators (SAEDs).

The scope of activities of the Emergency Medical Service includes;

1) departures to emergency cases;
2) transportation of patients with medical indications to hospitals;
3) emergency transportation of patients between hospitals;
4) Transportation of disabled individuals requiring specialist or nursing care.

The following are considered emergency cases:

1) accidents;
2) poisonings;
3) gastrointestinal bleeding;
4) risk of abortion, deliveries;
5) suspected insufficiency of coronary arteries and circulatory insufficiency.

Emergency calls include transportation orders placed by physicians and midwives regarding transportation of patients between hospitals. Sanitary transportation is considered an integral part of the healthcare system. Transportation of patients for diagnostic or treatment procedures that do not require hospitalization, as well as transportation of physicians to home visits is carried out in a non-emergency setting.

The organizational development of the EMS is aimed at:

1) providing medical care of multi-site and multi-organ injuries;

2) shortening the time to reach the injured patients;
3) establishing specialist centers for the treatment of such injuries. Following the delivery of patients with multi-organ injuries to the nearest hospital, the care of these patients is taken over by emergency care units in hospital emergency wards. These are multidisciplinary teams of physicians, nurses and paramedics, who perform a wide-scale diagnostics of the patient. According to the British physicians, this allows to provide aid in a timely manner and avoids potential omission of any procedural stage, thus leading to fast initiation of causal treatment.

Paramedics are independent individuals working by themselves or in groups with patients of all ages, depending of their professional competence. They are the main members of interdisciplinary teams who belong to different organizations. Successful performance of one's duties as a paramedic requires identification and understanding of social and economical conditions of patients. This helps in planning, providing and improving medical care.

Paramedics' duties are classified according to a five-grade system including the following grades:
- Emergency Medical Technician (EMT);
- Paramedic;
- Paramedic Practitioner (incl. Emergency Medicine Practitioner);
- Advanced Paramedic Practitioner;
- Consultant Paramedic.

The term "paramedic" and its meaning are subject to legal protection. Career development is a lifelong concept. In-service training creates basis for the development of college-level training methods.

Paramedics are capable of acting upon first contact with the patient without seeking help from other healthcare professionals. They are also responsible for the quality of care they provide to patients by adhering to principles and applying medical knowledge in their practice.

Paramedics of all grades should:
1) have the knowledge and understanding of changes occurring in the human body from neonatal to elderly age;
2) be capable of delivering aid to individuals and groups in a wide variety of situations, including aid in acute, primary and critical care conditions presenting complex and variable problems as resulting from multipathology disorders and injuries;
3) be capable to combine theoretical knowledge with practical skills and to develop problem solving schemes;
4) be able of critical self-assessment and drawing appropriate conclusions;
5) be able to apply clinical examinations and case studies in their paramedical practice in order to provide patients with optimum care;
6) be able to work in teams and cooperate with other professionals;
7) be able to understand patient's autonomy, internal reservations and rights as well as be able of providing support to patients;
8) be capable of referring the patient to a center of appropriate reference level in case the patient's needs are beyond the paramedic's capabilities.

Differences in the training programs of technicians and paramedics in the United Kingdom

The requirement for the training of technicians and paramedics are different. Part of the training is provided in ambulances and part is provided in hospitals; the training also includes a master-degree program.

The candidates go through an intensive initial training of about 12 weeks, including classes on anatomy, physiology, intensive care and ambulance driving. The theoretical part of the training is prepared by the Institute of Health Care Development (IHCD).

The clinical care is provided by technicians and paramedics in line with national clinical protocols (procedural standards). These are translated into local protocols which may be approved by local committees of hospital consultants, family practitioners, pharmacists, senior emergency service managers supervised by medical emergency executives. The list of skills and the list of drugs that can be administered by technicians is provided in schedule *A*.

After the basic training and after passing theoretical and practical exams, technicians work for one year under supervision of an experiences, trained technician or paramedic. At some centers, technicians keep books to record their practical skills. After a one-year training, technicians receive licenses for independent practice; however, they should take part in subsequent trainings every 3 years.

Technicians striving to obtain the paramedic degree must have at least 12 months of professional experience as qualified technicians and must be selected by their employing institution.

Today, paramedics in the United Kingdom are subjected to an at least two-month long, intensive training in:

1) anatomy;
2) physiology;
3) trauma surgery;
4) procedures to follow in emergency cases: including:
   a) pregnancy,
   b) pediatrics,
   c) psychiatry.

In addition, paramedics undergo practical training in emergency wards, operating rooms and invasive cardiology labs. During the training, paramedics have to

- perform at least: 25 intravenous punctures
- 25 intubations
- interpretations of ECG records. Next, they undergo training in:
  — Advanced Life Support (ALS);
  — Advanced Cardiac Life Support (ACLS);
  — Advanced Trauma Life Support (ATLS);
  — different medical scenarios in adults and children. These are preceded by practical training and serve as a basis.

to apply for a paramedic certificate.

Degrees of paramedic qualifications in the United Kingdom

Ambulance Clinician/Technician; Student Paramedic

Ambulance clinicians/technicians and student paramedics should have completed high school education and knowledge of the basic concepts of patient care. In addition, they must complete the basic training program organized by the employing institution in cooperation with High Education Institution (HEI) partners.

At this level, the staff is capable of issuing accurate initial diagnosis and plan further actions. Thanks to their knowledge and skills, the paramedics are capable of differentiating between life-threatening and non-life-threatening conditions, interpret and record basic observations and patient's personal, family and social history while providing aid to the patient. Using the information obtained from the patient, paramedics formulate conclusions regarding the nature of the disorder or injury and take actions to manage the patient and stabilize their conditions according to clinical guidelines. The scope of paramedics' activities includes protection of respiratory tract, defibrillation and pharmacotherapy.

In more complex cases requiring higher skills, paramedics should seek advice from more experienced colleagues.
At this stage of the training, high school graduates should focus on gaining their own experience and ability to draw conclusions so as to be able to face the upcoming challenges. In addition, they should be well-coordinated and efficient while providing aid to the patients.

The paramedics have to be able to work in teams and establish contacts with specialists in different areas. Thanks to the professional supervision, own reflections and discussions on every encountered case, the paramedics systematically improve their professional skills and as part of the life-long competence — improving process.

Registered paramedic

The registered paramedic must have the knowledge, understanding and capability of practical application of the principles or paramedic service as developed in cooperation with the High Education Institution (HEI), and taught to them while studying at that institution.

They should be ready for unassisted work as a team member. At this grade, a paramedic is capable of using their knowledge in unassisted work aimed at providing patients with best aid possible. This includes advanced airway patency protection procedures, intravenous fluid therapy

and pharmacotherapy using medicines available to registered paramedics, as well as other invasive procedures. Paramedics must also be able to foresee the future development of patient's condition and decide on the appropriate referral hospital depending on needs.

They should be proficient, co-ordinated and confident of their skills while delivering care to patients. It is important that a paramedic is capable to make an unassisted assessment of patient's condition and, based on own experience, to make a decision that would be best for the patients' needs. If needed, they should be able to explain the measures taken, step by step.

Through studying and clinical practice they should be able not only to improve their skills, but also to evaluate their personal strengths. They should also be able to embrace the role of a supervisor and mentor of others,

Paramedic assistant

A paramedic assistant should have bachelor's degree education compliant with the curriculum developed by the employing institution in collaboration with the HEI. This professional grade requires level 6 academic education.

Education at this level is associated with proficiency, co-ordination and confidence in delivering care. While observing appropriate procedural standards, paramedic assistants should be able to work alone or as team leaders.

Paramedic assistant's duties include physical examination and collection of the medical history of a patient. Being up-to-date with the results of scientific studies and capable of appropriately assessing clinical condition, paramedic assistants may provide advice regarding health promotion, prophylactics and prevention of injuries.

Thus-trained paramedics are prepared for unassisted preparation of healthcare programs. They may also act as mentors and supervisors of younger colleagues, as well as to provide trainings.

Advanced Paramedic Practitioner

The grade of Advanced Paramedic Practitioner requires a grade 6-7 academic education compliant with the curriculum developed by the employing institution in collaboration with the HEI.

Candidates are required to have obtained a master's degree.
A paramedic with such background will provide complete clinical safety to victims while working alone or as a team leader.

Advanced practitioners should be able to examine and manage patients in acute and chronic and to complete patients' full medical, social and family history.

With their knowledge and skills they should be able to develop care plans that might make it unnecessary for the patient to be hospitalized if there is no specific need.

Advanced practitioner should be up-to-date with the results of recent scientific studies and capable of appropriately assessing patient's clinical image. They may provide advice regarding health promotion, prophylactics and prevention of injuries.

Thus-trained paramedics are prepared for unassisted preparation of healthcare programs. They may also prescribe drugs not available to grade 2/ grade 3 paramedics. Thanks to their knowledge and experience, they may also act as mentors and lecturers

Consultant Paramedic

Consultant paramedics are organizational leaders. They must be professionally registered paramedics and have a minimum of 10 years of professional experience as paramedics.

The consultant paramedics embrace four areas:

1) Clinical practice experts – working at the forefront of their fields, leading clinical examinations and planning individual elements of examinations both by themselves and in teams. They work with professional organizations with the aim to develop guidelines to higher-grade paramedics. In addition, they develop clinical trials in collaboration with academic centers.
2) They are involved in research and other activities to support training, propose tasks to involve wider circles of medical professionals and carry out audits at all levels.

3) By combining education with training (e.g. by holding meetings), they promote evidence based clinical information across the whole range of clinical services and encourage professional culture.
4) They are professional leaders capable of incorporating conclusions regarding patients' condition with national health-care system guidelines and collaboration with various organizations, including Department of Health, Health Promotion Council, Quality Assessment Agency or the Commission for Health.

Consultant Paramedics may specialize in any branch of clinical care, in particular in:
— emergency pre-hospital and hospital care
— (including emergency medicine);
— critical and unscheduled medical care;
— ground and air rescue operations, typically
— provided by ambulance personnel.

In either branch, paramedic consultants should be involved in the development of standards for the functioning of rescue services.

The initial concept of emergency services included prompt response to emergencies, delivery of first medical aid and transportation of patients to hospitals.

Over recent 25 years, this role has changed dramatically and now includes pre-hospital care, oftentimes requiring advanced clinical skills. Current requirements oblige paramedics to constantly improve their skills which elevates required educational level to academic levels.

The clinical rescue personnel may be divided into medical care assistants, technicians and paramedics. Most ambulance personnel start their work as assistants, later on being trained to be technicians. After another twelve months of practice they may start training to acquire the paramedic degree.
After this training, they may be registered as paramedics.

The existing training curriculum is verified via Edexcel. The system encompasses data from practical training and academic-level education.

Pre-hospital care in serious ailments and injuries in the UK

Patients with serious ailments or injuries are considered a priori as requiring transportation to hospital (for further treatment).

Ambulance care is available at telephone numbers 999 or 112.

After determination of the accident location, ambulances are notified by short wave radio or mobile phones from the Emergency Notification Centre (ENC). Many ambulances are equipped with geolocation systems allowing the dispatchers to identify units (mostly ground units) closest to the accident site.

Digital terminals are also used to record regular ambulance tasks, such as times of departure to and return from the accident site or the hospital, thus reducing the load on the radio band, which is required for transmission of other data.

The calls are classified into three categories:
— "A" — if the condition may be life-threatening;
— "B" — if the condition is serious, but not immediately life-threatening;
— "C" — if the condition is neither serious, nor life-threatening.

The category is determined by the Advanced Medical Priority Determination System (AMPDS) used by the dispatchers to receive alarm calls.

The British government has defined standards for ambulance services. According to these standards:
1) 75% of category A calls should be received and provided for within 8 minutes after determination of accident site;
2) 95% of category B and C calls should be provided for within 14 minutes in urban areas and 19 minutes in non-urban areas (urban areas are defined as areas with population density of more than 2.5 person/acre).

The personnel of call-receiving ambulances consists usually of paramedics and technicians. The decision to mobilize a particular team is mate by senior dispatcher who has to have skills but does not have to have experience in delivering first pre-hospital care (this role is not performed by physicians).

Besides mobilization of an appropriately equipped and manned ambulance, it is possible to mobilize a single paramedic riding a motorcycle or driving a car, particularly in urban agglomerations or in cases of remote locations.

Both in case of category A, as in case of category B/C calls, the response to the call may be provided by immediate response vehicle manned by paramedics or emergency care technicians equipped with devices to provide the patient at the accident site, or by a first aid unit comparable to ambulance. Aid may be provided by a physician, fire brigade personnel or the police. If the patient is provided for within 8 minutes by non-medical personnel and a fully manned and equipped personnel should arrive within 14-19 minutes (depending on the area), the dispatcher may decide that the ambulance arrival is redundant.

Many emergency services are supported by dispatchers present at sites of more complex events, e.g. accidents on major roads.

In order to reduce the time required to respond to a call, special software is used to plan and deploy teams (motorway junctions, railroad stations) at sites with large numbers of calls. This offers better chances to patients in densely populated areas.

Volunteer first aid units are used to provide prompt arrival of caregivers to victims in some suburban areas.

They are comprised of personnel not employed in emergency care, but trained by the ambulance personnel and equipped with additional gear (oxygen, airway clearing devices, automatic external defibrillators (AEDs)).

If available, Air Ambulance units are also used to rescue the victims. Currently, there are 12 such units in the UK. All units except for London Air Ambulance are manned with paramedics or technicians.

The London Air Ambulance teams always include a physician (completing their specialization or having 2nd degree specialization in anesthesiology and intensive care), who had completed an intensive training in accident site management and pre-hospital care.

The Air Ambulance takes part in rescuing victims with extensive injuries and provides immediate transportation to hospital following resuscitation procedures typical for resuscitation rooms performed at accident sites. The dispatcher may also mobilize a volunteer physician from the Immediate Medical Care system.

References:

1. Black John J. M., Davies Gareth D.: "Resuscitation", "International EMS Systems: United Kingdom", 2005, no. 64, p. 21-29.
2. British Paramedic Association College of Paramedics: A Curriculum Framework for Ambulance Education, February 2006, Official Website of BPO.
3. Jakubaszko J.: „Założenia organizacyjne systemu medycyny ratunkowej", – artykuł" Procedury organizacyjno – ratownicze i lecznicze w nagłych stanach zagrożenia życia", POZKAL, Inowrocław 1996 , s.11-17.
4. Koronkiewicz A., Murakowski M., Nowacki W.: „Systemy organizacji i finansowania pomocy doraźnej i transportu sanitarnego w wybranych krajach Europy na tle sytuacji w Polsce", Centrum Organizacji i Ochrony Zdrowia, Warszawa 1994.
5. Zawadzki A.: „Medycyna ratunkowa i katastrof:, PZWL, Warszawa 2006.
6. Doraźna pomoc lekarska, pod red.: Kamiński B., Dziak A. PZWL Warszawa 1988.

Physiology

Energy expenditure as the basis for determination of nutritional demand in soldiers

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Summary:

The study summarizes the history of studies to determine the nutritional demand in soldiers of different armies, both in Poland and worldwide. Standard energy values of food rations as used for planning and providing nutrition to soldiers over the last century were presented.

Key words: energy expenditure, food rations, military service .

Introduction

Good nutrition is one of the fundamental factors allowing soldiers to maintain high physical fitness and good mental condition. Such conditions may only be achieved by proper nutrition that covers all nutritional demands of the body.

The main principle of rational nutrition is that the food should deliver appropriate amount of energy to match the energy expenditure. In nutrition, the energy expenditure values are the measure of calorific demand of human body that may be covered only by the food intake. Thus, the knowledge of daily energy loss is the basis for determination of energy values of nutritional standards for populations homogenous in terms of gender, age, body weight and height, performing similar works and living in similar conditions.

The question of daily energy expenditure, energy value of food and, in consequence, the energy balance, are of particular importance in the army. Knowledge of the physical burden associated with soldiers' training, type of military unit and the specificity of service should be an essential element in nutrition planning which has to cover the energy demand and provide the body with all required nutrients in appropriate quantities and ratios.

History of the studies of energy demand in soldiers

History of determination of nutritional demands and in particular the energy demand in soldiers dates back to the 19th century. Soldiers' nutrition was usually the subject of interest for military healthcare services, as it directly affected the soldier's health and the efficacy of their action. Hence, in 1863, responsibility for nutrition in the US Army was bestowed by law to the military healthcare service [1]. The regulations were verified in 1877 and have remained in force ever since, including appropriate amendments. According

to these regulations, Medical Corps officers are also responsible for soldiers' nutrition:

"The officers of the Medical Department of the Army shall unite with the officers of the line (under such rules and regulations as shall be prescribed by the Secretary of War) in superintending the cooking done by the enlisted men; and the Surgeon General shall promulgate to the officers of said Corps such regulations and instructions as may tend to insure the proper preparation of the ration of the soldier." [2]

About 1870, first studies were conducted in Europe to measure the physiological load of soldiers burdened by the accouterment of different weight, training at different ambient temperatures. These and subsequent studies conducted in Europe and the US led to determination of energy expenditure of humans undertaking various forms of physical activity, e.g. marching, including the carried load. The above studies, albeit encumbered with large margin of error, showed that soldiers may be burdened with energy expenditure in the range of 5,000-6,000 kilocalories per day, depending on the accouterment weight and outside temperature [3]. However, determination of energetic and nutritional needs of soldiers was at that time based mainly on the average consumption of food. The food ration proposed at the end of World War I by the Quartermaster General of the US Army Medical Corps was based on the results of the studies on the quantities of standardized food consumed by the soldiers in 400 canteens in years 1917-1918.

The results of the studies allowed to determine the mean energy value of food consumed at the level of 3,633 kcal with the actual values falling within the range of 3000 to 4000 kcal [4,5]. Subsequent study of the energy demand in soldiers, based on calculations of the energy values of food rations were conducted in the US in 1941. The study covered a total of several hundred units of infantry, air force, armored troops, artillery, engineering troops, chemical troops, cavalry, quartermaster troops, logistic services troops, medical troops, military training centers and others. The mean daily energy value of food consumed by soldiers was 3,694, ranging from 3,132 to 4,135 kcal. The highest energy value was measured for food rations dispensed in autumn season (September-November — 3,960 kcal), while the lowest energy value was measured for rations dispensed in spring season (March-May — 3,570 kcal) [6,7,8,].

The results did not differ significantly from these obtained in years 1917-1918. A study conducted in 1943 in 99 canteens of the US Army ground forces and encompassing 130,000 food rations showed that the mean energy value of a daily ration was 3,468 kcal, ranging from 2,774 to 4,644 kcal [9]. Finally, a study to determine the energy demand in all US Army troops was undertaken and completed in the spring of 1945 [10]. The mean energy value of the food rations consumed by soldiers was 3,744 kcal and ranged from 3,471 to 4,078 kcal. The mean energy value determined in the study was very similar to the values obtained for food rations in the studies conducted during both World war I (3,633 kcal), and World War II (3,694 kcal).

During the World War II, the energy value of food rations in the British Army was higher than that in the American food rations and amounted to 5,127 kcal in January 1942. Due to the overly high weight of the rations, the energy value was reduced to 4,562 kcal in May 1942 [11].

Results of subsequent studies served as basis for revisions of nutritional standards for the American society; changes in the nutritional recommendations for soldiers followed these revisions.

Studies of the energy expenditure of soldiers in Poland

Also in Poland, studies of energy expenditure of soldiers in active service were conducted as early as before World War II [12,13].

The nutritional tables for Polish soldiers, developed in early 1920s, determined the minimum nutritional demand of soldiers. However, the energy and nutritional value of rations actually used was insufficient, leading to hunger among soldiers. Therefore, the nutritional standard was revised and the energy value was established at 2,900 kcal and later at 3,800 kcal [14].

The history of studies of the energy expenditure of soldiers of the Polish Army dates back to 1925, when major dr. Gustaw Szulc determined the energy load of soldiers in military service.

Table 1: Changes in the nutrition standards in the US Army (1943–1985) [15].

Normative document	Standard*	Energy † (kcal)	Protein (g)	Fat (%kcal)	Calcium (mg)	Iron (mg)	Vit. A (IU)	Thiamin (mg)	Riboflavin (mg)	Niacin (mg)	Vit. C (mg)
FNB RDA‡	1943	3.000	70	—	800	12	5.000	1.8	2.7	18	75
	1945	3.000	70	—	800	12	5.000	1.5	2.0	15	75
AR 40-250§	1947	3.600	100	—	700	—	5.000	1.6	2.2	16	50
	1949	3.600 ¶	100	—	700	—	5.000	1.6	2.2	16	50
		3.000#	100	—	700	—	5.000	1.6	2.2	16	50
Tri-Service Regulation**	1968	3.400	100	<40% †††‡	1.400	18	5.000	1.4	2.0	22	60
	1969	3.400	100	<40% †††‡	800	14	5.000	1.7	2.0	22	60
	1970	3.400	100	<40%	800	14	5.000	1.7	2.0	22	60
	1976	3.200	100	<40%	800	18	5.000	1.6	2.0	21	60
MRDAs AR 40-25**	1985	2,800-3,600	100	<35%	800-1,200	10-18	1,000 (µg RE)	1.6	1.9	21	60
MRDAs AR 40-25**	1985	Na (mg/1.000 kcal)	P (mg)		Mg (mg)		Zn (mg)	I (µg)	Vit. B6 (mg)	Folacin (µg)	Vit. B_{12} (µg)
		1,700 "goal"	800-1,200		350-400		15	150	2.2	400	3.0

* **Male personnel:** † — Moderate climate; ‡‡ — National Research Council (1941, 1945); § U.S. Department of the Army (1947, 1949); ¶ — Physically active; # Sedentary-type service.
** U.S. Departments of the Army, the Navy, and the Air Force (1968, 1969, 1970, 1976, 1985);
†† — < 40% supply; ‡‡ — < 45% per ration (1968); < 42% per ration (1969); < 40% per ration (1970).

These studies led to publication of first energy expenditure tables for soldiers performing various tasks during service-related military trainings. The value of the daily energy expenditure was determined at the level of 3,876 kcal which gave a slightly negative energy balance compared to the energy value of the food ration being 3,800 kcal [12]. During the first twenty years after World War II, food rations of Polish soldiers were based on data from the Soviet Army.

Studies on the daily energy expenditure of the soldiers of the Polish Army were taken up again in the late 1960s in the Military Institute of Hygiene and Epidemiology. The studies were initially of evaluative character, and the obtained results served as basis for revision of soldiers' food rations. More than ten years of studies were concluded by the collective study titled "Tabele wydatków energetycznych żołnierzy polskich różnych rodzajów wojsk i służb" [Energy expenditure tables for Polish soldiers of different arms and services], published in 1982 and being the only publication of this type to date [16]. Data in tables allowed for easy calculation of the daily energy expenditures of soldiers as well as classify the respective workload.

In the last two decades of the 20th century, studies of daily energy expenditure encompassed most training procedures compulsory for soldiers in mandatory military service, soldiers in training centers and students of military academies. The studies were conducted by the Military Institute of Hygiene and Epidemiology, and the obtained results served as basis for revision of energy values being in force at that time. The values of the energy expenditure of soldiers during a typical training day depended on the type and character of the unit and fell in the range of 3,339.5-4,651.6 kcal (13.99-19.49 MJ) (Table II [14].

Table 2: Mean daily energy expenditure values for soldiers of different types of units of the Polish Army.

Unit type	Daily energy expenditure	
	Kcal	MJ
Ground troops	4270.5	17.89
Mechanized infantry	4274.0	17.89
Armored troops	4319.0	18.10
Mountain infantry	4062.5	17.02
Air cavalry	4100.0	17.18
Air cavalry — military range	4594.4	19.25
Representative Company	4550.3	19.06
Battleships at docks	4000.0	16.76
Battleships at sea	4200 – 4700	17.60–19.00.
Missile base ships	4507.1	18.88
Divers' training	4282.9	17.94
Students in military academies	3535.0	14.81
Students of the Military Medical Academy	3339.5	13.99
Students of the Military Medical Academy — military range	4121.3	17.27
Students of the Military University of Technology	3737.3	15.66
Pilots at training camps	4651.6	19.49

Conclusion:

Currently, the service in the Polish Armed Forces is a professional service, and thus, the results of the studies on the energy expenditure resulting from military training, which served as basis for determination of the energy values of food rations used in soldiers' nutrition have lost some relevance. However, studies of the energy expenditure associated with military training are still being conducted in students of military schools and academies as well as in soldiers at service in some air force units and Polish Navy battleships, as well as during military range trainings. The results of these studies serve as a basis for determination and/or revision of the energy and nutritional values of the food rations used in the nutrition of soldiers in the Polish Army.

References:

1. Rev. Stat. 1174, February 27, 1877, sec 1174.
2. Act of March 3, 1863, 12, Stat. 744: U.S. Code 1863,10:104.
3. Dezel W.L. Battelfield Mobility and the soldiers load, USMC CSC 1992.
4. Murlin J.R. Miller C.W.: Preliminary results of nutritional surveys in United States Army Camps. Am. J. Pub. Heath, 1919, 9, 401-411.
5. Chamberlain W.P, Durham G.C.: The well balanced ration. The Quotermaster Review 1, 1922, 16/17, 52-58.
6. Howe P.E.: Nutritional problems of the Army. Mil. Surgeon 1942, 90, 253-266.
7. Howe P.E.: The dietaries of our military forces. An. Am. Acad. Polit. & Social Sc., January 1943, 72-79.
8. Effect of recent developments in nutrition on the rationing of the Army. Connecticut M. J. Mar 1942, 6, 157-161.
9. Howe P.E., Berryman G.H: Average food consumption in the training camps of the United States Army, 1941-1943. Am. J. Physiol. 1945, 144, 588-594.
10. Simultanous survey of food consumption in various camps in United States Army, 22-28 May 45. AFML., RPT. Nr 36, Mred Nutr Lab. Apr 48.
11. Coates J.B.: Troop rations in the United Kingom. Personal heath measures and immunization. w: Hoff E.C., Hoff P.M. Preventive medicine In Word War II, Office of the Surgeon General Departament of the Army, Washington 1955, vol. III, 124-131.
12. Szulc G.: Wydatek energii żołnierza polskiego i jego potrzeby pokarmowe. Lekarz Wojskowy, 1925, 6, 2.
13. Szulc G. Higiena odżywiania lotnika. W: Fiumel A., Higiena Lotnika — Podręcznik Zbiorowy do Użytku Personelu Latającego. Warsaw1938.
14. Bertrandt J. Kłos A.: Wydatek energetyczny podstawą planowania żywienia w Wojsku Polskim. Żywienie człowieka i metabolizm, 2001, XXVIII, Supl., 185-191.
15. Schnakenberg D.D.: Nutritional Criteria for Development and Testing of Military Field Rations. An Historical Perspective. In: Not Eating Enough: Overcoming Underconsumption of Military Operational Rations. National Academy Press, Washington, D.C. 1995, 91–107.
16. Rdzanek J., Jędrasiewicz T., Kłos A., Frańczuk H., Karpińska H., Krzyżański B, Bertrandt J.: Tabele wydatków energetycznych żołnierzy polskich różnych rodzajów wojsk i służb. WIHiE, Warszawa 1982.

Physiology

Sodium and potassium content of daily food rations of students of the Main School of Fire Service in Warsaw

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Summary:

Introduction: Besides carbon, hydrogen, nitrogen and oxygen, human body contains about 60 other elements, most of which are classified as minerals. They account for ca. 3% of body weight in neonates and about 4% of body weight in adults. Since human body is unable to synthesize minerals, they have to be supplied with food in appropriate amounts and ratios. Among macroelements, i.e. elements with human body content of more than 0.01% and safe or recommended intake of more than 100 mg, sodium (Na) and potassium (K) play a particular physiological role.
Material and methods: The goal of the study was to assess the content of potassium and sodium in daily food rations (DFRs) dispensed for consumption and actually consumed by the students of the Main School of Fire Service (MSFS) in Warsaw. The study material consisted of daily food rations dispensed for consumption to MSFS students. Sodium and potassium content in analyzed samples was determined by atomic absorption spectrometry (AAS).
Results: Mean sodium content of the analyzed DFRs was 7,039.4 ± 1,097.6 mg, compared to 6,271.1 ± 996.2 mg in actually consumed meals. Mean potassium content of the analyzed DFRs was 3,477.7 ± 637.2 mg Actually consumed rations included 3,099.1 ± 550.6 mg of potassium. Sodium and potassium supply was different in individual months of the study.
Conclusions: The sodium content of daily food rations both dispensed for consumption and actually consumed was several times higher than the recommended standards. The potassium content of daily food rations was lower than the standard value. Rations dispensed for consumption covered 99.4%, while rations actually consumed covered 88.9% of the standard demand. Attempts should be made to reduce the sodium intake by raising consumers' awareness of the detrimental health effects of excess salt and by appropriately selecting the products included in the diet.

Key words: sodium, potassium, food ration.

Introduction

Civilization brings many threats to the quality of human nutrition and contributes to the development of bad nutritional habits in the population. According to the World Health Organization, inappropriate nutrition at young age significantly impacts the development of numerous chronic non-infectious diseases at adult age. This

pertains to cardiovascular and gastrointestinal diseases, as well as to some cancers [1].

Minerals are not synthesized in human body They must be delivered to the body with food and drinks in appropriate quantities and ratios. In special cases, they may be supplied as dietary supplements to the food rations. Minerals play dual role in human body: they are either building materials (calcium, phosphorus, iron) or they regulate the biochemical processes in the body (potassium, sodium, magnesium, copper, zinc) [2]. Many authors observed too low supply of calcium, magnesium and iron accompanied by excess amounts of sodium and phosphorus in daily food rations of students [3,4].

In the context of the important role of minerals in the maintenance of good health, as well as prevalent abnormalities consisting in their too-low (calcium, magnesium, potassium, iron) or too-high (sodium, phosphorus) intake, appropriate supply of these elements in food rations is reasonable. As shown by the studies of the nutritional habits of Poles, these habits are far from current recommendations, also with regard to the supply of appropriate standard amounts of minerals [5].

Sodium and potassium are elements found in many food products. Salt, i.e. sodium chloride, is widely used to enhance the taste of food products; in addition, being a good preservative, it is widely used in food processing. The intake of sodium is an important element of public health, as reduction of this intake allows to reduce the mean arterial pressure in the population.

Potassium, originating mostly from fruits and vegetables, plays many physiological roles and is involved in similar processes as sodium. Therefore, the sodium-potassium balance is essential for normal functioning of the system.

The goal of the study was to assess the content of potassium and sodium in daily food rations dispensed for consumption and actually consumed by the students of the Main School of Fire Service in Warsaw.

Material and methods

The study was conducted between November and July during the academic year 2011/2012. The study material consisted of daily food rations dispensed for consumption to MSFS students. Sodium and potassium content was determined in DFRs dispensed for consumption and in plate leftovers. Actual intake of sodium and potassium was the difference between the content of these elements in DFRs dispensed for consumption and the content of these elements in the leftovers, Daily food rations collected for analysis were weighed, shred and homogenized. The samples were collected from the homogenate [6]. Sodium and potassium content in analyzed samples was determined by atomic absorption spectrometry (AAS) using a GBC AVANTA Σ apparatus. The sodium content was determined by flame technique at $\lambda = 330.2$ nm. The accuracy of the analysis of certified standard was 94.2%. Potassium was determined at $\lambda = 766.5$ nm. The accuracy of the analysis of certified standard was 99.4%. CsCl was used as the deionizing buffer in concentration of 2000 μg/mL [7]. The obtained results were subjected to statistical analysis [8].

Results

The mean energy value of the tested daily food rations dispensed for consumption was 3,211.2 ± 362.5 kcal. The protein content in the DFRs was 107.7 ± 18.5 g accounting for 13.4% of total ration energy. The fat in the amount of 103.6 ± 22.1 g accounted for 29%, and carbohydrates in the amount of 462.0 ± 362.6 g accounted for 57.6% of the energy value in the daily food rations. The energy value of actually consumed daily food rations, i.e. rations dispensed for consumption minus the plate leftovers was 2,944.8 ± 338.5 kcal. Protein, fat and carbohydrates accounted respectively for 13.3%, 27.7% and 59% of total energy value.

Mean sodium content in the analyzed DFRs dispensed for consumption was 7,039.4 ± 1,097.6 mg The sodium content of the leftovers accounted for 10.9% of total sodium content; thus, the actually consumed daily food ration contained 6,271.1 ± 996.2 mg of sodium. (Table 1).

Mean potassium content in DFR dispensed for consumption was 3,477.7 ± 637,2 mg, ranging from 2,441.7 mg to 4,773.1 mg. Similarly as in the case of sodium, potassium content of plate leftovers accounted for 10.9% of total potassium content in the dispensed DFR. Therefore, the actually

consumed rations delivered 3,099.1 ± 550.6 mg of potassium.

Variability in the sodium and potassium supply was observed in the dispensed DFRs in individual months (Table 2).

Considering the seasonal changes in the supply of elements, the lowest and the highest sodium content in the consumed DFRs was observed in January and June, respectively. The lowest potassium content was also observed in January, while the highest potassium content was measured in November.

Table 1: Mean sodium and potassium content of the daily food rations of the MSFS students, in mg.

Element (mg)	Per DFR dispensed for consumption	Per DFR actually consumed	Adequate intake (AI)
Sodium (Na)	7,039.4 ± 1097.6	6,271 ± 996.2	1,500
Potassium (K)	3,477.7 ± 637.2	3,099.1 ± 550.6	4,700

Table 2: The supply of sodium and potassium in the consumed daily food rations in individual months of the study.

Study month	Mean content of sodium in individual months	Mean content of potassium in individual months
November	6,686.3	3,880.3
December	5,582.7	2,692.2
January	4,365.1	2,486.0
February	5,627.4	2853.9
March	6,716.5	2,855.5
April	5,943.7	3,198.3
May	6,460.5	3,592.0
June	7,168.9	3,449.3
July	6,862.9	3,224.8

The adequate intake (AI) is 1,500 mg/individual/day for sodium and 4,700 mg individual/day for potassium [9].

Comparison of the obtained contents of analyzed elements with the adequate intake values revealed that the sodium content in the dispensed and consumed DFRs exceeded the AI by the factor of 4.7 and 4.2, respectively, while the potassium content did not cover the adequate intake and accounted for 74% and 65.9% of the AI value for the dispensed and consumed rations, respectively. Sodium and potassium content of dietary food rations was determined for different populations, including students of various Polish universities. Studies conducted by other authors regarding the sodium and potassium content in daily food rations of students of various universities in Poland suggested the adequate intake being exceeded for sodium and not met for potassium (Table 3) [3, 4, 10, 11, 12].

Sodium is added to food products because of its taste, as well as to enhance other tastes, to preserve food products by inhibiting the growth of microorganisms that make food go bad, and to achieve appropriate food texture. Excess salt is a risk factor of arterial hypertension and its complications (brain stroke, myocardial infarction, circulatory insufficiency), as well as atherosclerosis,

Table 3: Table 3. Sodium and potassium content of the food rations of students of various universities in Poland.

School	Year of the study	Sodium content in male students' food rations	Potassium content in male students' food rations	Sodium content in female students' food rations	Potassium content in female students' food rations
Department of Pharmacy, Jagiellonian University Medical College	2003 2004	1940.9 ± 1150.8 1678.6 ± 1120.8	3168.2 ± 1205.7 2962.8 ± 1284.3	1791.0 ± 1059.7 1551.0 ± 1032.7	3011 ± 1109.9 2816 ± 1181.2
Warsaw University of Life Sciences	2005	3971 ± 901.2	3277 ± 894.7	3070 ± 991	2789.9 ± 710.1
Medical University of Warsaw	2003/2004	3263 ± 1460	3719 ± 1194	2074 ± 860	3089 ± 819
Medical University of Bialystok	2003/2004 2008/2009	3710 ± 1694 2302 ± 687	3364 ± 1590 2115 ± 716	2110 ± 970 2910 ± 1178	2870 ± 1405 2346 ± 780
Wroclaw University of Economics	2008 autumn 2008 winter	2981 ± 2241 3811 ± 2434	3086 ± 1394 3882 ± 1670	2328 ± 1398 1789 ± 1141	2599 ± 969 2518 ± 933

osteoporosis and some cancer diseases, i.e. major non-infectious chronic diseases. The World Health Organization (WHO) recommends that adult salt intake does not exceed 5 g per individual per day; despite this, actual salt intake in Europe is much higher, reaching as much as 8-12 g. [13]. Also in the US the dietary sodium supply significantly exceeds the established norms; in years 2007-2008, the average sodium intake was 3,266 mg/d. [14].

According to WHO's recommendations, daily intake of sodium from all sources should be reduced to less than 2 g of sodium (5 g of salt). This pertains to both the salt content in ready-made food products (cured meat, bread, cheese, processed food, food mixes etc.), and salt added to food prepared by consumers themselves. Poland is a country with high salt consumption. It is estimated that the intake of sodium chloride in Poland exceeds current WHO's recommendation of 5 g of salt/day as much as three times. A panel study of households conducted in 2009 revealed that the [monthly] salt purchase was 0.26 kg per individual, which translates into daily intake of 8.5 g. This was only the salt that was used in the household for cooking and adding salt to cured meat, vegetables, dairy as well as to the prepared dishes, such as soups, sauces and meats. Estimation should also include salt contained in ready-made food products. Results of all-Polish studies show that cured meat, bread, processed food and frozen food delivers another 4.4 g of salt per day. For comparison, the daily intake of sodium in Belgium is 4.15 ± 1.01 g/day (3.8 ± 1.2 – 4.9 ± 1.2 g) [15].

Considering the high intake of salt and its adverse health effects, programs aimed at reducing the sodium chloride intake were initiated in many countries. In Finland, where the program to reduce the salt intake has been in place since 1975, the average salt intake was reduced from 12.0 g to 9.3 g/d in males and from 9.3 to 6,8 g/d in females. A similar trend was observed in the United Kingdom, where a program to reduce salt consumption was introduced in 2003. A reduction in the salt intake from 9.5 g to 8.6 g/d was observed by 2008 [16].

Conclusions

1) The content of sodium in both rations dispensed for consumption and actually consumed by students exceeded the adequate intake norms several times which, upon long-term intake, might be a cause of diet-dependent civilization metabolic diseases.

2) The potassium content of daily food rations was lower than the standard value.

3) Far-flung activities should be undertaken to raise the health awareness regarding the adverse effects of dietary salt on human body in both personnel responsible for planning and providing students' board and the MSFS students.

References:

1. Diet, nutrition and the prevention of chronic diseases. Report of a Joint WHO/FAO Expert Consultation. World Health Organization, Geneva 2003.
2. Brzozowska A.: Składniki mineralne w żywieniu człowieka. W Gawęcki J., Hryniewiecki L.: Żywienie Człowieka . Podstawy Nauki o Żywieniu. PWN Warszawa,2000.
3. Paśko P., Krośniak M., Chłopicka J., Zagrodzki I., Zachwieja Z.: Ocena sposobu żywienia studentów Wydziału Farmacji Collegium Medium Uniwersytetu Jagiellońskiego w latach 2003-2004 Żyw. Człow. Metab. 2005, supl.1 660-667.
4. Czapska D., Ostrowska L., Stefańska E., Karczewski J.: Ocena zawartości wybranych składników mineralnych w całodziennych racjach pokarmowych studentów Uczelni Medycznej w latach 2003/2004 i 2008/2009. Brom. Chem. Toksykol. 2009, 3, 725-727.
5. Górnicka M., Gronowska-Senger A.: Jakość wyżywienia wybranymi składnikami mineralnymi w gospodarstwach domowych. Żyw. Człow. Metab. 2005, supl. 1, 9-17.
6. Rutkowska U. Wybrane metody badania składu i wartości odżywczej żywności. PZWL W-wa 1983.
7. Poradnik użytkownika GBC SCIENTIFIC Equipment Pty Ltd 1996.
8. Patrie A., Sabin C.: Statystyka Medyczna w zarysie. PZWL Warszawa 2006.
9. Jarosz M., Szponar L., Rychlik E.: Woda i Elektrolity. w: Jarosz M., Bułhak-Jachymczyk B. Normy żywienia człowieka. Podstawy prewencji otyłości i chorób niezakaźnych., PZWL, Warszawa 2008.
10. Przysiężna E., Wasilewska A.: Realizacja norm żywieniowych na wybrane składniki mineralne i grupy produktów spożywczych w dietach studentów Akademii Ekonomicznej we Wrocławiu. Bromat. Chem. Toksykol. 2008, 2, 151-159.

11. Bujko J., Myszkowska-Ryciak J., Nitka I.; Ocena spożycia składników mineralnych wśród studentów SGGW w Warszawie. Żyw. Człow. Metab 2005, supl 1. 655-667.
12. Ziółkowska A., Ostrowska A.: Porównanie spozycia wybranych pierwiastków w całodziennych racjach pokarmowych warszawskich studentów medycyny w latach 2001-2004. Żyw. Człow. Metab. 2005, supl 1, 646-650.
13. Busch J et al. (2010). Salt reduction and the consumer perspective. New Food 2/10:36-39.
14. US Department of Health and Human Services, US Department of Agriculture. Dietary guidelines for Americans, 2010. 7th ed. Washington DC: US Department of Health and Human Services, US Department of Agriculture; 2011.
15. Sekuła W.: Badania indywidualnego spożycia żywności. 2010, www.gis.gov.pl.
16. Bibbins-Domingo K et al. (2010). Projected effect of dietary salt reductions on future cardiovascular disease. New England Journal of Medicine 362(7):590-599.

Emergency Medicine

Cardiac arrest under special circumstances. Part II: poisoning, …, anaphylactic reaction, …, traumatic injuries

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Summary:

In this publication, we discuss several issues related to cardiac arrest occurring under special circumstances such as: hypothermia, near drowning, poisoning, pregnancy, electric shock, anaphylactic reaction, episode of acute, severe asthma, traumatic injuries.

Key words: Safar's ABC scheme, resuscitation, rescue, dealing with an unconscious person.

Introduction

This publication is a continuance of an article titled *Cardiac arrest under special circumstances. Part I: hypothermia, near drowning* published in the previous number of Military Pharmaceutics and Medicine (Issue V, No. 3). In this section, we discussed the rules of management of cardiac arrest due to: poisoning, pregnancy, electric shock, anaphylactic reaction, acute episode of severe asthma and traumatic injuries.

Drug overdose and poisoning

Poisoning rarely leads to cardiac arrest, but is one of the main causes of death in people under 40 years of age. It is also the most frequent cause of non-traumatic coma in this age group. Suicidal poisoning with medicaments or addictive substances constitutes the main reason for hospitalizations. Accidental poisoning is most common among children. Criminal poisoning is rare. At times, it is not possible to immediately state whether loss of consciousness or cardiac arrest is a result of poisoning. Therefore, this cause of come is important to exclude.

Large-scale exposition to chemicals or radiation may occur as a consequence of industrial accidents or warfare. In such cases, it is important that rescue services are not exposed to dangers of contamination. Proper personal protective equipment should be used. Decontamination and transporting victims into safer areas is usually the task of special services.

Resuscitation

The basics of suicidal poisoning management ("overdose") involve supportive treatment based on the ABC scheme directed at preventing circulatory and respiratory arrest in hope that, in time, the substance will be eliminated from the system. Airway occlusion and respiratory arrest secondary to disrupted consciousness is a frequent cause

of death. Suicidal poisonings are often associated with excessive alcohol consumption.

After clearing the airway and restoring airway patency, the presence of respiration and pulse is checked. Mouth-to-mouth ventilation should not be performed when dealing with poisonings due to agents such as cyanides, hydrogen sulfide, corrosives or organophosphorous substances. Patient's lungs are ventilated through a pocket mask or a facemask set using the highest possible oxygen concentrations. Precautions should be taken in paraquat poisoning, as high oxygen concentrations can exacerbate lung damage.

Aspiration of stomach content to the lungs occurs in a considerable proportion of poisonings. Therefore, unconscious patients without pharyngeal reflexes should be intubated early. So-called fast induction with cricoid cartilage compression is performed in order to reduce the risk of aspiration. Preferentially, it should be performed by a trained anesthesiologist or a person with appropriate experience.

BLS and ALS should be commenced during cardiac arrest. Pulseless electrical activity (PEA) usually results from use of medicines exerting negative inotropic effect, but is associated with better prognosis than PEA from primary cardiac causes. Cardioversion is indicated in life-threatening tachyarrhythmias with the exception of Torsades de Pointes (look below).

Drug hypotension is a frequent phenomenon in suicidal poisoning. It usually responds to filling of vascular bed with fluids, although it sometimes requires use of inotropic drugs.

During resuscitation, we must undertake actions to identify the poison (or poisons). Patient's relatives, friends and the ambulance team can usually provide important information. Physical examination can reveal diagnostic clues (smell, puncture marks, tablets left in the oral cavity).

Specific therapeutic actions

In poisoning management, we can formulate few specific therapeutic guidelines useful in emergency situations. Particular emphasis should be put on maintenance of vital functions, oxygenation, compensating acid-base and electrolyte imbalances.

Gastric lavage with addition of activated carbon is justified up to 1 hour after poison ingestion. It is usually performed following intubation. Late gastric lavage exerts little influence on poison absorption and can even induce its movement further along the gastrointestinal tract. Elimination of poison from the system can be accelerated through hemodialysis or hemoperfusion.

Effective specific antidotes include:
1) N-acetylcysteine in paracetamol poisoning;
2) high doses of atropine in organophosphorous insecticide poisoning;
3) sodium nitrate, sodium thiosulfate or EDTA in cyanide poisoning, digoxin-specific antibodies in digoxin poisoning;
4) flumazenil in benzodiazepine poisoning, naloxone in opioid overdose.

Tricyclic antidepressants

Suicidal tricyclic antidepressant overdoses are frequent and may lead to convulsions and arrhythmias. Threat to patient's life exists within the first 6 hours following ingestion. Widening of QRS complexes (over 0.16 seconds) indicates elevated risk of arrhythmias. Sodium bicarbonate can provide some cardiac protection and prevent arrhythmias in high-risk patients.

Opiates

Opiate overdose causes respiratory depression, pinpoint constriction of pupils and coma. Pethidine overdose may result in convulsions. Naloxone is a specific opiate antagonist. The recommended dose is 0.4-0.8 mg i.v. (drug is administered slowly in the amount that is needed to obtained an effect) or 0.8 to 1.2 mg in an intramuscular or subcutaneous injection (which is easier in drug abusers with difficult venous access). Time of action of naloxone is shorter (45-70 minutes) than opiates (up to several hours), necessitating administration of additional doses at times.

Cocaine

The following may occur in cocaine poisoning due to excessive sympathetic stimulation:

tachycardia, hypertensive crisis and cardiac ischemia. Small doses of benzodiazepines (midazolam, diazepam, lorazepam) constitute first-line treatment. Nitrates are used as second-line treatment – they counteract cardiac ischemia. Tachycardia and sudden blood pressure elevation caused by toxic effect of cocaine can be alleviated by labetalol (alfa and beta receptor blocker).

Drug-induced bradycardias

They may respond to intravenous atropine at doses that do not exceed 3 mg (although higher doses are needed in organophosphate poisoning) or temporary external electrostimulation. Glucagon can be used in bradycardia induced by beta-blockers, improving cardiac contractility and increasing the heart rate.

Torsades de Pointes

This phenomenon is associated with toxicity of various substances administered for therapeutic or suicidal purposes. The most important principles of management of such cases include intravenous administration of magnesium, correction of electrolyte imbalance and overdrive pacing.

Further management and prognosis

Persisting loss of consciousness without changing body position can lead to sore formation and rhabdomyolysis. Electrolyte (particularly potassium) and glucose concentrations, as well as arterial blood gases should be closely monitored. Body temperature should also be overseen, as disturbances of thermoregulation occur frequently. Overdose of some substances may lead to either hypo – or hyperthermia. It is important to preserve blood and urine samples for further biochemical tests. We should be constantly prepared for prolonged resuscitation, particularly in young people, as the poison can be metabolized or excreted during that time.

Pregnancy

Resuscitation of a pregnant woman involves two people. However, the emphasis is put on effective actions aimed at saving the life of a mother. At the same time, it is the best mode of action to maintain the wellbeing of a fetus. Sudden cardiac arrest in a mother is most often associated with changes occurring in woman's organism in the third trimester of pregnancy. Causes of cardiac arrest in a mother include bleeding, pulmonary embolism, amniotic fluid embolism, premature placental detachment, eclampsia and drug toxicity. Cooperation with an obstetrician and a neonatologist should be established early.

Course of resuscitation

All rules of BLS and ALS apply to pregnant patients. Delayed stomach emptying occurs in the first trimester of pregnancy, which increases the risk of aspiration of gastric contents. Therefore, early intubation is recommended, preferably with an assistant applying pressure on cricoid cartilage. Intubation may be sometimes difficult due to anatomical changes taking place during pregnancy (short and wide neck, large mammary glands, edema of epiglottis). Diaphragm is elevated and its mobility is reduced by the enlarged uterus during the last trimester of pregnancy and higher ventilation pressures are required for effective ventilation.

In order to improve venous return and cardiac output, it is necessary to reduce the pressure exerted by the uterus on inferior vena cava and aorta (aortocaval compression) through:

1) placing a sand-filled sac, a pillow or a prefabricated wedge (Cardiff type) under the right buttock and lumbar area;
2) manually moving the uterus leftward;
3) tilting the patient to the left on an operating table or a long board.

Chest compressions are performed in a standard manner, although they are more difficult to execute due to mammary gland enlargement and diaphragmatic stiffening.

Circulating blood volume in a pregnant woman is large, but cardiac arrest may occur as a result of hypovolemia due to an occult internal hemorrhage. Blood is drawn for cross matching and intravenous fluid administration is commenced. Early surgical treatment aimed at stopping the hemorrhage is of most importance.

Arrhythmias

Cardiac arrhythmias are treated according to standard management schemes.

Further management

Immediate cesarean section is indicated following five minutes of ineffective resuscitation, improving the likelihood of survival of the mother as well as the fetus. It is a difficult decision, but it must be made without unnecessary delay. Extraction of a fetus removes the aortocaval compression. ALS should be continued during and after the operation.

Electric shock

Electric shock can occur at home, in a factory or as a result of a lightning strike. Most traumatic injuries caused by electricity in adults take place at work. On the other hand, children exposed to the greatest risk at home. In any given moment, there are 2000 thunderstorms around the globe and 1000 people around the world die because of it every year.

Severity of injury caused by electricity depends on the type of current (alternating or direct), its voltage, amount of energy it produces, resistance to current flow, path of the current through the patient as well as the surface area and time of contact. Skin resistance decreases due to moisture, increasing the likelihood of injury.

Contact with alternating current can lead to tetanic skeletal muscle spasm. It prevents detachment from the source of current and may lead to respiratory arrest. Alternating current is able to induce ventricular fibrillation if it acts on a cardiac muscle during a vulnerable period, analogously to a phenomenon called R-on-T. Sometimes, electrical current causes cardiac ischemia due to coronary artery constriction. Flow of current across the chest (from one upper limb to another) is more often fatal than a vertical flow path (from an arm to a foot) or astride (from one foot to another). Diffuse tissue damage may occur on the path the flowing current.

A lightening strike causes acute and massive discharge of DC current, leading to depolarization of the entire cardiac muscle. It poses a threat of asystole or ventricular fibrillation. Due to heart's automatism, hemodynamically effective sinus rhythm returns sometimes. Respiratory muscle paresis may be the reason for respiratory arrest and secondary cardiac arrest occurs if appropriate actions are not taken. Lightning may also cause diffuse neurological damage, including encephalopathy and peripheral nerve damage.

Diagnosis

Circumstances of an accident are not always clear to a rescuer and he should pay special attention to the presence of contact burns at the point of current entrance and exit.

Rescue actions

The rescue team must make sure that all sources of electrical current are turned off and cannot approach the victim until it is completely safe. One should remember that high-voltage current (higher than that in home power outlets) might flow through the ground within a diameter few meters from the victim. On the other hand, it is safe to approach victims of a lightning strike, although it is reasonable to move them to a safer place.

Course of resuscitation

BLS and ALS should be commenced immediately. Restoration of airway patency is sometimes difficult if there are electrical burns around the face and neck. In such cases, early intubation should be performed, as diffuse soft tissue edema develops quickly, leading to airway obstruction. Electrocution can result in head and vertebral injury. Therefore, the vertebra should be immobilized until full clinical assessment. Muscle paresis, especially following high-voltage current discharge (industrial conditions), can persist up to 30 minutes and ventilatory support may be necessary during that time.

The most common initial arrhythmia following high-voltage alternating current discharge is ventricular fibrillation, which needs to be treated with a defibrillation attempt. Direct current discharge more frequently leads to asystole. Standard management should be undertaken in arrhythmias. Smoldering clothing and footwear should be removed in order to avoid further thermal damage. In case of diffuse tissue injury, it is sometimes necessary to commence intense intravenous fluid resuscitation. It is important to maintain proper urine excretion, which enables

systemic excretion of myoglobin, potassium and other products released by damaged tissues.

Patients with serious thermal injuries often require surgical intervention.

Further management and prognosis

Immediate commencement of resuscitation in young patients with cardiac arrest caused by electric shock often brings positive outcome. There are reports of effective resuscitation even after prolonged ALS. All patients after serious electric shock and patients with circulatory or respiratory problems, loss of consciousness, cardiac arrest, electrocardiographic abnormalities, soft tissue injuries and burns require hospital monitoring.

Anaphylactic shock

It seems that phenomena related to anaphylaxis are increasingly more common. It is certainly associated with growing frequency of allergies over the course of two or three past decades.

Diagnosis of anaphylactic reactions

There is no generally accepted definition of anaphylactic reaction. The term "anaphylaxis" usually refers to immoglobulin E (IgE)-mediated hypersensitivity reactions occurring in typical situations. Anaphylactoid reactions are similar, but are not associated with hypersensitivity. For simplicity, we will use the term anaphylaxis for both types of reactions unless they are clearly distinguished. Their symptoms and management are similar, so this distinction is only important when considering further treatment. Both of those reactions may be associated with various degrees of angioedema, urticaria, dyspnea and hypotension. Some patients die due to acute, irreversible bronchospasm or laryngeal edema. Among other symptoms are the following: rhinitis, conjunctivitis, abdominal pain, vomiting, diarrhea, sense of unrest. There is usually skin discoloration: patient's face becomes red or pale.

Cardiovascular depression is a common symptom, particularly when it comes to reactions to intravenous agents or insect stings. It is caused by vascular dilatation and movement of plasma into the extravascular space. Circulatory failure or arrhythmias are associated mainly with a drop in blood pressure and are rarely caused by primary heart disease or intravenous administration of adrenaline. Anaphylactic reactions present with various degrees of severity and can develop quickly, slowly or, rarely, in a biphasic manner. Rarely, symptoms may be delayed (it happens in case of latex allergies) or persist over 24 hours. Such reactions may be associated with exposition to various agents. The most frequent causes include insect bites, reactions to drugs, contrast agents or some foods. Peanut and hazelnut allergies are particularly dangerous.

Muscle relaxants can induce anaphylaxis and anesthetic agents constitute an important cause of anaphylactoid reactions. Absence of established symptoms and wide scope of clinical picture can pose diagnostic difficulties. In any case, it is necessary to acquire full medical history (with particular focus on past allergic reactions) and perform physical examination. Special attention should be paid to the condition of the skin, heart rate, blood pressure, upper airways and auscultation.

If possible, peak expiratory flow should be measured and documented. Distinguishing between anaphylaxis, panic attack or vasovagal episode can be sometimes difficult. All of these phenomena can occur, e.g. after vaccination. Full clinical assessment facilitates making this distinction.

Comments on management

There is a common agreement that adrenaline is the most important drug used in management of anaphylactic reactions. As an alfa receptor antagonist, it abolishes peripheral vessel dilatation and reduces the edema. Its activity toward beta-receptors causes airway dilatation, increases contractility of cardiac muscle and inhibits histamine and leukotriene release.

Adrenaline is most effective if administered immediately after the occurrence of a reaction, but is not devoid of risk, particularly when given intravenously. Intramuscular adrenaline is a very safe drug. Undesirable effects are incredibly rare and the only case of myocardial infarction following its intramuscular administration involved a patient with high risk of coronary artery disease. At times, there is doubt whether the complication (e.g. myocardial ischemia) is a

result of the allergen itself or adrenaline administered for therapeutic purposes.

In rare cases adrenaline may fail to abolish clinical symptoms of anaphylaxis, particularly in late reactions or in patients treated with beta-blockers. In such instance, other means of management grow in significance, especially replenishing of circulating blood volume. Antihistamines (H receptor blockers) should be routinely used in all cases of anaphylactic reaction, which facilitates attenuation of vasodilatation occurring as an effect of histamine action. These drugs may not be effective in some anaphylactoid reactions that are partially induced by other mediators, but their use is safe. It should be emphasized that use of antihistamines only may not be sufficient for saving patient's life. Administration of H2 receptor blockers should also be considered.

Corticosteroids are thought to work too slowly, as the effect of their administration may appear as long as 4-6 hours following intravenous administration. However, they may help in immediate control of an acute episode and play a significant role in prevention or shortening the time of prolonged reactions.

Resuscitation

All victims should be placed in a comfortable, supine position. Suspected allergen is removed (e.g. drug infusion or blood transfusion). Supine position with or without leg elevation may facilitate correction of hypotension, but makes breathing difficult. If conditions allow, high-flow oxygen should be administered (10-15 l/min).

BLS or ALS is commenced in case of cardiac arrest. During resuscitation, it may be necessary to administer higher doses of adrenaline. Infusion of large amounts of fluids is sometimes necessary.

In all patients with clinical signs of shock, airway edema or apparent breathing disturbances, adrenaline should be administered intramuscularly, which accelerates its absorption. Signs such as inspiratory wheezing, rhonchi, cyanosis, severe tachycardia and poor capillary return should evoke a suspicion of severe reaction. Adults should receive 0.5 ml of adrenaline in a 1:1000 (500 micrograms) solution. This dose should be repeated after about 5 minutes if clinical signs persist or become more severe (particularly when disturbances of consciousness are present as a result of hypotension). In many cases there may be a necessity of administering several doses, especially when improvement is short-lasting.

Intravenous administration of adrenaline in a 1:10 000 (under no circumstances should it be 1:1000) solution is associated with complications and it should be reserved for patients in deep shock posing an immediate threat to life, and to special situations, e.g. during anesthesia. Even greater dilution of adrenaline in a ratio of 1: 100 000 allows for more precise dosing and increases the safety, as the risk of unwanted effects is reduced. This drug is given under constant heart rate and ECG supervision, which constitutes the minimum monitoring. Doctors experienced at intravenous adrenaline administration may choose this route of administration in patients with signs of severe anaphylaxis.

Airway occlusion may occur as a result of soft tissue edema. Early intubation should be performed in such cases. Any delay can make it extremely difficult. Antihistamine drug acting on H1 receptors [e.g. dimetindene (Fenistil®)] should be administered in slow intravenous injection, but H2 blockers can also be used (e.g. ranitidine).

Hydrocortisone (sodium succinate preparation) should be used following a severe episode and prevents the late sequelae from occurring. It is particularly important for patients suffering from asthma (who are at greater risk of severe or even fatal anaphylaxis) if they were treated with corticosteroids before. Hydrocortisone is administered in a slow intravenous injection. Fluid infusion should be commenced if there is significant blood pressure reduction and patient does not respond quickly to administered medicines.

Anaphylactic reactions in adults – treatment by first-aid providers

Patients who suffered an episode of anaphylaxis, even of moderate degree, should be warned against the possibility of early return of symptoms and, in some circumstances, they need to be hospitalized for observation for next 8-24 hours. It refers especially to cases of:

1) severe reactions with slow onset – evidence of idiopathic anaphylaxis,

2) reactions in patients with severe asthma or strong asthmatic component,
3) reactions associated with the possibility of continuous exposure to the allergen,
4) patients who underwent biphasic reactions in the past.

If there is bronchospasm not responding to standard management, inhalation of beta-2 receptor antagonist, e.g. salbutamol, may be of some help.

Additional tests and further management

Measuring mast cell tryptase levels can retrospectively facilitate the diagnosis of anaphylaxis. Ten milliliters of blood should be drawn to a tube containing clot activator between 45 minutes to 6 hours after the episode.

Following successful management of anaphylactic reaction, it is important to identify the allergen in order to avoid recurrence of the condition in the future. Therefore, patient should be referred to a specialist outpatient clinic. Patients at great risk of anaphylactic reaction can keep at all times a special, adrenaline-filled syringe for self-administration and wear a warning bracelet.

Acute episode of severe asthma

Acute episode of severe asthma is almost always a reversible state and we must assume that such patients can be saved. The majority of deaths occur outside of the hospital. Several factors contribute to it, such as:
1) patient and his relatives do not recognize the severity of asthmatic episode and turn to medical help too late;
2) emergency services and family doctors do not always act fast enough;
3) patients with mild asthmatic episodes are discharged home after being provided with medical assistance and suffer from sudden deterioration of their condition.

It is important to treat all asthmatic exacerbations aggressively in order to prevent future life-threatening recurrences and cardiac arrest. National guidelines were published on management of acute asthma exacerbations based on early oxygen administration, use of beta-2 receptor blockers (salbutamol), corticosteroids and aminophylline.

Cardiac arrest in patients with severe asthma may occur as a result of:
1) hypoxia due to severe bronchospasm and airway obstruction by secretions;
2) arrhythmias due to hypoxia or beta receptor agonist and aminophylline toxicity;
3) tension pneumothorax.

Life-threatening asthmatic episode is recognized based on the absence of breath sounds, cyanosis and poor respiratory drive. It may be accompanied by bradycardia and hypotension. Patient appears exhausted, confused or falls into a coma. Arterial blood gas measurement reveals hypoxia, acidosis accompanied by normal or elevated carbon dioxide partial pressures.

Acute management

Patient status will quickly deteriorate, leading to respiratory arrest and secondary cardiac arrest if proper management is not immediately commenced. Such patient should be quickly moved to a facility where proper care and monitoring is available. High oxygen concentrations are administered. First-line therapy in acute asthma is inhalation of beta-2 agonists. It usually begins with administration of salbutamol (5 mg in 5 ml of saline) in nebulization mixed with oxygen, or in 4-6 puffs using an inhaler with a spacer. This dose can be repeated at 15-minute intervals or, if necessary, it can be administered continuously. Corticosteroid therapy should be commenced at an early stage (during first 30 minutes). Prednisolone at a dose of 30-60 mg orally, 200 mg of hydrocortisone i.v. or both drugs should be given if patient's condition is very severe.

If this treatment gives no effects, subcutaneous administration of adrenaline (0.3 mg) can prevent the necessity of artificial ventilation. The same dose of adrenaline (0.3 mg) can be repeated twice in 20-minute intervals.

If drugs administered so far are not effective, other actions are taken such as: inhalations with anticholinergic drugs (ipratropium 0.5 mg in nebulization), intravenous infusion of aminophylline (5 mg/kg infusion in 30-45 minutes), intravenous magnesium sulfate (2-3g) or administration of a breathing mixture containing helium and oxygen in a 70:30 ratio. Performing chest x-ray examination early is instrumental.

Such patients often suffer from substantial dehydration and intravenous infusion of fluids is beneficial.

Mechanical ventilation is only considered when all conservative methods fail. Decision regarding commencement of mechanical ventilation should be based on the degree of patient exhaustion, not on blood gas analysis. Noninvasive ventilation may prevent the necessity of tracheal intubation and invasive mechanical ventilation.

Achieving normal blood gas values during mechanical ventilation can be difficult due to high airway resistance. It is sometimes necessary to use special techniques of assisted ventilation with patient sedation (e.g. using anesthetic gases or ketamine).

Resuscitation

BLS and ALS rules apply during cardiac arrest. However, there are some additional requirements, which should be remembered: patient ventilation is sometimes difficult due to high airway resistance. Under such circumstances, ventilation with a facemask is associated with high risk of stomach distension. Therefore, it is important to perform tracheal intubation early. High airway pressures necessary to maintain proper minute ventilation increase the risk of tension pneumothorax. Prolonging inspiration and expiration time is often necessary in order to avoid increase in intrinsic end-expiratory pressure (i-PEEP or auto PEEP). Indirect cardiac massage is difficult or impossible in a patient with hyperinflated chest. Prolonging the expiration time may partially overcome this difficulty. If experienced personnel is present, opening of thoracic cavity for direct cardiac massage should be considered. Arrhythmias are treated according to standard therapeutic schemes.

Traumatic injuries

Cardiac arrest secondary to blunt trauma is associated with very poor prognosis. In cases of cardiac arrest after penetrating trauma, patient can be sometimes saved if conditions for undertaking therapy by personnel experienced in direct cardiac massage (with opening of thoracic cavity) are met.

Causes of cardiac arrest following trauma include:
1) severe brain injury,
2) hypovolemia due to massive blood loss,
3) hypoxia secondary to respiratory arrest,
4) direct injury to vital organs (heart or great vessels),
5) comorbidities (e.g. cardiac arrest in a driver, which preceded the traffic accident),
6) tension pneumothorax,
7) cardiac tamponade.

Resuscitation

Early assessment and commencement of appropriate actions can prevent cardiac arrest. It is important to identify and undertake appropriate management of life-threatening injuries as soon as they are diagnosed. Fast transport to a hospital is crucial, as immediate surgery is often necessary. Rules of BLS and ALS in trauma patients are the same as in cardiac arrest due to other causes. However, one should remember that: cervical spine should be protected during restoration of airway patency.

It is important to exclude the presence of tension pneumothorax. This complication may be indicated by worsening lung compliance or hyperresonant percussion sound. In such instance, pleural cavity should be immediately punctured with a needle (in the second intercostal space, in the midclavicular line).

Pulseless electrical activity (PEA) due to hypoxia, hypovolemia or both, constitutes the most common mechanism of cardiac arrest in trauma patients. Therefore, administration of 100% oxygen, replacement of circulating blood volume or attempt at stopping the hemorrhage (direct compression, surgery) are necessary.

Thoracic cavity can be opened in a small proportion of patients with penetrating chest trauma and PEA in order to commence direct cardiac massage and simultaneous management of cardiac tamponade and control of hemorrhage. Immediate and proper management of the discussed conditions can prevent occurrence of cardiac arrest. Resuscitation method may have to be modified if cardiac arrest takes place in special situations described above.

References:

1. R.G. Wilcox: How to cope with cardiac arrest. Żródło: http://www.libramed.com.pl/wpg/NumeryArchiwalne/05/04.html
2. Marzena Wojewódzka-Żelezniakowicz, Sławomir Lech Czaban, Piotr Szczesiul, Anna Nielepiec-Jałosińska, Jerzy Robert Ładny: Hipotermia poresuscytacyjna – wskazania, sposób prowadzenia, skuteczność kliniczna, powikłania stosowania, Postępy Nauk Medycznych, 12/2009
3. White L. Audit of cardiac arrest procedure and outcome. A thesis submitted in partial fulfilment of the requirements for the degree of Bachelor Medical Sciences, University of Nottingham Medical School 1992.
4. European Resusciation Council Working Party, Adult advanced cardiac life support: the European Resuscitation Council Guidelines 1992 (abridged). BMJ1993; 306: 1589
5. Niemann JT. Cardiopulmonary resuscitation. N Engl J Med. 1992; 327: 1075-1080.
6. Praca zbiorowa Anestezjologia i intensywna opieka, red. Laura Wołowicka, Danuta Dyk, Wydawnictwo Lekarskie PZWL, 2008.

Emergency medicine

Prevalence of atrial fibrillation in emergency medicine practice

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Summary:

Introduction: Atrial fibrillation is a condition of heterogeneous etiology and diverse clinical picture. It is a challenge for the system of Emergency Services.
Aim of the study: The aim of this study was to analyze selected epidemiological data of patients with atrial fibrillation treated at the Emergency Department of the M. Kopernik Provincial Specialist Hospital in Lodz between 01.2010 and 12.2010.
Material and methods: Study included 422 patients with atrial fibrillation (237 women and 185 men) aged 25 to 96 years (mean age — 73.51 years).
Results: Atrial fibrillation was more common in women than in men (56% vs. 44%). Mean age was higher in the female than the male population (76.5 vs. 69.3 years). The majority of medical interventions concerned patients aged 80-89 years.
Conclusions: In our material, atrial fibrillation involved mainly patients older than 70 years. Atrial fibrillation is more common in women than in men. Atrial fibrillation occurs most often during winter season, between 10 and 12 o'clock.

Key words: atrial fibrillation, seasonality, medical emergency response team.

Introduction

Despite considerable advancements in the diagnostics and treatment that took place in the recent few years, atrial fibrillation (AF) still poses a serious clinical and social problem [1]. It is the most common form of arrhythmia encountered by the Medical Emergency Response Teams [2].

According to the guidelines of European Society of Cardiology, atrial fibrillation is a type of arrhythmia that presents on an ECG as absolute rhythm irregularity, i.e. completely irregular RR intervals. Moreover, there are no discernible P waves on an ECG, atrial cycle length between the following atrial activations is variable and less than 200 ms, leading to hemodynamic disturbances [2, 3]. These changes often result from irregular and excessive ventricular rates as well as atrioventricular dyssynchrony.

Prevalence of AF in general population is estimated at 0.4-1.0% and increases with age, reaching 8% in people over 80 years old. Median age of patients with AF is about 75 years. Results of prospective studies indicate that yearly incidence of AF increases with age from less than 0.1% in people below 40 years old, to 1.5% in women and 2% in men above 80 years old [3].

Aim of the study

The goal of the study was to assess selected epidemiological parameters associated with atrial fibrillation among patients of hospital Emergency Department (ED).

Material and methods

In this study we retrospectively analyzed patients with atrial fibrillation treated at the Emergency Department of M. Kopernik Provincial Specialist Hospital between 01.01.2010 and 31.12.2010.

Analyses were conducted using Statistica v. 8.0 software. A t-student test, rank Wilcoxon test, chi-square match test, chi-square test for contingency tables and Cramer's V association coefficient were used for analysis. All tests were performed at a significance level α=0.05.

Results

In 2010, during the time of the study, 422 patients were treated for atrial fibrillation (AF) at the Emergency Department of the M. Kopernik Provincial Specialist Hospital.

Women constituted 52% of 422 patients with AF. Atrial fibrillation was noted in 185 men, which constituted 46% of the study group. Analysis revealed statistically significant influence of gender on the diagnosis of atrial fibrillation ($p<0.01$).

In the studied group patient age ranged from 25 to 96 years. The majority of AF cases occurred in the 80-89 age group (n=139; 33%), followed by the group aged 70-79 years (n=125; 30%). Patients aged less than 40 years comprised only 2% of the entire study group (n=6). There is a statistically significant difference in the ages of patients treated in EM due to atrial fibrillation ($p<0.001$) (Fig. 1).

Mean age of patients was 73.51 years (SD 12.65), mean age of women being 7 years higher (76.5 years) than that of men (69.3 years). The above results were statistically significant ($H=27.62940$; $p = 0.0000$). Figure 2 depicts mean ages of men and women in the studied group.

In order to illustrate the yearly cycle of atrial fibrillation occurrence, the study group was divided depending on the month of hospitalization (Fig. 3). Most cases of atrial fibrillation were noted in February (n=48; 11%), followed by October (n=39; 9%) and April (n=38; 9%). In August (n=29; 7%), July (n=30; 7%) and March (n=31; 7%) we observed a reduction in the number of diagnoses. Statistical analysis revealed significant differences in the incidence of atrial fibrillation episodes in a yearly cycle ($p<0.01$).

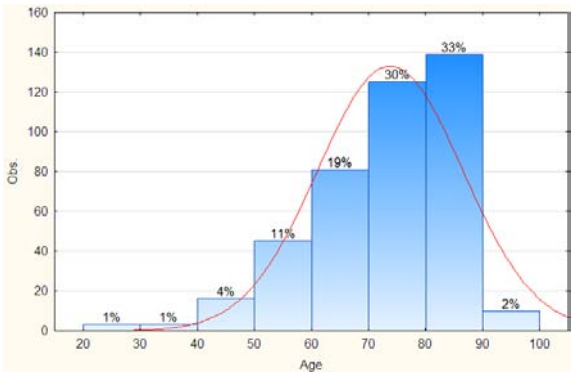

Figure 1: Patient ages in the studied group.

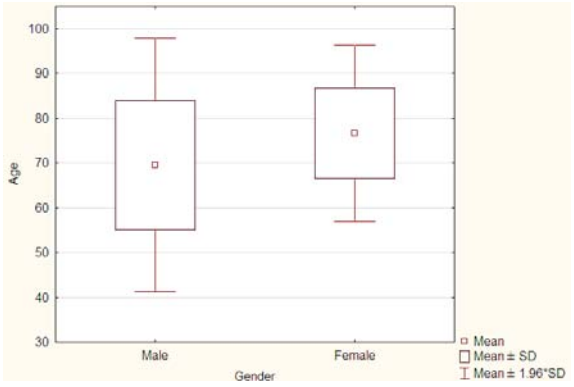

Figure 2: A box-and-whisker plot depicting mean ages of men and women in the studied group.

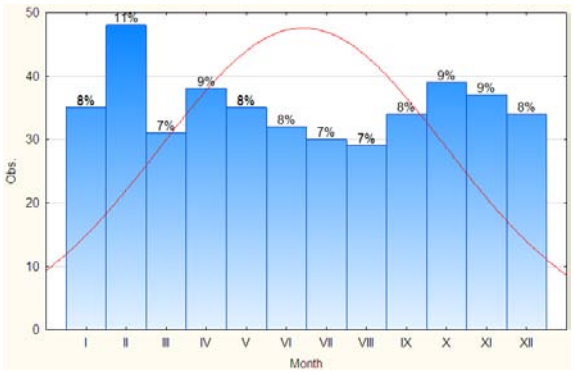

Figure 3: Incidence of atrial fibrillation in a yearly cycle.

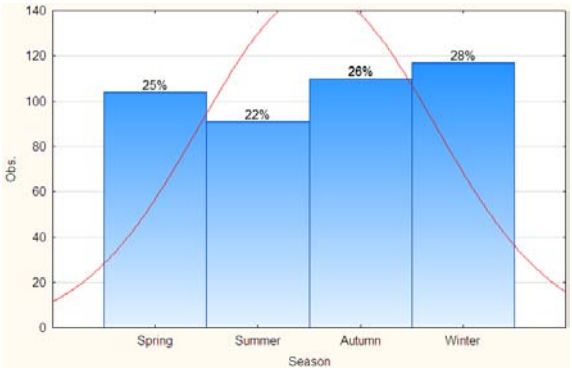

Figure 4: Prevalence of atrial fibrillation depending on the season.

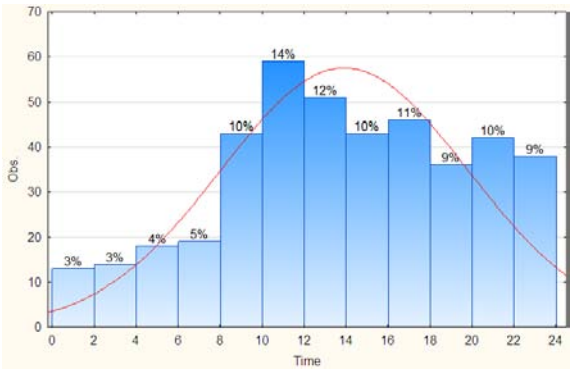

Figure 5: Daily cycle of atrial fibrillation episodes.

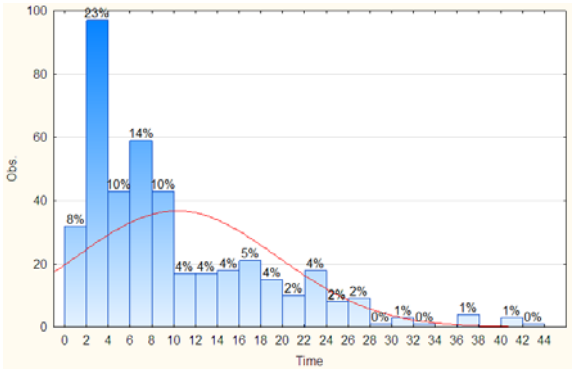

Figure 6: Length of patient stay at the Emergency Department [hours] .

Additional analysis was conducted on months grouped into seasons. Analysis revealed increased incidence of atrial fibrillation during winter (n=117; 28%), followed by autumn and spring (Fig. 4). During summer, we observed a reduction in the number of AF patients (n=91; 22%). The above results are also statistically significant (p<0.01).

Incidence of episodes of atrial fibrillation among ED patients was analyzed in relation to a daily cycle. The majority of admissions to ED occurred between 10:00 and 11:59 (n=59; 14%) as well as between 12:00 and 13:59 (n=51; 12%). There were only 27 cases noted between 0:00 and 3:59, which constituted 6% of all patients (Fig. 5). There is a statistically significant association between occurrence of AF episode and the time of day (p<0.001).

Pharmacological cardioversion was used in 265 cases to restore sinus rhythm. Effectiveness of this type of cardioversion was 33%. Electrical cardioversion was performed in 6 cases and it was effective in 66% of cases. Together, sinus rhythm was restored in 140 cases (33%) (p<0.001).

Mean length of stay at the ED was 10 hours (p=0.001). A detailed distribution of treatment and observation time of patients at the Emergency department is shown in Figure 6.

In case of most patients therapy at the hospital Emergency Department ended in discharge home (n=215; 51%). One hundred and eighty-one patients were admitted to a different ward and 19 patients were transported to a different hospital. In 7 cases treatment ended in death (Fig. 7) (p<0.001).

Discussion

Atrial fibrillation is the most common form of arrhythmia. The task of Medical Emergency Response Teams and hospital Emergency Departments is to quickly perform the initial diagnostics and stabilize vital functions of

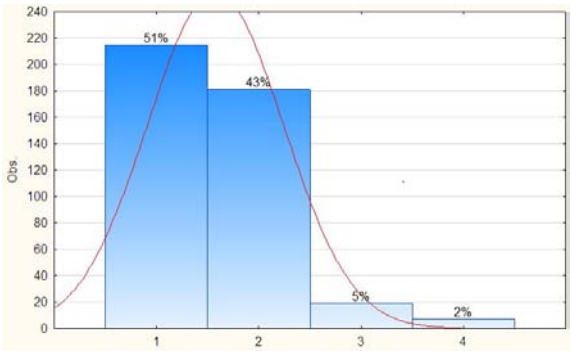

Figure 7: Incidence of atrial fibrillation in a yearly cycle.

Legend:
1 – discharge home.
2 – admission to a hospital ward.
3 – transfer to a different hospital.
4 – death.

patients in life-threatening or health-threatening conditions [7].

In the analyzed material atrial fibrillation was more common in women (56%). Other authors also noted the predominance of women among patients with atrial fibrillation, e.g. Gluszak *et al.* — 52% [8], Lubitz *et al.* — 54% [9], Mashal *et al.* — 55.3% [10] and Lengyel *et al.* — 70% [11]. Male predominance was shown in studies by, i.a. Olsson *et al.* — 56.5% [12] and Arribas-Leal *et al.* — 72% [3].

Studies conducted by the Gluszak research team showed that atrial fibrillation is most common in winter [8]. Our own observations corroborate this tendency. In this study, the highest incidence of atrial fibrillation was noted in February, and the lowest in March, July and August. On the other hand, Murphy *et al.* showed that atrial fibrillation episodes occur most often in December and are rarest in June [16].

The peak of admissions due to atrial fibrillation falls between 10:00 and 11:59. A statistically significant reduction in AF admissions was observed during early morning hours — between 0:00 and 3:59.

Electrical and pharmacological cardioversion was the reason for the return of sinus rhythm in 140 patients. In our study, effectiveness of electrical cardioversion reached 66% and was higher than that noted in the studies by Kanji *et al.* (27%) [17].

Conclusions

1) In our material, atrial fibrillation mainly concerned patients above 70 years old.

2) Atrial fibrillation is more common in women than in men.

3) Atrial fibrillation occurs more often during winter season and between 10 and 12 o'clock.

References:

1. Valderrama, A. L., S. B. Dunbar, and G. A. Mensah. "Atrial fibrillation: public health implications." Am.J.Prev.Med. 29.5 Suppl 1 (2005): 75-80.
2. Abarbanell, N. R., et al. "Prehospital management of rapid atrial fibrillation: recommendations for treatment protocols." Am.J.Emerg.Med. 19.1 (2001): 6-9.
3. Arribas-Leal, J. M., et al. "[Epidemiology and new predictors of atrial fibrillation after coronary surgery]." Rev.Esp.Cardiol. 60.8 (2007): 841-47.
4. Conen, D., S. Osswald, and C. M. Albert. "Epidemiology of atrial fibrillation." Swiss.Med.Wkly. 139.25-26 (2009): 346-52.
5. Friedlander, A. H., et al. "Atrial fibrillation: pathogenesis, medical-surgical management and dental implications." J.Am.Dent.Assoc. 140.2 (2009): 167-77.
6. Vinson, D. R., et al. "Managing Emergency Department Patients with Recent-onset Atrial Fibrillation." J.Emerg.Med. (2010): 45:51.
7. Ustawa z dnia 8 września 2006r o Państwowym Ratownictwie Medycznym (Dz.U. 2006 nr 191 poz. 1410).
8. Gluszak, A., et al. "Episodes of atrial fibrillation and meteorological conditions." Kardiol.Pol. 66.9 (2008): 958-63.
9. Lubitz, S. A., et al. "Association between familial atrial fibrillation and risk of new-onset atrial fibrillation." JAMA 304.20 (2010): 2263-69.
10. Mashal, A., A. Katz, and P. Shvartzman. "Atrial fibrillation: a primary care cross-sectional study." Isr. Med.Assoc.J. 13.11 (2011): 666-71.
11. Lengyel, M., et al. "[Use of anticoagulant therapy in non-valvular atrial fibrillation. Analysis of a Hungarian cohort]." Orv.Hetil. 145.10 (2004): 517-20.
12. Olsson, L. G., et al. "Trends in stroke incidence after hospitalization for atrial fibrillation in Sweden 1987 to 2006." Int.J.Cardiol. (2012): 23-27.
13. Watanabe, E., et al. "Seasonal variation in paroxysmal atrial fibrillation documented by 24-hour Holter electrocardiogram." Heart Rhythm. 4.1 (2007): 27-31.
14. Coulibaly, I., et al. "[Atrial fibrillation: epidemiological data from the Cardiology Institute in Abidjan, Cote d'Ivoire]." Med.Trop.(Mars.) 70.4 (2010): 371-74.
15. Schneider, A., et al. "Epidemiology and patient outcome after medical emergency team calls triggered by atrial fibrillation." Resuscitation 82.4 (2011): 410-14.
16. Murphy, N. F., et al. "Seasonal variation in morbidity and mortality related to atrial fibrillation." Int.J.Cardiol. 97.2 (2004): 283-88.
17. Kanji, S., et al. "Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients." J.Crit Care 27.3 (2012): 326-28..

History of medicine

Autopsy marks on anthropological material contributing to research on history of anatomy in Poland

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Summary:

In this publication on the development of anatomical studies in Poland we used anthropological (from archeological excavation sites in Poland) as well as written sources. Bone material found in our region bears signs of removal (sawing off) of the cranial vault. It is difficult to determine whether these autopsies were judicial or anatomopathological. Few of such skulls were examined, but there is data indicating that post-mortem examinations were commenced in the late middle Ages. They were probably not public, as such autopsies have been conducted in Poland since the 17th century. Doctors and barbers were undoubtedly curious what the human body holds. Anatomical textbooks from the middle Ages showed how to conduct an autopsy. Most skeletons with traces of post-mortem examination are dated to modern times, period of greatest development of surgery and anatomopathology itself. The need for anatomical studies for scientific as well as didactic purposes has been noted since renaissance.

Key words: anthropology, anatomopathology, anatomical studies, history of medicine, post-mortem examinations.

Human body, physique and functions of specific organs have been the subject of interest for doctors and philosophers since antiquity. Initially, in prehistoric times, people involved in therapeutics could acquire anatomical knowledge during management of companions' wounds and traumatic injuries. Such information can be also obtained from the corpses of hunted animals. By observing animal anatomy, the hunters concluded that a human must be built in a similar fashion [1].

In the ancient Egypt, internal organs were removed from the body using special tools during mummification. However, ancient Egyptians' knowledge on the location of organs in a human body was rather ritual and they did not take advantage of it during treatment. It was mainly supposed to preserve the body, so that the deceased Pharaoh or other official could use it after death [2].

Alcmaeon of Croton (4th century B.C.) stated, that philosophical considerations are not sufficient to understand anatomy and post-mortem examinations are necessary. He performed animal autopsies. Based on his observations, he came to a conclusion that all thoughts and impressions are formed in the brain.

Rapid development of anatomical studies occurred in the 3rd century B.C. in Alexandria, which became the focus of the scientific world in the ancient times. Autopsies as well as vivisections were conducted on convicts. Two famous

anatomists-doctors, Herophilus and Erasistratos, worked there.

In the Roman world, autopsies of human remains were prohibited due to ethnic and religious reasons. Anatomy known from the writings of Galen (a doctor, who lived in the 2nd century A.D.) is that of animals: pigs and apes.

In the Middle Ages, knowledge of anatomy was based on schematic pictures and writings by Hyppocrates and Galen. A papal or royal permission was required for performing an autopsy. A human being was considered a microcosmos — reflection of the surrounding macrocosmos [4].

Thanks to artists, painters and sculptors, interest in human physique increased during renaissance. In the history of medicine, the 16th century is known as a "century of anatomists." In 1543, Andreas Vesalius published his work: *De humani corporis fabrica libri septem*, where he pointed out two hundred of Galen's errors. This date is considered the border between medieval and modern anatomy. Vesalius' drawings portray the skeletal, cardiovascular systems and musculature, with the corpse depicted in a vertical position instead of lying down on the examination table [5].

At the turn of the 15th and 16th century the first anatomical theaters are created in Padua, Montpellier and Basil. They were particularly numerous in the 17th century.

In this publication, based on anthropological data (acquired from archeological excavation sites), we will try to demonstrate how anatomical studies developed in the region of Poland and when they were commenced. We will try to compare these data with written sources. Traces of post-mortem examinations found on the skulls and other parts of the skeleton prove that barbers and doctors were interested in how a human being is built.

Skulls found during archeological excavations with openings encompassing the entire or almost entire skull vaults are examples of probable post-mortem examinations. We possess several such skulls from Poland, but most of them are not precisely dated. It is difficult to unequivocally assess whether these autopsies were anatomopathological or judicial.

Names of the medics appear for the first time in the written sources from 13th century. There were 25 medics and physicians noted during that time. Wroclaw was the greatest medical center of the 13th century. There are several doctors from this city mentioned in the published documents. There were also doctors in Cracow, Legnica and Poznan. The number of qualified medics increased in the 14th century. Written sources list doctors in Cracow, Wroclaw, Glogow, Bytom, Gniezno, Wloclawek as well as in Pomerania. Physicians focused around princely and bishops' courts, as well as Jagiellonian University in the 15th century [6].

In the 14th century, the first post-mortem examinations were performed in Italy: Padua, Venice, Florence and in France: Montpellier. In renaissance, many artists, including Leonardo da Vinci, were interested in studies on human anatomy. His biographers report that he witnessed autopsies in the Santa Maria Novella hospital and perhaps performed some of them personally. He undertook the trouble to study all stages of human development, beginning with infancy and ending with senescence. He described the skeletal, cardiovascular, nervous systems and musculature [7].

According to the written sources, the first known public autopsy in Poland was performed in 1613 in a village called Pruszcz, located near Gdansk, on a deformed newborn baby. In the 16th century, a gymnasium in Gdansk was the only place where regular lectures on anatomy took place. In 1580, a separate chair of anatomy and medicine was formed in Gdansk [8]. The first autopsy was performed at the Jagiellonian University in Cracow by Rafal Jozef Czerwiakowski in 18th century [9]. Thus, written data indicate that post-mortem examinations were first performed in Poland at the turn of 17th and 18th century.

The first skull to be discussed was found in Opole, in a cemetery dated to the 14th century. Articles by prof. Adam Paluch describe it as a trepanation skull [10, 11]. However, it stands out between other trepanation skulls due to orifice dimensions and technique of its execution. This opening is particularly wide and was performed after death. The skull was found during excavations in the Opole Market Square and its features

indicate male sex of the deceased. Unfortunately, no postcranial skeleton was found [12].

A large bone fragment was removed posthumously from the skull: a fragment of coronal suture (coronal suture forms a border of the orifice, suture pattern is visible at the superior margin), part of the right parietal bone and a large fragment of left occipital bone, reaching all the way to the left temporal bone. Opening encompasses almost entire sagittal suture (a fragment of sagittal suture is visible as it joins with lambdoid suture) and has the following dimensions: 102x94mm (external lamina) and 95x84mm (internal lamina). Possibly, such large skull fragment was removed for bone amulets or a drinking goblet (such practice was known in the Middle Ages and previous eras). Thus, this procedure was performed after persons' death for magical reasons. In Middle Ages, bones of the dead and pieces of their clothing were often used for magical or therapeutic purposes. They were used for bewitchments. We can present an example of such procedure from Lithuania, where four female skulls (14th-16th century) were found with round orifices performed posthumously. Bone fragments serving as amulets were acquired this way [13]. There is a suspicion that in folk medicine, human skull grated into powder, served with food or drinks, was considered treatment for some aliments [14].

There is also another possible explanation. Such large opening was done in order to look inside the human head and curiosity was the reason for post-mortem examination. The margin of the orifice is uneven and jagged, particularly on the right side, while the inferior orifice margin is evenly filed off. Part of calvaria was probably removed using a saw (sharp and smooth) and the bone was broken at the coronal suture.

A canon from Opole, master Pawel, who served as a town physician in 1261, was mentioned in published documents [15]. Opole lies near Wroclaw, which in the Middle Ages was the focus of qualified physicians. The doctors acknowledged in written sources practiced in Cracow, Bytom and Glogow in the 14th century. Names of doctors who practiced in Silesia were also preserved: Tomasz — the titular Bishop of Serepta, Jan of Grodkow, Jan of Glogau. There were two centers of development of Polish medicine in the 14th-15th century – Cracow and Wroclaw [9].

The second skull in question (also containing a large opening) comes from the St. Nicholas Church in Torun. Skeletons found during archeological excavations are dated to 14th and 18th century. A large, oval fragment of calvaria, including a fragment of left and right parietal bones and posterior part of frontal bone were removed from a male skull. Body of the sternum was also cut with a sharp instrument, which may be an evidence of attempted removal of internal organs [16]. The person performing the autopsy was probably not very experienced in such maneuvers. Orifice margins are quite even, thus a sharp tool with a smooth blade was possibly used and tool marks are visible on the edges of the opening. Superior part of the skull (entire cranial vault) was sawn off, while the posterior portion of frontal bone lamina was broken off. In this case, the resected bone was found together with the skull and only the fragment of broken off frontal bone is lacking. The 15th century documents mention a doctor who practiced in the region of Torun. This autopsy may be also related to the activity of the Academic Gymnasium in Torun, which offered anatomy lectures. This facility was created in the 16th century, but its development falls on the period of 17th century.

Similar skulls from 16th and 18th century bearing traces of autopsies (the superior part of calvaria was also removed) were discovered at the excavation site in Holy Spirit in Brzesc Kujawski (Kujawsko-Pomorskie Province). There were a total of 5 such skulls excavated at cemeteries near the hospital and the church. An iron saw was probably used here to remove calvaria [17]. Functioning of the first hospital in Brzesc is dated to 13th-14th century. Medieval hospitals functioned mainly as shelters, taking care of the poor and ill travelers. With time, since renaissance, they gained increasingly more medical character.

Another skull, which is an example of post-mortem examination, was dug out from a cemetery in Dabrowna (Warmia and Mazury Province) dated to 14th-17th century. It belonged to an adult male. Calvaria was removed (part of frontal bone, large fragments of parietal bones, part of occipital bone) using a metal saw — the cut ran over the

supraorbital arches. Bones were not broken off in this case [18].

Three skeletons found in a cemetery in Sandomierz dated to the end of 18th and mid-19th century also wore the signs of post-mortem examinations, as indicated by the marks found on skulls – cut-off cranial vaults as well as rib cuts (thoracic cavity was opened in this fashion). The poor and the homeless who died in the hospital or in prison were buried in this cemetery [19]. In such cases autopsy could be performed in order to identify the cause of death (when it was difficult to determine it otherwise – such autopsies were judicial) or to train future doctors. These autopsies could be related to the activity of the provincial physician in Sandomierz or the Jagiellonian University.

Three skulls with removed calvarias were found during rescue works conducted in the cemetery in Wroclaw, which was used from the 2nd half to the end of 19th century. Due to poorly preserved material, it is difficult to draw more precise conclusions with regard to these remains [20]. Hospital care has been developing in Wroclaw since medieval times. In the 19th century, some of Wroclaw hospitals contained autopsy rooms [21, 22]. Anatomopathological studies developed particularly rapidly during this period. History of Faculty of Medicine in Wroclaw reaches the beginnings of 19th century; therefore these autopsies could be didactic in character.

Openings in the skulls collected in Torun, Brzesc Kujawski and Dabrowna are similar in shapes; similar autopsy techniques were used here with cranial vaults likely removed using a saw. Skulls found at the two latter sites have calvarias removed above the supraorbital arches. In case of the skull found in Opole, this procedure was conducted carelessly and the orifice is asymmetric. Skulls found in Torun and Dabrowna bear cutting marks at the bone edges, indicating little experience of the operator. Skulls from Opole and Torun bear signs of broken off bone fragments. Since there were hospitals in Brzesc Kujawski and Dabrowna, they could constitute sources of anatomical knowledge but it is also possible that these autopsies were judicial.

In the surgical school in Boulogne post-mortem examinations were conducted as early as in 13th century. Anatomy handbook by professor of medicine, Mondina de Luizzi (1270-1326) from Boulogne, became the fundamental literature used for teaching anatomy and autopsies were performed based on it. Mondina de Luizzi conducted the first autopsy in the presence of students in 1315 on the corpse of a woman condemned to death. His publication does not resemble modern anatomy handbooks, which describe specific organs. It is rather a guide to performing a post-mortem examination and gaining access to the organs of the abdomen, thoracic cavity and head [23]. One of the illustrations from a book "Anathomia" by Guido da Vigevano (1280-1349) from 1345 depicts a doctor performing an autopsy and opening the skull. He removes the skull vault by making an incision above supraorbital arches, through parietal bones and occipital bone. He uses a knife (perhaps a kind of chisel) and a hammer. He hits the end of the knife with a hammer in order to remove the superior portion of the skull [24]. Interestingly, the corpse is depicted in a vertical, not horizontal position (as in the later work by Vesalius). Six of eighteen illustrations from this handbook concern neuroanatomy. Frontal and sagittal sutures are shown on the skull; dura mater and brain are also revealed. Guido da Vigevano probably did not distinguish the arachnoid in his studies [23].

Such autopsy technique described in this handbook had to be widespread. Skulls from Torun, Dabrowno and Brzesc Kujawski bear signs of autopsies conducted in such manner, although the last incision ran throughout the entire had, from supraorbital arches, through parietal bones to the occiput. On the skulls from Opole and Torun, incisions were made along coronal suture or by the posterior part of frontal bone lamina and do not pass through occipital bone. This technique was also used in the skull from Opole, but symmetry was not preserved while cutting off the cranial vault.

It is worth noting that anthropological material bearing signs of autopsy was also found during excavations in other European countries. Material from England is most often dated to 18th and 19th century and comes from cemeteries located by shelters and hospitals for the poor as well as cemeteries located near medical schools. Bodies of criminals were often subjected to post-mortem examinations. Signs of autopsies were noted on

the skulls (removed calvaria), ribs, clavicles and vertebral bodies.

Bone marks indicate that autopsies were performed in order to establish the cause of death, but also served the purpose of educating future doctors. For example, limb amputations were practiced on cadavers. Autopsies were conducted on female, male cadavers, but also on bodies of children and fetuses. There is a lot of anthropological material from 18th and 19th century London showing that autopsies were frequent atthat time [25].

Italian anatomist, Giovanni Battista Morgagni (1682-1771) thought that it is a duty of a doctor to perform post-mortem examinations of his patients. He supposed that disease is localized in a particular organ [4].

Great development of anatomical studies occurred from the second half of 20th century, as indicated by anthropological excavation data as well as written sources. This fact is related to progress in the field of surgery and anatomopathology itself. General anesthesia and introduction of antiseptics and aseptics to operating rooms, improved hemostasis led the surgeons to broaden the range of procedures and advance deeper into human tissues. The significance of anatomopathological studies in clinical medicine was also emphasized. Doctors linked disease symptoms they saw in their patients with anatomopathological picture seen on an autopsy table. Therefore, post-mortem examinations were supposed to be a way to explain pathological changes. Karl von Rokitansky (1804-1878), a Czech who co-created the new Viennese school also known as anatomopathology school in the history of medicine, had great contributions to pathological anatomy [4, 26].

Modern medical textbooks pertaining to the issue of post-mortem examinations also describe cranial opening. Soft tissues should be first separated: skin, dense connective tissue layer, tendinous cap of the epicranial muscle, loose connective tissue layer and periosteum of calvaria. Incision runs about 2.5 cm above the superior margin of the orbit and posteriorly about 1 cm above the external occipital tuberosity. External lamina is cut with a saw and separated from the diploe using a chisel. External and internal lamina can be also simultaneously cut with an oscillation saw [27]. Therefore, in the medieval times soft tissues also had to be removed before uncovering the bone. Saws and chisels were used for cutting bones.

Autopsy techniques evolved together with the progress of medical sciences. Particularly the 19th century is related to development of post-mortem examinations. During that time, Rudolf Virchow (1821-1902) — the creator of cellular pathology — and previously mentioned Karl Rokitansky (1804-1878) exerted great influence on the examination technique [28].

Medical historians also use art for their studies. In the 17th century, many painters depicted doctors performing autopsies. The painting by Rembrandt "The Anatomy Lesson of Dr Joan Deyman" (1656) depicts a medic performing an autopsy of human brain using a scalpel. An assistant standing to the right of doctor Joan Deyman holds calvaria, removed (sawn-off) in order to uncover the brain. We find signs of such procedures in anthropological material. Unfortunately, only the middle portion of the painting remained, while three quarters of it was burnt in the anatomical theater fire [29, 30].

Osteologic data suggest that autopsies were commenced in Poland during late Middle Ages. They were not public. Material acquired from historical cemeteries indicates (we analyzed six archeological sites for the purpose of this publication) that sections were carried out earlier than suggested by written sources. However, development of anatomical studies in Poland as well as in other European countries falls on 18th and 19th century. Possibly, cadavers for the autopsy came from cemeteries by the hospitals and churches. First autopsies resulted from scientists' curiosity, need to search for the cause of the disease and death. Didactics played a smaller role.

At the turn of Middle Ages and renaissance as well as in renaissance, people began to realize the necessity of performing anatomical studies for educational purposes. Until 18th century, public autopsies excited emotions from both municipal and church officials and they usually involved convicts' bodies. Cadavers for anatomopathologic autopsies could come from warfare, they could belong to the homeless, prisoners

or victims of epidemics. However, acquiring cadavers for autopsies without school's approval was not easy.

Judicial autopsies were quite superficial. They were conducted by surgeons (with guild education) under supervision of medical doctors. Skulls bearing signs of autopsy from the region of Poland are dated from the 14th until 19th century, i.e. from Middle Ages until modern times. Anatomy and its teachings came a long way during that time. In the Middle Ages, people still based on the teachings of Galen. Beginning with renaissance, judicial as well as anatomopathological autopsies provided increasingly more knowledge on human physique.

References:

1. Gulczyński J, Iżycka-Świeszewska E, Grzybiak M. Short history of the Autopsy. Part I. From prehistory to the middle of the 16th century. Pol J Pathol. 2009; 3: 109-114.
2. Elhadi MA, Kalb S, Perez-Orribo L, Little SA, Spetzler FR, Preul CM. The journey of discovering skull base anatomy in ancient Egypt and the special influence of Alexandria. Neurosurg Focus. 33 (2); 2012: 1-13.
3. Debernardi A, Sala E, D'Aliberti G, Talamonti G, Franchini FA, Collice M. Alcmaeon of Croton. Neurosurgery. 2010; 66 (2): 247-252.
4. Brzeziński T. Historia medycyny. PZWL; Warszawa 1988.
5. Vesalius A. De humani corporis fabrica. Corvina/ Magyar Helikon; Budapest 1972.
6. Jankowski J. Historia medycyny średniowiecznej w Polsce. Człowiek, populacja, środowisko. Prace Dolnośląskiego Centrum Diagnostyki Medycznej Dolmed we Wrocławiu. Wrocław 1988.
7. Vallentin A. Leonardo da Vinci. Książka i Wiedza; Warszawa 1951.
8. Sokół S. Historia chirurgii w Polsce. Cz. 1. Chirurgia okresu cechowego. Wydawnictwo PAN; Wrocław 1967.
9. Seyda B. Dzieje medycyny w zarysie. Tom II. PZWL; Warszawa 1973.
10. Paluch A. Ślady występowania zabiegów trepanacyjnych na ziemiach Polski i Czechosłowacji w starożytności i średniowieczu. Archeologia Polski. 1975; 20: 411-454.
11. Paluch A. Trepanacja-zabieg leczniczy i magiczny. Z otchłani wieków. 1971; 37: 37-40.
12. Gawlik S. Zagadnienia trepanacji czaszek w populacjach pradziejowych z uwzględnieniem trepanowanej średniowiecznej czaszki z Opola. Maszynopis pracy magisterskiej. Uniwersytet Opolski. Zakład Biologii Komórki, Katedra Biologii Stosowanej i Eksperymentalnej. Promotor: prof. Adam Latała; Opole 2003.
13. Talko-Hryncewicz J . O trepanowanych czaszkach XIV-XVI w. z cmentarzyska w Łankiszkach pod Naczą na Litwie. Rozprawy Wydziału Mat-Przyrodniczego AU w Krakowie. 1918; LVIII:161-164.
14. Jaguś I. Lecznictwo ludowe w Królestwie Polskim na przełomie XIX i XX wieku. Kieleckie Towarzystwo Naukowe; Kielce 2002.
15. O zepsuciach w ogólności czyli z dziejów higieny i medycyny – informator z wystawy. Opole 1997.
16. Kozłowski T. Trepanowane czaszki ze zbiorów Zakładu Antropologii UMK w Toruniu. In: Rożnowski F, editor. Biologia populacji ludzkich współczesnych i pradziejowych; Słupsk 1992.
17. Kapica Z. Człowiek w regionie Brześcia Kujawskiego. Studium archeologiczno-antropologiczne. In: Głębowicz B, editor. Monografia Brześcia Kujawskiego; Włocławek 1970.
18. 18. Łuczak B, Lorkiewicz W. Świętosławski W. Przypadek sekcji pośmiertnej z cmentarzyska nowożytnego (XIV-XVII w.) w Dąbrównie. Zmienność biologiczna człowieka; 1995; 2:79-83.
19. Walewski P, Krzemińska A. Żywi i martwi. Co ma człowiek w środku? Polityka. 2004; 35: 72-74.
20. Guszpit P, Kitliński B, Kwiatkowska B, Roczek M. Wyniki ratowniczych badań archeologiczno-antropologicznych w związku z remontem i adaptacją nowej siedziby MPK Sp. Z o. o. przy ul. B. Prusa 75-79 we Wrocławiu; Wrocław 2006.
21. Słoń M. Szpitale średniowiecznego Wrocławia. Wydawnictwo Neriton; Warszawa 2000.
22. Wójtowicz M. Dawne szpitale Wrocławia. Muzeum Przemysłu i Kolejnictwa; Wrocław 2006.
23. Rengachary SS, Colen Ch, Dass K, Guthikonda M. Development of anatomic science in the late middle ages: the roles played by Mondino de Liuzzi and Guido da Vigevano. Neurosurgery, 2009; 65(4):787-794.
24. Lyons AS, Petrucelli RJ. Ilustrowana historia medycyny. Wydawnictwo Penta; Warszawa 1991.
25. Mitchell DP, Boston C, Chamberlain TA, Chaplin S, Chauhan V, Evans J, Fowler L, Powers N, Walker D,Webb H, Witkin A. The study of anatomy in England from 1700 to the early 20th century. J. Anat. 2011; 219: 91–99.
26. Prichard R. Selected Items From the History of Pathology. Am J Pathol. 1979; 97(2): 276.
27. Weber CJ. Sekcja zwłok. Podręcznik Shearera. PZWL; Warszawa 2000.
28. Skowronek R, Chowaniec Cz. Ewolucja techniki sekcyjnej – od Virchowa do Virtopsy®.Arch. Med. Sąd. Krym. 2010; LX: 48-54.
29. Cabane P. Rembrandt. Wydawnictwo Imbir; Warszawa 2010.
30. Salcman M. The Anatomy Lesson of Dr. Deyman, Rembrandt van Rijn. Neurosurgery. 1995; 36(4):865–866.

Emergency Medicine

Infusion solutions supply in critical circumstances and disasters

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Summary:

Proper supply of infusion fluids to appropriate destinations during critical situations and catastrophes depends on meeting the requirements of distribution and logistics. The need for central storage of fluid reserves and subsequent decentralization of medical supplies for immediate casualty management under extreme circumstances is directly related to appropriate quantitative and qualitative supply. Effectiveness of emergency rescue services and appropriate medical services depends on gathered fluid reserves, particularly blood products, which should be immediately delivered to the victims of catastrophe according to their needs. Created norms for the use of infusion fluids during mass events as well as their distribution should fulfill international standards and criteria developed for the rescue services.

Key words: infusion fluids — critical circumstances,disasters.

Standards of conduct and practice in critical circumstances and during catastrophes developed by appropriate military services and special emergency rescue services ensure effective supply of goods based on operating medical equipment that proves effective in all conditions. The system of supply of infusion fluids is based on the norms of consumption of blood replacement and blood-based products. It should fulfill the fundamental requirements for infusion into human circulation. Infusion fluids are administered in order to replenish the intravascular volume, e.g.: following a massive hemorrhage in a form of crystalloids and/or colloids (sterile aqueous solution of chemical substances devoid of pyrogens, non-toxic, iso – or hyperosmolar to blood plasma). Infusion fluids may be divided into crystalloids or colloids.

Crystalloids

Crystalloids are aqueous solutions, inexpensive to produce, easily available, free of allergens, containing mineral salts: sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium acetate or sodium lactate in proportions allowing for intravenous infusion in men. The most frequently used fluids are: normal saline [0.9% sodium chloride solution], multi-electrolyte solution [PWE], Ringer and lactated Ringer solution and a mixture of normal saline and 5% glucose solution [in 2:1 proportion].

Administration: for short-lasting replacement of plasma volume, as they quickly diffuse into the extravascular space following intravenous infusion.

Colloids

Colloids are aqueous solutions of multiparticle substances – usually glucose polymers or gelatin derivatives – their production is more expensive than crystalloids. Colloids may disrupt coagulation or cause allergic reactions [anaphylactic shock]. The most commonly used fluids include HES [hydroxyethyl starch, molecular weight of 45000], Voluven [6% and 10%] and Gelafusin – 3-5.5% solutions of synthetically modified gelatin with molecular weight of 25000-35000.

Use: to restore plasma volume deficiencies, as they are slower to diffuse into the tissues and fill the vascular bed well by maintaining osmotic pressure. Colloid osmotic pressure of dextran 70 is about 8.0 kPa and that of dextran 40 is about 23 kPa [it is 3.5-4 kPa in case of plasma]. A 3.5% dextran 70 solution and a 2.5% dextran 40 solution are isosmotic to plasma, while water binding capacity in the circulation amounts to 20-25 ml/g of dextran.

Oxygen-carrying products [so-called, true blood replacement products]

Oxygen-carrying products are compounds of recombined hemoglobin and perfluorocarbons [Fluosol DA], possessing the ability to bind oxygen and carry it to the tissues. As this preparation is non-toxic, its characteristics and clinical usefulness for life-saving purposes was tested on severely wounded soldiers with traumatic chest and lung injuries, accompanied by massive hemorrhages. They remain at a phase of clinical studies.

According to numerous publications based on experiences in critical circumstances, including mass catastrophes and results of warfare, provision of infusion fluids during hazardous times and in special situations should take into account the most common injuries.

Supply of infusion fluids encompasses three most important issues:

1) storage of large amounts of infusion fluids ready for immediate use and/or,
2) rapid initiation of fluid production in the absence of production in the existing factories that have storage capabilities in pharmaceutical warehouses,
3) logistics and organization of distribution points.

The most severe and most common traumatic injuries requiring administration of infusion fluids include massive hemorrhages and burns. Massive injuries constitute about 20% of cases, 25-35% of which require immediate filling of the vascular bed in order to maintain adequate intravascular pressure and restore proper tissue perfusion in the presence of progressing ischemia, as well as to secure renal filtration pressures.

Massive hemorrhage always requires administration of blood replacement fluids to fill the vascular bed and maintain systolic blood pressure of 85 mmHg until blood or plasma preparations may be given.

A safe reserve that should be secured for the casualties amounts to about 4.5 liters of fluid per person [blood and/or blood replacement fluids], including:

- 1-1.5 l of plasma/person,
- 0.5-1.0 l of full blood/person,
- 2-3 l of blood replacement fluids/person.

Experiences acquired to date indicate that, in case of mass injuries, provision of plasma products and blood constitute one of the largest problems. The amount of infusion fluid needed per person is the source of discrepancies in available literature. Blood replacement fluids constitute an alternative during life-threatening situations, critical circumstances and large-scale catastrophes, when we deal with signs of shock, including dehydration, hemorrhage with loss of <1000 ml of blood volume.

Supply of blood and blood products is always insufficient under life-threatening circumstances. Therefore, infusion fluids constitute fundamental measures of securing mass events. Predicted demand for infusion fluids in critical situations is about 5 mln liters for a period of 10 weeks, which should be secured by the national pharmaceutical industry. The time of storage for infusion fluids depends on the type and packaging, as well as

means of storage of strategic reserves for a period of 3-5 years.

The need for constant replenishing infusion fluids during critical situations may not be possible to accomplish. Therefore, it is strategically important to fulfill the following criteria:

1) The necessity to store infusion fluids – storage decentralization
2) Diversification of production and logistics as well as infusion fluid storage should be the decision of central crisis management supply and be available to all subordinate rescue services.
3) Provision of supply fluids is particularly important during mass bodily traumas caused by burns and radiation injuries. It increases to 100% compared with other injuries.
4) The most important and most relevant for clinical practice infusion fluids are the following solutions: dextrans, Ringer, lactated Ringer solutions, colloid solutions.
5) Coordination of actions and cooperation with countries possessing readily available reserves and/or production lines ready to replenish storage deficiencies within an integrated logistics network of NATO member countries.
6) Joint multinational strategic programs and missions for gaining practical experience, resulting in adequate supply and reaction time during critical situations and/or catastrophes.

References:

1. Hołyński J, Hołyński J: Organizacja zaopatrzenia medycznego w medycynie ratunkowej i katastrof, Łódź, 2000,T.CCXL.
2. Mosiniak T: Medycyna katastrof-system zapatrywania w płyny infuzyjne i leki. Biuletyn WAM, 1993; 1.
3. Holm C: Resuscitation in shock associated with Burns. Tradition or evidence-based medicine? Resuscitation, 2000; 44(3): 157–64.
4. Czermak C I wsp: Burn shock fluid resuscitation and hemodynamic monitoring. Chirurg, 2004l 75(6): 599–604.
5. Hemington-Gorse SJ: Colloid or crystalloid for resuscitation of major burns. J. Wound Care, 2005; 14(6): 256–58.

Emergency medicine

Scope of knowledge regarding administration ofoxygen therapy among firefighter rescue teams from Volunteer Fire Departments (OSP)

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Summary:

Introduction. A fire brigade is often the first rescue service at the scene of an accident. Until arrival of emergency medical services securing casualties, including oxygen supplementation to those who require it, remains the responsibility of firefighters.
Aim of the study. To evaluate the knowledge regarding administration of oxygen therapy to accident victims among firefighter rescue teams.
Material and methods. The study was conducted in 2011 and included 100 firefighters working in Volunteer Fire Departments in the area of mazovian and lodzkie provinces. We used questionnaires and statistical methods.
Results. Almost 60% of respondents knew when to use the oropharyngeal tube. As much as 61% were able to indicate that a passive oxygen therapy set is included in a PSP R1 kit. Knowledge on the following issues was inadequate: time designated to assessment of patient's respiratory rate (43%), definition of saturation (30%), causes of unreliable pulse oximetry results (25%), proper adult ventilation volume using a self-inflating ambu bag (15).
Conclusions. Due to the specific nature of firefighter rescue teams' work, evaluation of knowledge on principles of oxygen therapy is justified, as it may influence patient survival. Knowledge of firefighter rescue teams on patient oxygen supplementation is inadequate.

Key words: firefighter, medical response, oxygen, casualty, knowledge.

Introduction

Fire Department is unquestionably the leading rescue service in Poland. Authors' own experience shows that, in some situations, State or Volunteer Fire Department teams arrive at the scene of the event before medical emergency response teams. We have to realize that every minute of delay in providing aid, even at a basic level, to the victim reduces the chances of recovery [1, 2]. Firefighter rescue teams, due to the actions they perform, are trained in providing first aid. Training programs also include principles of administering oxygen therapy to the patients who need it [3]. Supplementation of oxygen via nasal cannula and assisted breathing using a self-inflating (resuscitation) ambu bag are only some of the major methods

of administrating oxygen therapy by firefighter teams.

Figure 1: Self-inflating ambu bag with reservoir.

Unfortunately, literature lacks scientific reports on the problem of education of firefighter rescue teams on application of oxygen therapy to accident casualties. Therefore, it seems important to conduct research on the level of knowledge regarding oxygen supplementation among fire department rescue teams.

Aim of the study

The goal was to assess the level of education on oxygen therapy administration to accident victims among firefighter rescue teams working in Voluntary Fire Departments.

Material and methods

Study included a group of 100 people working in Volunteer Fire Departments in the region of mazovian and lodzkie provinces. Our research tool consisted of author's self-prepared questionnaire, which included 15 questions evaluating the level of knowledge of oxygen therapy among firefighter rescue teams working in Volunteer Fire Departments. The study was conducted in the fourth quarter of 2011.

Research data were encoded in Excel and compiled using statistical software STATISTICA 8.0. Normality of distribution of variables was tested using significance level indicated by p-value for Kolmogorov-Smirnov test. In case of normal distribution we used a t-student test to analyze mean differences. Results were considered statistically significant for p-value < 0.05.

Results

Men predominated among 100 of questioned subjects. They constituted 85% of cases (n=85). Fifteen percent of respondents were women (n=15; p<0.001). Mean age in the study group was 28.43 ± 5.53 years. There were 40 people aged 20-24 years, 42 subjects in the 25-29 age group, 11 respondents were aged 30-34 years, 4 were between 35 and 39 years old and there were 3 persons in the 45-49 age group. There were no respondents 40-44 years of age.

Figure 2 presents how firefighter rescue teams self-evaluated their level of knowledge of oxygen therapy. In this question, respondents were supposed to assess the level of knowledge of oxygen therapy using a five-point scale, where „1" indicated no knowledge and „5" meant excellent knowledge.

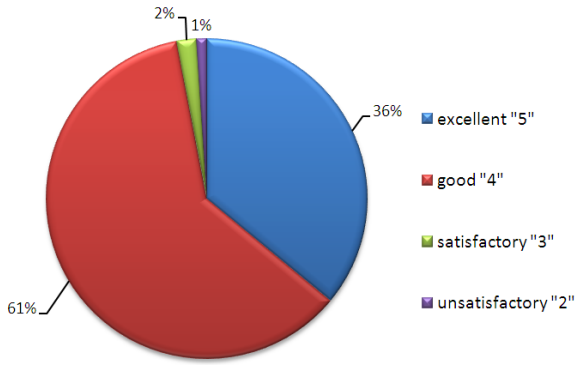

Figure 2: Self-evaluation of knowledge regarding oxygen therapy performed by firefighter rescue teams.

Level of knowledge, according to self-evaluation, was high and the score amounted to 4.32 ± 0.56 pts. As many as 36 of questioned respondents considered their knowledge excellent and 61 evaluated it as good, 2 as satisfactory and 1 person rated it unsatisfactory. No one chose an answer „1", which indicated lack of knowledge. There was a great disparity between self-assessed knowledge and the results of the objective evaluation test (Fig. 2).

Figure 2 presents a comparison of good and wrong answers on a test expressed in percentages. Only 35% of all answers were correct.

Question 1. In the first question respondents were asked to indicate the values of oxygen concentration that can be achieved through a face mask

with reservoir. Only 35% of respondents pointed to the correct answer – „100%".

Question 2. This question inquired what kind of oxygen therapy is provided through nasal cannulas. In this case, nearly a half of respondents (46%) gave correct answers by indicating passive oxygen therapy.

Question 3. This question asked respondents to point to indications for oxygen therapy. Of all respondents, 32 persons were able to choose correct indications for administration of oxygen therapy to patients during a rescue operation.

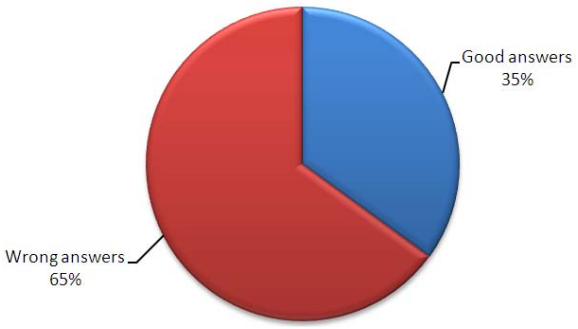

Figure 3: . Assessment of knowledge regarding oxygen therapy among firefighter rescue teams

Question 4. In this question respondents were supposed to answer by what percentage the concentration of oxygen in the breathing mixture raises for every 1 l/min of increased oxygen flow through nasal cannulas. Only 11% of all respondents gave correct answers ($p<0.001$).

Question 5. Firefighter rescue teams were asked to identify which emergency kit includes a passive oxygen therapy set. Sixty-one percent correctly indicated the PSP R1 kit. Distribution of provided answers is presented in Figure 3.

Question 6. In the entire studied group 52% of respondents were not able to tell the distance used for fitting of the oropharyngeal tube. The correct answer „the distance from incisors to the angle of jaw" was indicated by only 48% of subjects.

Question 7. This question was also related to the use of oropharyngeal tube. The respondent was asked to indicate the state, in which this instrument may be applied for restoring airway patency. Subjects could choose from the following answers: „confused patient," „somnolent patient" and „ deeply unconscious patient." The majority of respondents, as much as 59%, answered correctly that oropharyngeal tube should be only used in case of deeply unconscious patients.

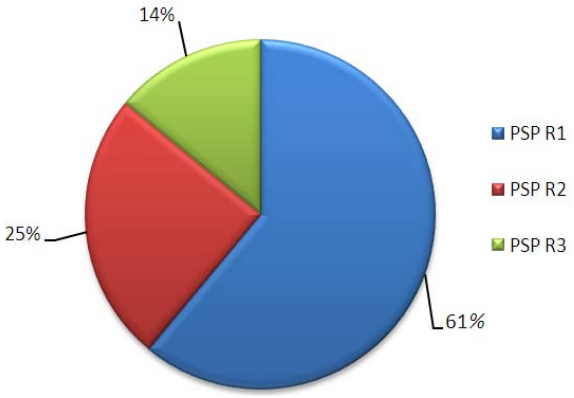

Figure 4: Answers provided by respondents to question 5.

Question 8. From all available answers („using suction to aspirate fluid content from oral cavity," „passive oxygen therapy," and „inserting an oropharyngeal tube") participants were to point to the action, which is not a part of the procedure of establishing airway patency. Forty-three subjects correctly indicated „passive oxygen therapy," while 57 people gave wrong answers ($p<0.001$).

Question 9. This question was designed to test respondent's knowledge of the use of a self-inflating ambu bag. The respondent was supposed to identify an incorrect statement regarding an ambu bag. Correct answer – „a self-inflating ambu bag allows for achieving maximum oxygen concentrations of 75%" – was given by 46% of respondents.

Answer 10. Similar to the previous question, this one was related to the use of self-inflating ambu bag. Respondents were supposed to indicate the proper ambu bag ventilation volume in an adult. The correct answer was 500-700 ml and it was given by only 15% of respondents ($p<0.001$).

Question 11. Cardiopulmonary resuscitation is one of the most stress-inducing experiences a firefighter may come in contact with. In this question, the respondent was to indicate the time required for assessment of patient's breathing according to current guidelines. Thirty-nine subjects answered correctly „10 seconds" ($p<0.001$).

Question 12. In the twelfth question we asked respondents about the meaning of the term „saturation." Only 30% of them were able to identify saturation as blood oxygen concentration. As much as 70% of subjects gave wrong answers. A detailed distribution of answers given by respondents is depicted in Figure 4.

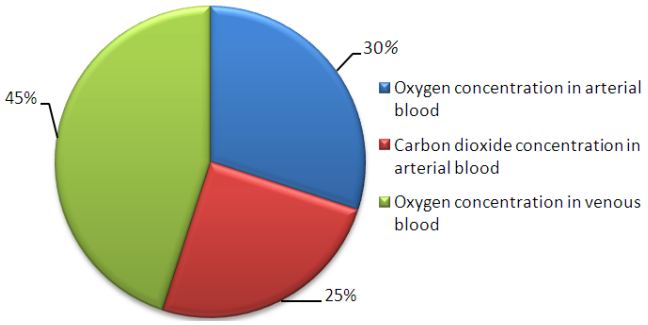

Figure 5: .Answers provided by respondents to question 12.

Question 13. This question also referred to assessment of saturation level. Among the provided answers („carbon monoxide poisoning," "cyanide poisoning," „hyperthermia") respondents were to choose the state, in which saturation measurement would be unreliable. Only 25% gave a correct answer, while 75 people responded incorrectly.

Discussion

Oxygen, an element necessary for human existence, is also used as a drug [4, 5, 6]. Just like in any other case of drug administration, supplementation of oxygen should be given according to indications and with careful dosing. For that purpose firefighter rescue teams, who are often the ones to administer first aid to victims before arrival of medical emergency services, undergo first aid training. First aid course, which lasts 66 hours (involving 25 hours of theory and 41 hours of practical training), includes issues related to supplementation of oxygen therapy to casualties [3].

Unfortunately, there are no reports in the literature on the problem of knowledge regarding principles of oxygen therapy among firefighter rescue teams. Therefore, it is not possible to compare our results to those obtained by other authors.

The level of self-confidence among firefighters from the studied group was high and amounted to 4.32 points. There was a great disparity between their self-evaluated knowledge and test results, as evidenced by a 61% rate of incorrect answers given by respondents. At this point, it is safe to say that members of firefighter rescue teams overstate their knowledge of oxygen therapy administration.

At the scene of rescue operation firefighter rescue teams may administer oxygen therapy to the patient according to first aid procedures. Oxygen therapy may be divided into passive and active types [7]. In passive therapy oxygen is inhaled due to patient's preserved ventilatory function, while in case of active oxygen therapy forced ventilation (replacement breathing) is used [7, 8]. In our material, only 46% of respondents knew the difference between methods of passive and active oxygen therapy, as demonstrated by indicating patient ventilation via nasal cannulas as an element of passive oxygen therapy.

Symptoms of hypoxia include: skin cyanosis (if deoxygenated hemoglobin concentration falls below 5 g/l) [4, 8]. Moreover, we may observe excessive respiratory muscle work, which is a sign of dyspnea. In case of central nervous system hypoxia patient may be restless or aggravated. Severe hypoxia may be associated with loss of consciousness. The simplest, non-invasive method of evaluating the level of blood oxygen saturation at the site of rescue operation is pulse oximetry. Only 30% of respondents in our study group possessed the knowledge that saturation is a measure of oxygen content in arterial blood.

Despite pulse oximetry being a routinely used method of saturation measurement, in some situations this measurement may be unreliable (erroneous). An example of such situation is carbon monoxide poisoning. As carbon monoxide has almost 250-fold greater affinity to hemoglobin than oxygen, bonds created as a result of coupling of hemoglobin with carbon monoxide and carboxyhemoglobin formation are extremely strong. It leads to tissue hypoxia. In the above situation, pulse oximeter may show normal values despite the true level of arterial blood oxygenation being significantly lower. Carbon monoxide poisoning is dangerous, as the most susceptible organs such as the cardiovascular system and central nervous system are damaged first. In severe carbon

monoxide poisoning therapy in a hyperbaric chamber is the treatment of choice [9]. From our study group, 25% of subjects were familiar with situations, in which pulse oximetry could be unreliable. Due to the possibility of airway obstruction, manual methods of establishing airway patency applied first and followed by instrumental methods, firefighter rescue teams should possess the knowledge of oropharyngeal tube insertion. Guedel tube is supposed to prevent tongue slipping toward the posterior pharyngeal wall and causing airway obstruction. A tube that is either too large or too small may cause obstruction; hence it is important to know how to choose a proper one. Size of the tube should be fitted to each particular patient by placing the tube against patient's cheek. Tube collar (at the inlet) should be located near the incisors, while its end should reach mandibular angle. A tube fitted in such manner ensures airway patency, but dos not prevent from regurgitation – passive movement of stomach contents into the esophagus without a gag reflex – or from vomiting. Fifty-two percent of respondents knew how to appropriately fit an oropharyngeal tube. A rescue worker should remember that oropharyngeal tube should only be used in deeply unconscious victims. Most of the surveyed firefighters were familiar with this principle, as much as 59% answered correctly.

Conclusions

Due to the character of firefighter rescue teams' work, it is justified to examine the knowledge regarding administration of oxygen therapy among firefighters, as it may influence patient survival.

Knowledge of oxygen therapy among firefighters is inadequate.

References:

1. Szarpak, Ł. "Zintegrowany system ratownictwa elementem bezpieczeństwa państwa", [w:] „Katastrofy naturalne i cywilizacyjne. Dylematy współczesnego bezpieczeństwa", Wyższa Szkoła Oficerska Wojsk Lądowych im. gen. T. Kościuszki, Wrocław 2011, s.127-138.
2. Ziemba R. "Criteria of procedures in life-threatening states". Military pharmacy and medicine 2012, 5(2): 62-68.
3. Rozporządzenie Ministra Spraw Wewnętrznych oraz Ministra Obrony Narodowej z dnia 23 grudnia 2011 r. zmieniające rozporządzenie w sprawie szkoleń w zakresie kwalifikowanej pierwszej pomocy (Dz.U. 2011 nr 299 poz. 1778).
4. Powrie, K. and S. M. Smith. "Editorial: Emergency oxygen for adults guideline--a change in oxygen therapy practice?" J.Clin.Nurs. 19.5-6 (2010): 601-02.
5. O'Driscoll, R. "A breath of fresh air: a new UK guideline for emergency oxygen therapy." Br.J.Hosp. Med.(Lond) 69.12 (2008): 670-71.
6. Ziemba R (ed): ABC Ratownika – pierwsza pomoc w nagłych, IndexCopernicus, 2011, pp. 55.
7. Austin, M. and R. Wood-Baker. "Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease." Cochrane. Database.Syst.Rev.3 (2006): CD005534.
8. Small, G. and P. Barsby. "How much is enough? Emergency oxygen therapy with COPD." Emerg.Nurse 8.8 (2000): 20-24.
9. Van, Meter K. "Hyperbaric Oxygen Therapy as an Adjunct to Pre-hospital Advanced Trauma Life Support." Surg.Technol.Int. XXI (2011): 61-73.

Emergency Medicine

Sustainable development in light of international cooperation

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Summary:

Numerous developed countries as well as those entering this path have established strategies of sustainable development. Areas of activity presented in this work illustrate the wide scope of parameters and challenges for maintaining sustainable development, both on a local as well as global scale.

Key words: hsustainable development, European Union directive, areas of action, eliminating the effects of environmental pollution, Rio declaration.

Balanced development – scope of the concept

Sustainable development is defined as a broadly understood social goal, encompassing balanced environmental quality accompanied by achievement of social and economical goals. The term "sustainable" may be defined as maintaining environmental capacity in time. It also encompasses aspects such as: availability of natural resources, waste assimilation, cultural values, heritage values, climate stability and maintaining biodiversity. Such environmental capacity may be measured using environmental indexes such as: size of protected areas, size of ecosystems, number of species, level of pollution and size of resources, particularly with regard to irreplaceable materials.

This term is a result of previously mentioned report created by the former Norwegian prime minister, current director of World Health Organization, Gro Harlem Brundtland, titled "Our common future." The English term "Sustainable development" was used there. Finding an analogous Polish expression that would properly reflect the sense of words contained in the mentioned document was somewhat troublesome. Following numerous discussions, we translated these words as: "trwały i zrównoważony rozwój" (steady and balanced development), although there are some in favor of "ekorozwój" (ecodevelopment) or "trwały rozwój" (steady progress).

A concept of "balanced development" as a shorter version of the previous expression also appears in various documents and reports. This general concept lies at the foundations of environmental politics of many countries. However, some scientific uncertainty and diverse opinions indicate, that there is still a problem concerning the value of environmental capacity. However, there are indexes, which may prove as useful operative instruments for comparison with policy goals and environmental standards, both domestic and international.

Strategic environmental evaluation is an instrument for comparison of analyzed plans and

programs with environmental politics and strategies on a national level.

Special value of such evaluation is increasingly more often recognized among European countries. As an example, the goal of European Union directive on strategic environmental evaluation was to ensure proper level of assessment at a stage of strategic decisions in all member countries. This project is considered a step toward ensuring balanced development and therefore, means of achieving goals of the European Union Fifth Environmental Action Program: "Towards Sustainability."

It is an effect of the accepted Rio Declaration on "Environment and Development" and, above all, Agenda 21 on actions undertaken at the turn of the 20th and 21st century in order to ensure sustainable development. It is supposed to optimally balance the current status with the assumed, undertaken for the future. Therefore, strategic evaluation is considered an instrument allowing for inclusion of environmental aspects and sustainable development into the mainstream decision-making processes regarding development. As opposed to individual projects, strategic evaluation method is directed toward programs at early stages of planning. Such approach provides substantial benefits in terms of strategic evaluation of the program at an early stage of its development. Conditions necessary for balancing the development goals (particularly regarding the environment) are analyzed as an element of strategic evaluation.

Many developed countries, as well as those entering this path, have strategies of sustainable development already behind them in terms of their planning as well as describing specific dimensions of their environmental policies.

At a political level, goal descriptions are least detailed. Therefore, strategic evaluations are performed at the same level. They concentrate mainly around the analysis of political goals, and their environmental cohesion. In the sustainable development document, it signifies ensuring consistency with the goals of international and global policies expressed through agreements, conventions and other documents.

Why then, are strategic evaluations so important? They include aspects of sustainable growth into internal decision-making processes. Sustainable growth is directed at fulfilling the needs of a contemporary man in such manner that would not prevent the future generations from utilizing environmental resources. This requirement results in the necessity of maintaining balance between goals and environmental, economical and social criteria.

Effects analyzed as a part of strategic evaluation may be divided into four groups:

- traditional environmental factors, such as ecological effects, quality of water and soil, quality of the air, noise levels, landscape, consequences for the population – analyzed with regard to their international, domestic and regional significance;
- outcomes associated with imposing balance, which encompass the threat o irreversible, cumulative or secondary effects such as: exploitation of non-renewable resources, loss of biodiversity, valuable natural ecosystems, as well as long-term productivity of forests or rural areas;
- induced changes in use of the land, particularly in relation to urbanization and expansion of municipal peripheries;
- political effects of breaching international agreements and other domestic policies.

Assessment of significance (or importance) of predicted effects is a key element of strategic environmental assessment process. However, up to date, no index was agreed upon, which would measure the degree of attained sustainable progress, encompassing various indexes and determining how a given factor should be weighted against other ones. Sustainable balance does not only determine beneficial effects. They may be unfavorable or, at the least, of little benefit. All of those effects should be considered through an advanced grading system, even more so when various factors undergo evaluation. Evaluation criteria must be established for selected problems in order to determine the significance of predicted outcomes.

At a strategic level, it is indicated to assess the risk of occurrence of significant outcomes (benefits, losses, conflicts) instead of making prognoses, which in turn should be performed at a

level of evaluation of a particular investment. For example, it concerns the risk of effects leading to secondary enterprises or conflicts with various development plans. In this context, the risk of occurrence of outcomes derived from secondary projects was defined as a product of probability of effect occurrence and intensity of this effect.

While determining the outcome risk, the following aspects should be taken into consideration:
- environmental absorption capacity or sensitivity;
- the scale or extent of the effect, e.g. the degree to which environmental quality may be disrupted;
- will the effects lead to sustained or temporary changes?;
- domestic or international obligations, goals and environmental quality standards,
- to what degree is reduction of the effects possible?;
- significance of the effect on a national level;
- Strategic evaluations allow for inclusion of environmental considerations at a possibly earliest stage of planning, as in the case of social and economical aspects.

Principle no. 4 of the preamble "Environment and Development" states the following: "In order to achieve sustainable development, environmental protection shall constitute an integral part of the development process and cannot be considered in isolation from it." Principle no. 8 strengthens those ideas, particularly in the fragment pertaining to the necessity to "reduce and eliminate unsustainable patterns of production and consumption" by some countries. Economical instruments are vital to realization of those goals (Principle no. 16), according to the principle: "the polluter should, in principle, bear the cost of pollution, with due regard to the public interest and without distorting international trade and investment."

Areas of action for sustainable development

In order to face the challenges of the environment and growth, cosignatory nations decided on a new form of universal cooperation. It compels them to get involved in constant and constructive international dialogue inspired by the necessity of establishing more effective and just world economy, taking into consideration the growing co-dependence of societies and the fact that sustainable development should be a priority for those societies. Conference's "Documents" state that: "in order to achieve this new cooperation, it is important to avoid confrontation and create an atmosphere of true cooperation and unity…" (5). In this mission, particular emphasis is put on strengthening of internal and international policy and establishing multidirectional cooperation adjusted to new conditions.

National economical policies and international economic relations are associated with sustainable development. It should be noted that, in this regard, its reactivation and acceleration requires both a dynamic international supportive action, as well as decisive national policy. Both of those factors should act in parallel. A dynamic and stable world economy based on safe foundations gives a chance for progress. Therefore, support of international economic circle is a determining factor.

The role of developing countries, free of excessive external debt is noted in this process. Therefore, financial policy must serve it, without restriction of access to other markets.

Data obtained in the 80's regarding this aspect are fundamentally negative in all cases. Therefore, a change of this state is encouraged. For that purpose, an international atmosphere supportive toward national efforts for growth should be built up. It is the only requirement for healthy internal economic policies of developed and developing countries toward achieving global progress in the area of sustainable development.

Accordingly, global economy should create an atmosphere promoting achievement of goals stated in Agenda 21 regarding environmental protection and development through:
- promotion of sustainable growth as a result of trade liberalization;
- mutual dependence of trade and environmental protection;
- ensuring proper funds for developing countries and taking care of international debts;
- support for macroeconomic enterprises toward environmental protection and development.

National efforts must be directed toward mutual dependence of the elements of international economical system and needs of humanity in the field of safe and stable natural environment. Therefore, it remains their intention to establish agreement at the tangent points in areas such as: environmental protection, trade and development and took place during meetings of existing international organizations as well as in their individual internal policies. An optimal, just, safe, non-discriminatory and far-sighted, multilateral trading system concordant with sustainable development may lead to optimal distribution of global production. It is in the interest of all participating partners, but providing developing countries with access to the world market and export, together with healthy macroeconomic and ecologic policy, will exert positive influence on environmental protection.

Thus, it will contribute to the field of sustainable development. Healthy economic policy and management, effective and far-sighted public administration, consideration of environmental problems during a decision-making process as well as progress-oriented and democratic government also act in its favor. It allows for participation in economic management of all involved parties under specific conditions of individual countries. Removal of the existing anomalies in international trade is of great significance here, as it allows the developing countries to access funds needed for financing investments necessary for ensuring sustainable development. Therefore, significant and progressive increase of preferences for agriculture (including internal regulations, access to the market and export subsidies), industry and other economical sectors seems necessary for prevention of large losses generated by more efficient producers, particularly in the developing countries, when different preferences are used. Therefore, there is a place in agriculture, industry and other branches of economy for initiatives for trade liberalization and creation of an economic policy, in which production would be more closely related to the needs of environmental protection and development. Liberalization of trade should be considered on a global scale, so that particular sectors of the economy could contribute toward achieving sustainable development.

International trade, influenced by various factors creating new areas of activity as well as new possibilities in this domain, determined an even greater significance of international economic cooperation. In the past few years, world trade developed faster than world production. However, it should be noted that the expansion of world trade was unevenly distributed and only a small number of developing countries was able to achieve a perceptible increase in export. Pressures from the protectionists and unilateral economic policy restrain functioning of open, multilateral trade system, exerting a negative influence, particularly on the export of the developing countries. It should be noted in this regard, that economic integration intensified during the past few years, which should boost the world trade and increase the trading as well as growth capabilities of developing countries. Also, a great number of those countries introduced bold reform policies, including ambitious, autonomic trade liberalization during the past several years. Simultaneously, far fetched reforms and deep restructuration processes taking place in Central and Eastern European countries, pave their way to integration with the world market and international trade. Growing attention is directed at increasing the role of enterprise in economy and promotion of competition. Generalized System of Preferences (GSP) turned out to be a useful instrument of economic policy despite the fact that its goals were not entirely fulfilled and a system of trade facilitation based on electronic data interchange (EDI) increased the commercial effectiveness of public and private sectors. Solutions between environmental protection and forms of trade are diverse and were not specified to date.

Rapid implementation of various agreements of the Uruguay Round regarding multilateral trade negotiations will result in further liberalization and expansion of global trade. It will augment trading and growth capabilities of the countries entering the path toward development and ensure greater security and farsightedness of international trade.

Goals, recommendations and feasibility were determined in light of the described areas of action. It also included mutual dependence of trade and environmental protection, support for economic actions promoting sustainable growth.

Another area of action that could contribute to the safety of long-term progress is the fight against poverty. It may be divided into the following sections:
- providing the poor with sustainable access to the means of supporting their basic needs;
- facilitating integration of sustainable access to the means of support with environmental protection.

Changing the consumption model, which is a broad topic and its problems are mentioned in numerous chapters of Agenda 21, serves those areas. They are primarily located in the chapters related to the use of energy, transport, waste as well as economic instruments and transfer of technologies. The areas of action include the following:
- balancing the models of consumption and production,
- undertaking appropriate policies and economic strategies by individual countries in order to eliminate the imbalanced consumption models. The goals of the former area include the following:
- promoting a model of consumption and production, which would not lead to ecological damage and fulfill the needs of humanity,
- achieving better understanding of the role of consumption in the process of sustainable development as well as introduction of more balanced consumption models.

Poverty and degradation of natural environment are closely related. If poverty leads to ecological crises, the majority of cases of sustained environmental degradation result from an imbalanced model of production and consumption. Therefore, in the coming years, governments together with appropriate supporting organizations should strive to achieve broad goals, including:
- promotion of effective production processes and balanced consumption in the process of economic growth, taking into consideration the needs of the developing countries,
- developing strategies of internal actions, which will allow for introduction of balanced production and consumption models,
- strengthening the factors that support a production – consumption model consistent with sustainable development and promotion of actions for transfer of environment-friendly technologies to developing countries.

These goals pertain to the latter area of action.

In several chapters, areas of action are directly conformed to the security issues:
- environment-safe application of biotechnology (16),
- environment-safe utilization of toxic and dangerous chemicals, fighting illegal trading of those chemicals (19),
- environment-safe management of dangerous waste
- preventing illegal trade of dangerous materials (20),
- environment-safe management of solid waste and residues from wastewater treatment plans (21),
- safe and environmentally friendly management of radioactive waste (22),

Biotechnology, as a combination of genetic engineering, biochemistry and microbiology, is an area of intensely developing science, constituting a compilation of methods of genetic engineering. Not all fundamental environmental problems may be solved using biotechnological processes to attain sustainable growth. The reality must diminish the expectations. However, biotechnologists announce expectations of great contributions to, e.g. progress in health care, increase in food safety by introducing methods of sustained and ecologically sustainable agriculture as well as detoxication of dangerous waste. It should be accompanied by general partnership between countries with rich biological resources, but lacking the experience and investment funds necessary for utilization of those resources through biotechnological processes and countries with biotechnological experience. This experience refers to the scope of transformation of biological resources in a manner, which would allow them to contribute to sustainable development. Described areas of action promote the principles of creating environmentally healthy uses for biotechnology agreed upon by the international community, in order to raise public confidence and convince the community to support ecologically safe uses of biotechnology.

General policy indicates, that chemicals can be used to meet the economic and social needs of people around the world in a rational and largely safe manner. However, there is still a lot to do to ensure environmentally safe conduct with toxic

chemical substances. Two main problems arise in this area, particularly when it comes to developing countries:
- absence of sufficient scientific information allowing for assessment of risk associated with use of large numbers of chemical substances;
- lack of means for assessment of chemical substances owned and used by people.

The processes of severe chemical environmental pollution take place in various industrial centers around the world in the recent years. It is associated with threat to human health, genetic structure and reproduction, as well as to the environment. Elimination of the effects of contamination requires large expenditures and development of new technologies. Long-term effects of chemical environmental contamination leading to climatic changes were only recently recognized and understood. Also recently, the humanity realized the extent of those effects. A large number of international institutions are involved in works concerning chemical safety. Programs for its promotion were implemented in many countries. These works have international implications, as dangerous effects of chemicals know no national boundaries. However, significant aid for national and international enterprises in this area is necessary in order to work out methods of environmentally safe use of chemical substances.

Seven areas of action are proposed in this area:
- broadening and acceleration of international evaluations of chemical threats,
- unification of classification and labeling of chemicals,
- exchange of information regarding toxic chemicals and chemical threats,
- establishing programs for risk reduction,
- strengthening national capabilities and skills for effective toxic substance management,
- preventing illegal international trade of toxic and dangerous substances,
- deepening international cooperation in some areas of actions.

Effective control of production, storage, handling, recycling, transport, retrieval of raw materials and management of dangerous wastes are important for human wellbeing, environmental protection, as well as management of natural resources and sustainable development. Preventing formation of dangerous materials requires knowledge, experienced staff, resources and financial means, as well as technological and scientific potential. International trade of dangerous wastes, with partial breaching of national legislation and international policies, causing harm to the environment and public health in all countries, particularly the developing ones, is a matter of concern for the international society.

The master task in terms of management of vital processes involves the greatest possible minimization of dangerous waste production, as well as such management of waste products so that they would not cause harm to health and the environment. It encompasses four areas of action:
- promoting prevention of dangerous waste formation and minimization of the amounts of those products,
- promoting and strengthening international cooperation in management of cross-border movement of dangerous wastes,
- promoting and strengthening institutional powers with regard to dangerous waste management,
- preventing illegal international trade of dangerous waste products.

The General Assembly concurred that environmentally safe waste management is one of the main actions undertaken in order to maintain the wellbeing of global environment and to attain environmentally healthy, stable growth of all countries.

Areas of action described in this chapter of Agenda 21 are closely related to the following areas of action contained in other chapters:
- quality protection and use of inland water supplies (ch. 18);
- promoting sustainable development of human habitats (ch. 7);
- protection and promotion of human health (ch. 6);
- changing the model of consumption (ch. 4).

According to this, the extent of necessary actions should be based on a hierarchy of goals and concentrate on four main fields of action related to waste products. They are mutually interconnected and supportive of each other. They come down to:
- minimizing the amount of waste;

- maximization of environmentally safe use of secondary materials and waste recycling;
- promotion of environmentally safe elimination and processing of waste products;
- broadening the scope of services with respect to elimination and processing of waste products.

Radioactive waste is formed both during use of nuclear fuel as well as radioactive materials (in medicine, science and industry) Radiological risk and safety threats are diverse on the part of radiological waste: they range from very small to great.

Safe and environmentally harmless management of radioactive materials, including their minimization, transport and utilization is of great importance. Most countries with leading nuclear energy programs have undertaken administrative and technological systems of waste management. In many other countries, still preparing for nuclear programs or only using radioactive materials, there is still a need for creation of such systems, which is becoming increasingly urgent.

A fundamental goal of such program is to ensure safe management, transport, storage and utilization of radioactive wastes. It is directed at protection of human and environmental health and is contained within a broader framework of interactive and integrated approach toward their management within a broadly understood safety system.

The described areas of action illustrate the extent of parameters and challenges for maintaining sustainable development.

References:

1. Janikowski R., Wielokrotny model decyzyjny, jako narzędzie oceny oddziaływania projektowanej działalności człowieka na środowisko. JETU, Katowice, 1993.
2. Jendrośka J. Rządowy projekt ustawy o postępowaniu w sprawie ocen oddziaływania na środowisko oraz o dostępie do informacji o środowisku i jego ochronie, (w:), Problemy ocen środowiskowych, kwartalnik Nr 1(8), 2000.
3. Kozłowski S., Koncepcja ekorozwoju jako podstawa polityki ekologicznej państwa.(w:) B.Poskrobko (red.), Działalność gospodarcza a ochrona środowiska przyrodniczego, Biuro Badań i Wdrożeń Ekologicznych, Białystok 1992.
4. Kozłowski S., W drodze do ekorozwoju, PWN, Warszawa, 1997.
5. Patrz: Dokumenty końcowe Konferencji Narodów Zjednoczonych..., cyt. wyd., słowo wstępne.

Emergency medicine

Selected aspects of communication between emergency services and the mass media in crisis situations

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Summary:

We live in times where information is the supreme value. The mass media seek sensation and often misinterpret the situation, which usually occurs in the case of limited access to information. Due to their mediagenic nature, crisis situations as well as emergency actions taken to eliminate their consequences are undoubtedly a treat for journalists. Correctly performed rescue operations are essential during events that make people suffer or feel endangered. Nonetheless, appropriate conveying information about performed actions to the media, and then to the society, is a crucial element of rescue operations and influences both perception of emergency services and prevention from spreading speculation and panic in the society.

Key words: media, crisis situation, rescue operation, emergency services, panic.

Introduction

Continuous civilization development and growing population make us live in expanding agglomerations, which results in the fact that the issue of disasters is becoming increasingly important. Phenomena bearing marks of crisis, although varied and reaching different extents, which makes it difficult to define them precisely, have some common features [1-3]. Firstly, in view of the fact that nobody can expect crisis situations at a particular time and in a particular place, the affected population is usually helpless. Secondly, the extent of damage and number of people in need exceed the ability to satisfy all expectations. Another feature of crisis situations is their mediagenic nature [2,3].

For hundreds of years, since humans started to deal with disastrous events, the concept of catastrophe has evolved. At present, there are numerous definitions of "catastrophe"[4]. The most accurate one, with regard to the way of thinking in any situation that surpasses in extent the abilities of rescuers and bears the features of catastrophe, is a definition approved in the USA by the Federal Emergency Management Agency (FEMA) [5]. It defines catastrophe as an event causing death, injuries or damage to possessions, to an extent that makes routine emergency actions insufficient. According to this definition, catastrophe occurs suddenly and requires immediate, coordinated actions taken by many individuals and institutions.

Efficient crisis management is not only a medical emergency assistance provided to casualties. One of the basic conditions of effective

actions reducing the consequences of the event is a well-organised communication between emergency services units, including the fire brigade, the police, the medical rescue, etc., as well as between emergency services and the public. Due to technical advancements it is possible to exchange information via the electronic media, however, the basic way of contact between the emergency services, the authorities and the society is undoubtedly public media, including press, radio and television stations (TV and radio are electronic media) [3,6].

Communication with the media in crisis situations may be divided into three stages. The first of them includes actions preceding a crisis situation, and next two stages – actions during and after eliminating such a situation [1,2,6,7].

Actions preceding catastrophes

Communication infrastructure, consolidating all emergency services and the public, is an inherent element of the efficient security system. The above mentioned mass media, i.e. radio, television, press, and nowadays also the Internet, are main channels of conveying information. Lack of proper circulation of information between the emergency services leads to chaos, whereas, disturbed communication with the media results in misinterpretation of the event, which may raise many unfavourable interactions in the public, including panic.

Actions preceding a crisis situation are inherent preparatory stages for various emergency services and crisis panels. Continuous updating of knowledge by people who coordinate actions of emergency and crisis services, results in progressing improvement of professional skills [8,9]. Constant training, exercises and simulations help these services, to a greater or lesser extent, prepare for possible crisis scenarios.

Exercises should not only involve rescue services, but they should also include elements of cooperation with media [7,10]. In the future it will help avoid information chaos. It is important to become acquainted with the rules of the public media. It is also worth establishing and practising the method of appointing persons responsible for contacts with the media (spokespersons), creating healthy relationship with the media and preparing (adequately to the situation) necessary information for the public. Therefore, establishing procedures for crisis situations seems indispensable.

Media communication and legal provisions

Circulation of information between public services and media is regulated by legal acts, ethical codes and internal regulations. Thereby, such regulations impose duties on the emergency services workers, authorities and journalists. Informing the public about states of danger is defined by, among others, a notation in the UN Universal Declaration of Human Rights of 1984 [11]. In the face of a crisis situation, people would feel much safer to know that they receive reliable information about current actions and changes that may affect their lives and environment.

Act of 26 January 1984 – Press Law, conferred powers on journalists to obtain information about actions of government agencies, public companies and other organisational units, whereas, heads of such units, spokespersons or other persons authorized to convey information to media are responsible for providing such information [12]. However, according to the above Act, journalists should make every effort to be careful, reliable and honest while collecting and conveying press materials; they should check credibility of all obtained information and publish its sources. According to the Act, the media are obliged to publish (free of charge) statements issued on the basis of acts, announcements, ordinances or resolutions of the central administration authorities and government administration authorities in the province, and, what is important for this paper, they are obliged to publish (free of charge) announcements issued by the government administration authorities or local governments and concerning crisis situations defined in the Act on crisis management of 2007 [13].

Legal provisions concerning reliable conveying information about events and phenomena in the country and abroad, are also included in the Act on the state of natural disaster [14] or in the Act on National Broadcasting Council. Principles of correct collection of and publication of press materials may be found not only in the above acts

but also in ethical codes, including the Polish Code of Ethics for Public Relations Association and the Ethical Code of Journalists.

A great example of internal acts referring to the role of communication between the emergency (rescue) services and the media may be internal regulations of the National Fire Service of 1998, defining press-information activity within the NFS structures, including the actions of spokespersons and cooperation between NFS and journalists during crisis situations. In 2004, the Headquarters of the National Fire Service established principles of proper conduct for the commanding officer during a rescue operation. The above-mentioned guidelines categorically forbid the commanding officer to inform the media in the event place about the reasons, identity data and names of casualties. Guidelines also clearly define the way of taking over informational function by a person appointed to a post of a spokesperson.

Appointment of spokespersons

A deficit of information is commonly associated with crisis situations. From a point of view of the media, a crisis situation is a special opportunity to develop their own image among media market participants while gaining as much information as possible and reporting it to the public [15] . In order to avoid information chaos, it is important to take actions which guarantee that statements issued by all persons authorised to convey information are consistent, relevant and answer the questions instead of ignoring them using a phrase "no comments". A requirement of consistent communication is one of the most important elements connected with the entire management of communication in crisis situations. Consistency is necessary for information exchange between particular emergency services, organizations and the media. Therefore, it seems important to develop a strategy of communication with both internal (services) and external (media and public opinion) environment.

Misinterpretation of the event is a common action taken by the media, which results from shortage of information or conflicting data presented to the public. Thus, it is essential to appoint a person who will solely inform the media about progression of rescue actions from the onset of crisis. Such a person should be chosen much earlier and systematically prepared for his/her role, since in order to increase the level of reliability of the released statement, the speaker must show competence, enjoy respect, be reliable and dynamic, and enjoy a positive opinion. Such a person should have several crucial abilities:

- must be resistant to stress and control his/her own emotions;
- must have extensive substantive knowledge about activities of the emergency services and know the services which he/she is talking about;
- must have great interpersonal abilities and make contact easily.

Professional actions of a spokesperson build up trust of the media in emergency services and strengthen positive public opinion about their hard work [16]. Thus, it is so important to obey the rules defining what a spokesperson should or should not do.

Table 1: Principles of spokesperson's work.

Allowed	Not allowed
Release information only via a press spokesperson responsible for public relations.	Speculate on: • possible causes of the crisis situation; • number of fatalities; • further scenarios of events; • date of termination of the actions.
Create equal opportunities to obtain information by various types of media.	Provide information that can hinder the progress of rescue operations, raise panic or bring about any new threat.
Release only proven information	Issue official statements to incompetent persons
Supervise information outflow by: • own, frequent contacts with the media; • collecting all information in a version reported by the media to the public; • controlling movement of journalists in the endangered area.	Evaluate rescue operations when they are in progress. Lay the blame for the situation on anyone. Misinform the media.

Preparation of information

During a rescue operation, a lot of information asked by the media is unpredictable. However, there is still considerable amount of information that can be prepared earlier and successively released to the public. Such information includes:

- alarm information;
- instructions for behaviour in crisis situations,
- data concerning places and sources of information and help;
- data concerning services involved in the rescue operation;
- appeal to support services in relevant situations.

When preparing rules for cooperation with the media, all forms of communication should be taken into consideration [10,17]. The most popular forms of communication in crisis situations include: press note, statement, information, telephone response, written response, interview, talk, utterance and press conference.

Actions during a crisis situation

Communication with the media during rescue operations mainly includes: appointment of a 24-h duty spokesperson, collection of information from various services, preparation and conveying information to journalists, information management for the regional and national media, checking and correction of information that was released to the media, organisation of press conferences, responding and release of statements on the current situation, and coordination of journalists work in the area involved in rescue operations.

It is important to establish an information centre near the place of rescue actions [3,4,9]. Persons responsible for contact with the media should all the time monitor the situation and respond immediately to the needs reported by the media, if it is possible and not against the rescue operation.

Another important element regarding participation of the media in a crisis situation is to separate and adapt for journalists the area around the event site. This area is separated according to two important principles. The first of them is the superiority of rescue operations interest. This principle forbids the media to enter places, where it could pose a risk to the rescue action or to the media. The second principle, used while separating areas for the media during catastrophe, is the best possible availability of the media. The media should have possibly the best, acceptable "viewpoint" for observation of the rescue actions, to assure that when looking for a good place for taking pictures the media will not hinder actions taken by emergency services.

Persons responsible for contacts with the media are obliged to separate such areas, in agreement with persons in charge of the rescue operation.

Actions after eliminating a crisis situation

After termination of the rescue actions, persons responsible for contacts with the media are obliged to inform the local community about the current situation and taken precautions, and to inform the entire country about a situation in the particular region.

Unfortunately, it is often seen that the end of the rescue operation is the end of all actions aimed to eliminate a crisis situation. However, it should be an introduction to preparations connected with future actions. Conclusions should be drawn from all experiences, regardless of whether they were positive or negative; all actions should also be thoroughly analysed. Efforts put into analysing the particular action should help revise arrangements and prepare for future events.

Summary

When analysing this paper, it may be hypothesized that the public authorities, emergency services and mass media are all responsible for reliable conveying the current information in crisis situations.

However, cooperation with the media is not easy. Journalists are characterised by natural scepticism. They are more interested in criticising the services and government authorities responsible for controlling the crisis situation than in defending or justifying such services and authorities. Probability of negative comments given by the media during a crisis situation is almost 100%.

Although several acts, including the Act on the state of natural disaster and crisis management, imposed on the media an obligation to report any threat (in agreement with the local authorities), we should remember about the role of the way how information reaches editorial offices. Thus, it is important to work out methods of presentation to the media a problem of catastrophe or emergency.

Taking the above-mentioned actions increases the chances for peaceable, and at the same time, effective participation of journalists in a crisis situation.

References:

1. Beaudoin, C. E. "Assessment of a media campaign and related crisis help line following Hurricane Katrina." Public Health Rep. 123.5 (2008): 646-51.
2. Arnold, J. L. "Disaster myths and hurricane Katrina 2005: can public officials and the media learn to provide responsible crisis communication during disasters?" Prehosp.Disaster.Med. 21.1 (2006): 1-3.
3. Ng, K. H. and M. L. Lean. "The fukushima nuclear crisis reemphasizes the need for improved risk communication and better use of social media." Health Phys. 103.3 (2012): 307-10.
4. Barr, P. "Staying connected. Social media put to work when disaster strikes." Mod.Healthc. 41.36 (2011): 33.
5. Keim, M. E. and E. Noji. "Emergent use of social media: a new age of opportunity for disaster resilience." Am.J.Disaster.Med. 6.1 (2011): 47-54.
6. Schlecker, M. and E. Hirsch. "Incomplete knowledge: ethnography and the crisis of context in studies of media, science and technology." Hist Human Sci. 14.1 (2001): 69-87.
7. McLearn, D. "FDA crisis management and the media." PDA.J.Pharm.Sci.Technol. 50.3 (1996): 144-46.
8. Misterska, E., M. Glowacki, and Z. Wlodarczyk. "Mass-media and the transplantation crisis: the example of Poland." Med.Sci.Monit. 16.8 (2010): RA171-RA176.
9. Petriuk, V. A. and E. I. Pokrovskaia. "[Role of the mass media in eradication of the consequences of a natural disaster in summer 2002 in Karachai-Chercassian Republic]." Zh.Mikrobiol.Epidemiol.Immunobiol.6 (2003): 124-26.
10. Rich, E. "'I see her being obesed!': Public pedagogy, reality media and the obesity crisis." Health (London) 15.1 (2011): 3-21.
11. Uchwała Senatu Rzeczypospolitej Polskiej z dnia 10 grudnia 1997 r. w sprawie obchodów 50 rocznicy uchwalenia Powszechnej Deklaracji Praw Człowieka (M.P. 1997 nr 85 poz. 851).
12. Ustawa z dnia 26 stycznia 1984 r. Prawo prasowe (Dz.U. 1984 nr 5 poz. 24).
13. Ustawa z dnia 26 kwietnia 2007 r. o zarządzaniu kryzysowym (Dz.U. 2007 nr 89 poz. 590).
14. Ustawa z dnia 18 kwietnia 2002 r. o stanie klęski żywiołowej (Dz.U. 2002 nr 62 poz. 558).
15. Stokstad, E. "Gulf oil disaster. Hunting for plumes, learning to live in a media spotlight." Science 329.5987 (2010): 22-23.
16. Saxena, D. B., H. M. Shah, and P. Mishra. "Media response to disaster." Indian J.Med.Sci. 63.1 (2009): 28-29.
17. Spence, P. R., et al. "Media use and information needs of the disabled during a natural disaster." J.Health Care Poor Underserved 18.2 (2007): 394-404..

History of medicine

Anthropological and archeological sources in medical historian's studies

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Summary:

Medical historians most often refer to written sources in their studies on the matters of health and sickness over the centuries, but also take advantage of the materials acquired through excavations – in other words anthropological and archeological sources. Skeletal material may exhibit signs of sickness, traumatic injuries, therapeutic procedures such as trepanations or amputations, as well as procedures emphasizing one's social status in a society (e.g. skull deformities). Various items for use in medical procedures may be found during excavations. Archeobotanical material contains remnants of medical plants. Immovable sources: remnants of medieval hospitals or baths also point to the means of treatment utilized by given populations. Anthropological and archeological sources are often difficult to interpret. The description of medicine on Polish territories made on their basis is certainly fragmentary. Despite that, anthropological and archeological data are important sources of knowledge for a medical historian, as they allow investigation into human past all the way to the times when written sources were not available.

Key words: history of medicine, anthropology, archeology, skull trepanations, historical sources.

There are many multidisciplinary publications appearing in the current scientific literature. Many scientists representing various fields compile a common research project. In their work, medical historians also avail from various fields of knowledge, utilize research methodology not only from the area of history, but also ethnography, archeology and anthropology. Each historical work must be based on sources. In literature, we may find several definitions of a "historical source." According to a definition published by a historian, Jerzy Topolski, "the source" encompasses all information (in an information theory sense) on social history regardless where they come from, including the mode of information transmission (information channel) [1]. Based on the sources, one may attempt to reconstruct the lives of people in the past. Studies on the past, such as history and archeology are mutually complementary and overlapping.

In this publication we took interest in archeological and anthropological sources utilized by medical historians in their work. In our deliberations, we focused on the material obtained in Poland. The outline of periodization from neolithic to medieval times mentioned in our work also concerned Polish territories [2].

Archeological sources are material signs of human activity extracted from the earth or water (acquired through archeological methods). They

allow for reconstruction of various fields of life. During excavations we find items, which could have served during medical or hygienic procedures. Not many archeologists are concerned with medical or surgical instruments from prehistorical and medieval times. Hygienic items: knives, razors, pincers, and mirrors are more broadly described. There are numerous publications in foreign literature discussing surgical and medical instruments from the Roman period of Iron Age (since the 1st century A.D. until about 375 or the end of Roman Empire) found by the archeologists within the region of Roman Empire.

Anthropological sources (bone material) allow for observing pathological changes (injuries, illness) and traces of intentional procedures performed by the first "surgeons." Paleoanthropology is concerned with morphological analysis of human skeletal remains. The goal of those studies is to determine important biological features (sex, age, height, body mass) of individual and entire groups of people. Paleopathology is concerned with disease lesions, developmental changes and traumatic injuries visible on excavated skeletal material. It should be noted that this field of knowledge is at the border of paleoanthropology and medicine. We are mainly interested in the structure of health in a given population [3].

Very little room is devoted in Polish scientific literature to prehistoric medicine. It is probably a result of scarce sources and difficult access to them. There are publications concerning development of medicine in the Middle Ages. Here, we can already encounter written sources: chronicles, annals and letters. They provide information on the first Polish physicians, famines and epidemics that tormented the contemporary society.

Authors of numerous publications [4,5,6] pointed to the need for further studies on history of medicine based on anthropological sources. Finding the signs of diseases besetting people ages ago in skeletal material or soft tissues may help us understand pathological phenomena occurring in the body, as many diseases have been known since neolithic era (since about 5400 until 2200/2100 B.C.). Going back in time allows for noting disease symptoms and investigating the mode of transmission of some diseases, particularly the ones causing epidemics, with groups of people. Immunological changes occurring in a human as a result of civilization progress as well as environmental and social changes constitute another curious phenomenon. In prehistorical times, only biologically strong individuals reached adult age. Mortality of women in childbearing age was high and mean lifespan was shorter for women than for men. Today the situation became reversed, as we know from demographic studies [7].

Among the Slavs, as in case of other nations, medicine probably grew from everyday experiences, beliefs and customs. The cause of the disease was seen in natural factors such as: poor nutrition, dirtiness, infections, as well as supernatural factors: witchcraft and enchantments. According to the beliefs of ancient Slavs, deities were also responsible for health or sickness [8].

Archeological sources on medicine are scarce. First of all, we would like to understand how, with what and where people were treated. The most archeological sources, on which we may base our deliberations, come from early Iron Age (from the beginning of 1st century B.C. until about 4th century B.C.) and the Middle Ages (from 7th century until half of 16th century). Here, we can mention immobile sources: remnants of medieval hospitals and baths, as well as mobile ones: medical instruments, medicine containers (e.g. made from antlers), pharmaceutical containers. From the earliest times, people attributed therapeutic properties to various talismans made of bone, stone or fossils. Belemnites – fossilized mollusk shells (cephalopods), also called "lightning arrows", were particularly valuable. They were applied to the affected areas, but also ground to powder and given to drink. Belemnites were used for treatment of: rheumatism, colic, eye diseases and during childbirth; they also protected from bewitchment [9]. Use of talismans was popular in folk medicine. Animal horns and bones, as well as roots of particular plant species were most frequently used as materials.

Archeobotanical studies of plant fossils provide information on plants present in human environment, including edible ones, grown or derived from natural positions. Among the archeobotanical material, we may also distinguish therapeutic plants. Plants used in medicine could be grown in home gardens or gathered near human settlements, cities or villages.

According to the data from archeological excavation sites in the area of Poland, the following plants were used in medicine: poppy (hypnotic and sedative properties), Lithospermum officinale (antidiabetic properties, treatment of hypertension, hyperthyroidism, contraception), Sambucus nigra (diuretic, diaphoretic, antipyretic actions), Agrimonia eupatoria (antidiarrheal, antirheumatic, antihemorrhagic properties), Valeriana officinalis (sedative, hypnotic), Filipendula ulmaria (antipyretic, diaphoretic, diuretic and antirheumatic properties), Hyoscamus niger (anesthetic, analgesic, hallucinogenic properties) [10, 11, 12]. Many plants such as: red raspberry, black raspberry, blackthorn, wild strawberry, bog blueberry or cranberry, were acquired from natural habitats for consumption since prehistorical times. They were processed and turned into juices. They were rich sources of vitamins for contemporary people. Oil plants (common flax, hemp, opium poppy) could be also used for therapeutic purposes. Plant leafs (common hazel, broadleaf plantain), sprouts (common yarrow), flowers (mead wort, common elder), rootstalks (gromwell), roots (valerian, common chicory) and fruits (common elder) were used. Peppermint or cumin, spices used in medieval times, also had therapeutic properties. Use of some of these plants was continued in folk medicine and they are still utilized in modern medicine, thus their application had reasonable grounds. In folk medicine, some of them (opium poppy, common St. John's wort, Sambucus nigra) were ascribed magical properties.

The issue of medical instruments used from prehistoric times until Middle Ages is difficult to describe. On the basis of discovered archeological items we think, that stone or flint instruments (scrapers, recloirs, chipped stones), as well as tools made of organic materials such as bone and antler blades were used in skull trepanations in the neolithic era. In the following eras, people started making medical tools out of bronze and iron. With the evolution of other tools came the evolution of surgical instruments, although according to our knowledge, they derive from craft tools [13]. We possess the most information on medical tools from the following periods: La Tene (from 400 B.C. until the beginning of 1st century A.D.) and Roman period (from the beginning of 1st century A.D. until about 375). There are many publications in archeological literature on surgical and medical instruments from the period of roman influences, while descriptions of La Tene period are significantly scarcer. Therefore, we find it easier to classify antique medical instruments gathered in museum collections coming from those two periods. However, there are few classified medical tools from La Tene or Roman periods coming from Poland. Certainly, Polish museums may contain these kinds of items, which were not correctly identified. All medical tools dated to the La Tene or Roman periods were found in southern Poland, mostly in the Silesian region. In prehistoric times, Silesia was an area under Celtic expansion. The Amber Route ran through this region, along which we found numerous antiques from Rome and its provinces. Mercantile expeditions from Southern Europe traveled this road to the southern Baltic Sea and further, toward the northeast [14]. Over the centuries people probably used tools meant for other purposes, such as food preparation, hunting, leather dressing and magical or ritual acts to perform medical activities and minor surgical procedures. Medical tools from La Tene and subsequent Roman periods were decorated (with engravings, notches and ornaments) indicating that, despite the rational foundations of interventional medicine, it was still influenced by magic and rituals. Esthetic appearance of surgical tools was supposed to inspire patient's confidence. The art of decorating gradually progressed through the ages. Shapes of medical instruments from the Iron Age often resemble the 19th century or modern tools. A knife from La Tene period – "trephine," with a semicircular working surface, resembles the 19th century trepanation knives illustrated in contemporary medical books [15]. Trepanation drills from 16th century driven by a chord tied around the working part resemble "modiolus," used for the same purpose in the Roman period. Current surgical instrumentation includes types of tools similar to those from the Roman period such as: exploration probes, scalpels, catheters and specula. During the Iron Age we may note progress in the field of medical instruments. Roman medical tools are more diverse and more precise than those made in the La Tene period.

Like in the modern era, disease morbidity depended on host factors (given organism), its genetic makeup, environmental factors and features associated with particular pathogens.

Disorders observed on osteological material may be divided into several groups: injuries, specific and non-specific inflammatory diseases, degenerative changes, systemic diseases, tumors and tumor-like lesions, developmental changes, mastication organ disorders. Improper diet, vitamin deficiency as well as periods of starvation and parasitic diseases leave traces on the bones (particularly in young individuals, whose bones are still growing). Here, we can mention changes in the orbital floor, cribra orbitalia, frequently observed since the Neolithic Age, rickets – also occurring since Neolithic era, although less frequent, enamel hypoplasia or scurvy. Children suffering from the above disorders certainly had lesser chances of surviving to adult age.

Degenerative and deforming, age-related (older age category) and work-related (overload) lesions are also often frequently observed on the skeletons. Such changes are particularly common in the Medieval Age. It may also be related to gradual prolongation of human lifespan. There are lesions seen on vertebrae, including osteophytes, flattening of vertebral bodies, Schmorl nodules, and deformations of articular surfaces. Tuberculosis is an infectious disease noted in bone material since Neolithic age. Its prevalence was influenced by poor hygienic conditions, malnutrition and domestic animals. Signs of other infectious diseases, leprosy and syphilis, which occurred endemically at that time, started to show in the Middle Ages. In prehistoric populations, caries did not pose as big a problem as currently. Carbohydrate intake increased as late as in the Middle Ages. However, other diseases of the mastication organ were also quite common, including: greater teeth effacement compared to modern times, dental calculus and paradontosis [16, 17, 18]. In prehistoric and historic times, many diseases ran different courses than nowadays, were characterized by different range of occurrence and severity in given populations. Introduction of new medicines, particularly appearance of antibiotics, decreased mortality from infectious and inflammatory diseases. One should note that not all disorders leave traces on the skeleton and many diseases might be missed during such studies.

Skeletal material from Poland bears signs of intentional procedures: amputations and trepanations. While examining anthropological material, we can observe the process of development of interventional medicine. Trepanations constitute a broad issue and skulls with signs of trepanation coming from Poland are dated back to Neolithic Age, through the Bronze Age, early Iron Age, up to the Middle Age. However, signs of amputations are present only on the skeletons from Middle Age due to the fact that it was a very dangerous procedure associated with high risk of infection and there were no effective methods of stopping hemorrhages. Another group of intentional procedures are permanent deformations, which in Poland involved the skull. Two deliberately deformed skulls were found – one coming from Neolithic Age (the New Stone Era), the other from medieval times. They were both elongated in the lateral aspect, the forehead shifted posteriorly. Therefore, this custom was incredibly rare in Poland. Possibly, those individuals did not belong to local societies. Using bandages or wooden boards to exert pressure against the occipital, frontal or both skull regions altered the shape of the head. Performed in children, deformation changed skull proportions, particularly the length-to-width as well as height ratios [19].

Skeletal material obtained from medieval cemeteries indicates that people were able to reduce and stabilize fractures at that time. Certainly, the state and extent of such knowledge depended on given human populations. Undoubtedly, it was passed orally from one generation to another. Properly reduced fractures provide evidence of appropriate therapeutic techniques. Fractures were stabilized in wooden slates padded with moss and tied with a bandage [20].

In modern neurosurgery, skull trepanation involves drilling a hole to uncover the meninges and brain in order to perform a specific surgical procedure or evacuation of hematoma. Trepanation holes are made using a trepanation drill. One or more orifices are drilled during lobar skull opening [21]. In anthropology, trepanation is understood as intentional opening of cranial cavity through drilling, scraping or cutting four incisions. The reason for opening the cranial cavity was not to perform neurosurgical procedures, although it was probably a way of evacuating hematomas. In Poland, eight skulls bearing signs of trepanation — 5 male and 2 female — come from Neolithic era (the new Stone Age — from

about 5400 until 2200/2100 B.C.), five — all male — from the Bronze Age (from about 2200/2100 until half of 8th century B.C.), six – 4 male and 2 female – from Early Iron Age (from the second half of 8th century B.C. until the end of 7th century A.D.), and about twenty-eight — 16 male and 6 female — come from the Middle Ages (from the 7th century until half of 14th century A.D.). It should be noted that determining the sex of the buried person was not always possible. Larger number of skulls with signs of trepanation probably resulted from increasing population density, formation of large settlements and cities and, therefore, greater need for medical aid.

Most trepanations were performed in men. It was probably related to the fact that men were at greater risk of head traumas and injuries, e.g. during hunting, battles and fights. It is consistent with earlier epidemiological studies showing that, both in the Middle Ages and nowadays, men are more prone to traumatic injuries. In the medieval times, the number of skull injuries in men increased almost threefold.However, this relationship was not observed in women [22]. Skulls with trepanation holes were most often adult, although there were few belonging to young people or the elderly. Naturally, one should emphasize that the ages of these individuals were determined at the time of death. If the orifice is not obliterated, one may conclude that the person died during the procedure and the age at the time of death is consistent with the age, at which trepanation was performed. However, if the opening is well obliterated, it is then difficult to estimate the age range, within which trepanation was performed. Obliteration may be a proof of patient's survival for several months or years.

There are no children's' skulls bearing signs of trepanation in the materials obtained in our country. Possibly, this kind of procedure was rarely performed in young individuals. Fragile children's skeletons are quickly decomposed, which is the reason why the signs of trepanation are poorly visible. It is also likely that children did not suffer from conditions, which could be considered indications for such procedures. Possibly, children less often fell victims to severe head injuries in the past. However, such procedures were performed during the Greek-Roman times. In this region of the world, doctors were familiar with the works of Hippocrates and Galen, who mentioned trepanation as one of therapeutic methods [23].

There are also very few trepanation skulls from the Bronze Age and Early Iron Age found in Poland. It could be related to the custom of body burning (cremated human remains are placed in an urn or directly in the grave), as it is much more difficult to recognize changes related to disease or surgical procedures in burnt remains.

Trepanation was most often performed in the area of parietal (more often on the left side) and frontal bones, rarely on the occiput. Trepanation holes rarely involved more than one bone. In the studied cases, holes were located at the top of the head or at a lateral surface of the skull – in such cases they involved the squama of temporal bone and occiput. Trepanation holes rarely overlapped with cranial sutures, although there were few such cases collected in Poland. Surgeons probably distinguished between cranial sutures and bone fractures. Sizes of trepanation holes vary. Some are extensive (5-6 cm in diameter), while other ones are small (less than 1 cm). Trepanned skulls collected from Poland area most often contain only one hole. In two cases from neolithic times and two cases from the Middle Ages, we were dealing with two holes. No skulls with multiple trepanation holes were obtained from Polish region. The size and positioning of trepanation hole was certainly related to the location and extent of injury (in posttraumatic trepanations), but it could be related to the site, where the patient experienced pain, treatment method and applied tools.

In Poland, since the neolithic period until Middle Ages, trepanations were performed through scraping and cutting. The first method was safer, as it was associated with lower risk of brain damage. Tools with a cutting edge were used, but only for scraping the bone. Tool motion could be performed in a vertical or horizontal motion. Sometimes, both methods were used together and both neolithic and medieval skulls bear signs of such procedures. Literature emphasizes that the cutting method was used for acquisition of bone talismans (from the dead), although there are skulls found in Poland with trepanation holes indicating that this method was also used for therapeutic purposes, particularly in the medieval period and at the turn of Middle Ages and the modern era.

Skulls containing trepanation holes constitute a subject of scientific studies since 19th century. Literature cites, that the most frequent bodily injuries are head traumas, which involve 60% of general population [24]. In the prehistorical and medieval periods head traumas were probably also very common, which was likely related to battles, fights and hunting.

Often, due to poor skull condition, it is difficult to establish the indications for trepanation, particularly when the skull does not contain any external signs of trauma. Also, illness does not always leave marks on the skeleton. However, most trepanation procedures were probably performed for therapeutic reasons, in order to remove the fractured bone. Such procedures were often performed intuitively. Leverage and removal of fractured bone fragment or fragments, as well as polishing of sharp wound edges could bring immediate effects such as regression of neurological disorders or return of consciousness, as fragments of the damaged bone ceased to exert pressure against brain tissue.

Therefore, procedures were repeated in subsequent cases. First of all, treatment was aimed at removing the source of pain, which could have been caused by various pathological changes. Medieval skulls bear the signs of trauma particularly often. Such procedure was not easy to perform. It must have been done by a medic experienced in this field and equipped with appropriate tools. Indications for skull trepanation also included: pericerebral hematomas, inflammatory lesions or brain tumors.

Several skulls described in Polish anthropological and archeological literature as trepanned, are not such. Holes present on those skulls could have been made during excavations (skull damage by a probe), as a result of processes taking place in the soil, traumatic injuries, gunshot wounds or post mortem examinations (if the hole involves the entire or almost entire skull cap). Therefore, not all skull apertures should be considered purposeful therapeutic procedures. Particularly, very small openings, 2-3 mm in diameter [25], or very large ones involving several skull bones indicate that they have not been made during an intentional surgical procedure.

Another interesting issue concerns the problem of patient survival following trepanation. Many publications indicate that the fraction of successful procedures was high. Data on trepanation skulls from South America point to osteal reactions (signs of obliteration) in 55% to 70% of trepanned skulls [26]. In cases of trepanation from the area of Poland, Czech Republic and Slovakia, professor Adam Paluch states that the success rate amounted to about 81.7% [27].

Authors of publications on trepanations from the neolithic times performed in Denmark and Germany report 80% (Denmark) and 88% (Germany) survival following trepanation [28]. Possibly, such high survival rates were related to patient care following the procedure, wound dressing and use of newly made flint and stone tools, which constituted sterile medical instruments. The reasons for this include strong immunological systems of individuals subjected to the procedure (weaker individuals died in childhood). Survival after surgery also depended on patient's general condition, extent of injury or disorder constituting an indication for trepanation. Smaller openings certainly posed a smaller risk of wound infection. It is also possible that high survival rates following these procedures are associated with the fact that most of historical trepanations were epidural. Complications of this procedure included wound infection, but also intraoperative bleeding and meningeal or brain injury. They resulted from unskillful tool use and poor surgical technique. In the 19th and at the beginning of the 20th century trepanations were carried out in hospitals, which were characterized by poor hygienic and sanitary conditions. Therefore, mortality among patients undergoing this procedure was high.

One could also ask, who performed such procedures in the prehistorical and historical times? In large societies, knowledge of medicine and surgical procedures was passed from one generation to another. Experiences gained in performing such kinds of surgeries allowed for avoiding brain and meningeal injuries or infections. During the Iron Age (La Tene period) trepanations were most likely performed by "warrior surgeons," as evidenced by their funerary items, which included medical tools, beside armament. They were probably able to perform other minor surgical procedures. In the La Tene

period, the wounded and sick warriors were also cared for by their companions. Based on archeological findings, we may conclude that a "warrior-surgeon" was equipped with medical instruments, including the following tools: bone knives, exploration probes and hooks. In ancient civilizations, with development of the art of war and formation of armies, comes the gradual progress in the areas of medicine related to military actions and frequent injuries, particularly surgery. Surgical skills and treatment of injuries and wounds were especially important in carrying for wounded warriors. During the Roman period, trepanations were performed by military doctors (specially trained) that accompanied the legions.

Military surgery went through many stages of development. In the Roman army, a qualified military doctor replaced a warrior-surgeon of the La Tene period. When it comes to the Roman Empire, we are able to identify the doctor or a medic based on archeological studies and funerary equipment. However, in the Barbarian region identification is very difficult. Three burial sites from the Iron Age were identified in Poland, which contained tools described by the archeologists as medicine-related. Two graves belonged to warriors and one is thought to be a burial site belonging to a midwife [29, 30]. There was probably also folk knowledge regarding trepanations and other surgical procedures. People involved in the surgical craft benefited from this knowledge. In the Middle Ages, as a result of separating surgery from medicine, surgical occupation could be undertaken by people without medical education, who only possessed some practical skills. However, it is emphasized that barbers performed mainly minor surgical procedures, healed wounds, reduced dislocations and fractures or opened abscesses. They could also learn about medicine from the clergy, as their work also included shaving tonsures. In the Middle Ages, demand for surgeons was high. They worked in the cities and princes' courts. Ethnographic sources inform us that some occupations were also predestined to performing therapeutic or even surgical procedures, including: blacksmiths, shepherds, carpenters and beekeepers [31].

People who cared for animals could use their medical knowledge to perform certain procedures on men. The tools used by the mentioned craftsmen for their everyday work could also be useful for various medical procedures. In case of a blacksmith, the transformation of metals into specific items was particularly important, as it was attributed somewhat mystical properties, as in the case of transition from illness to health.

Trepanation skulls, dated back to 11th and 14th centuries, were also found in the medieval Cracow area. In case of a 14th century skull, the procedure could have been performed by either an experienced surgeon or a craftsman. Between the 16th and 18th century, guild surgeons were familiar with the trepanation technique, but rarely used it. It probably resulted from fear of patient's death. The only indication for trepanation included severe head injuries [32]. It was a way to decrease intracranial pressure or remove an epidural hematoma. In case of trepanation skulls from the turn of medieval and modern times, we may suspect that a guild surgeon or a craftsman performed that procedure.

Skeletons bearing signs of amputations also come from medieval cities: Wroclaw and Gdansk. Amputations performed by guild surgeons were also considered dangerous and were rarely performed.

The picture of medicine in Poland, which may be reconstructed on the basis of archeological and anthropological material indicates that, since Neolithic period, people tried to use everything from human environment for medical purposes: curative water springs (votive offerings found there indicate that contemporary societies ascribed the springs healing and magical properties), medical plants. They also made the first flint and stone tools for trepanation and other minor procedures. Therefore, we may note the evidence that surgery, herbal medicine and hydrotherapy have been shaping since prehistoric times. Archeological relics and skeletal material certainly give only a fragmentary picture of medicine in Poland in the prehistoric and medieval times. Despite that, they constitute an important source in the studies of medical historians. Knowledge of medicine was passed from one generation to another in small, often isolated, societies. Medicine, magic and religion coexisted throughout the ages and some magical/therapeutic practices were still popular among rural populations at the beginning of 20th century.

References:

1. Topolski J. Metodologia historii. PWN; Warszawa 1968.
2. Kaczanowski P, Kozłowski K. J. Wielka historia Polski. Najdawniejsze dzieje ziem polskich. Tom1. Wydawnictwo Fogra; Kraków 1998.
3. Piontek J. Biologia populacji pradziejowych. Wydawnictwo Naukowe UAM; Poznań 1999.
4. Lisiewicz J. Zagadnienia prehistorii medycyny w świetle antropologii archeologicznej i paleopatologii. Archiwum Historii i Filozofii Medycyny. 1970; 33:145-161.
5. Wierzbicka D. Zagadnienia paleomedycyny na Śląsku. Prace Medyczne 1977-1978. Opolskie Towarzystwo Przyjaciół Nauk. Wydział Nauk Medycznych. 1980: 5.
6. Gryglewski W. R. Paleopatologia w badaniach historyka medycyny. In: Meissner R, editor. Medycyna i farmacja XIX i XX wieku; Poznań 2007.
7. Malinowski A. Zmienność chorób zębów u mieszkańców ziem polskich w przeszłości. Archiwum Historii i Filozofii Medycyny. 1979; 42: 463.
8. Gładykowska-Rzeczycka J. Lecznictwo u Słowian. Sztuka i Medycyna. 1993; 3(1): 4-5.
9. Biegeleisen H. Lecznictwo ludu polskiego. PAU; Kraków 1929.
10. 10. Latałowa M, Jarosińska J, Badura M. Elbląg średniowieczny w świetle dotychczasowych materiałów archeobotanicznych. Archeologia Polski. 1998; 43: 145-166.
11. 11. Zemanek A, Wasylikowa K. Historia botaniki i archeobotanika w poszukiwaniu danych o użytkowaniu roślin w średniowiecznym Krakowie. Analecta. Studia i materiały z dziejów nauki. 1996; 5:123-138.
12. Badura M, Latałowa M, Jarosińska J, Święta J. Rośliny użytkowe w średniowiecznych i nowożytnych materiałach archeobotanicznych z miast północnej Polski (Kołobrzeg, Gdańsk, Elbląg). In: Czaia R, editor. Archaeologia et Historia Urbana; Elbląg 2004.
13. Brongers JA. Ancient Old-World Trepanning Instruments. Berichten ven de Rijksdienst voor het Oudheidkundig Bodemonderzoek. 1969; 19: 7-16.
14. Woźniak Z. Celtowie w Polsce. PWN; Kraków 1968.
15. Kirkup J. The evolution of the surgical instruments from ancient times to the twentieth century. Norman Publishing. California 2006.
16. Gładykowska-Rzeczycka J. Schorzenia swoiste ludności z dawnych cmentarzysk Polski. Przegląd Antropologiczny. 1982; 48: 44.
17. Gładykowska-Rzeczycka J. Schorzenia ludności prahistorycznej na ziemiach polskich. Gdańsk 1989.
18. Kwiatkowska B. Mieszkańcy średniowiecznego Wrocławia. Ocena warunków życia i stan zdrowia w ujęciu antropologicznym. Wydawnictwo Uniwersytetu Wrocławskiego; Wrocław 2005.
19. Tubbs SR, Salter GE, Oakes JW. Artificial deformation of the human skull: a review. Clinical Anatomy. 2006; 19: 372-377.
20. Jankowski J. Historia medycyny średniowiecznej w Polsce. Człowiek, populacja, środowisko. Prace Dolnośląskiego Centrum Diagnostyki Medycznej Dolmed we Wrocławiu. Wrocław 1988.
21. Mazurowski W, Ząbek M. Neurochirurgia. In: Bielecki K, editor. Narzędzia, protezy i szwy chirurgiczne; Warszawa 1995.
22. Strona internetowa http://global.sbs.ohio-state.edu Global History of Health Project
23. Mariani-Costantini R, Catalano P, di Gennaro F, di Tota G, Angeletti LR. New light on cranial surgery in ancient Rome. Lancet. 2000; 22(355): 305-307.
24. Chmurzyńska A, Kantor I, Jurkiewicz D. Urazy kości skroniowej. Lekarz Wojskowy. 1999; 75(3-4):173.
25. Andrzejowski J, Stanaszek ŁM, Mańkowska-Pliszka H. Modła, grób 169-pierwsza trepanacja czaszki z okresu wpływów rzymskich z ziem polskich. Wiadomości Archeologiczne. 2006; 48: 185-199.
26. Żukiel R, Jankowski R, Stachowska-Tomczak B, Blok T, Wieloch M. Operacyjne leczenie urazów czaszkowo-mózgowych w Ameryce przedkolumbijskiej. Neuroskop. 2001; 1(3): 74.
27. Paluch A. Ślady występowania zabiegów trepanacyjnych na ziemiach Polski i Czechosłowacji w starożytności i średniowieczu. Archeologia Polski. 1975; 20: 411-454.
28. Piek J, Lidke G, Terberger T, Von Smekal U, Gaab MR. Stone Age surgery in Macklenburg-Vorpommern: a systematic study. Neurosurgery. 1999; 45: 147-151.
29. Biborski M. Dalsze ratownicze badania wykopaliskowe na cmentarzysku kultury przeworskiej z późnego okresu wpływów rzymskich i wczesnej fazy wędrówek ludów w Mokrej, woj. śląskie. Badania archeologiczne na Górnym Śląsku i ziemiach pogranicza w latach 2001-2002; Katowice 2004:125-130.
30. Demidziuk K, Kokowski A. Żukowice, pow. Głogowski, woj. dolnośląskie, grób 41. In: Wandalowie strażnicy bursztynowego szlaku. Lublin-Warszawa 2004, s.290.
31. Półtorak Z., Lecznictwo ludowe rodzinnej ludności Opolszczyzny. Instytut Śląski; Opole 1989.
32. Sokół S. Historia chirurgii w Polsce. Cz. 1. Chirurgia okresu cechowego. Wydawnictwo PAN; Wrocław 1967.

Emergency medicine

Bioterrorism — nature of the problem

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Summary:

In the 20h century, terrorism became a threat to international safety. Over the past 100 years, terrorism became transformed and became a factor to a large extent determining the sphere of political, economical and social relations on local, regional and international levels. Advancing globalization and accompanying progress in the field of IT and telecommunication technologies facilitated emergence of new forms of this phenomenon and widening of its spatial scope.

Key words: terrorism, biological weapons, biological weapons development programs.

We should seek the genesis and beginnings of bioterrorism much earlier, although all forms of its employment fall, in a more intense shape, at the turn of the 20th and 21st century. Its issues, essence and nature should rather be combined with, rather than detached from, generally understood terrorism. Experts on the issue associate this phenomenon, which is now widespread and considered one of the main global problems, with a symptom of "degeneration of war." A growing number of civilian casualties constitute its illustration. Degeneration of war is accompanied by a tendency described by Boleslaw Balcerowicz as "lowering of war threshold" [1]. It is an inclination toward conducting warfare against a population of people completely uninvolved, intentionally at least, in any military conflict. Such actions are called "quasi wars" and their toll is based on the lack or low level of awareness among civilian population in a given region, city or territory of a given country. Destructive actions are no longer reserved for states, as main players in international relations and subjects of international public law. Suitably prosperous, although poorly armed ideologist or even an ideological maniac playing on fanaticism can evoke a conflict on an international scale. With that, he can perform a detonation not only in its mechanical sense, but also detonate the sense of common, individual and personal safety and introduce a broadly defined psychosis of fear.

Despite multiple publications on terrorism, it is difficult to establish a uniform definition of this phenomenon. It should be noted that there are about two hundred expressions in the whole literature. Phonetically, it is almost identical in all European languages and therefore, understood by everyone (fr. terrorisme, sp. terrorismo, rus. terrorizm).

Two definitions should be mentioned in relation to the problem of bioterrorism as an accepted façade of broadly defined terrorism. One of them is taken from an encyclopedia (published by PWN in Warsaw in 1993, page 864), defining terrorism as: " an activity of small extremist groups that, through murder, death threats, political murders, kidnapping of hostages or planes and

similar means despised by the international community, try to turn public attention to their statements or to force governments to succumb to their demands."

The other definition was created in 1996 by the Federal Bureau of Investigation and defined terrorism as: "unlawful use of force and violence against people and possessions (ownership) in order to frighten or force the government, civilian population or any other sector of the state system to support political or social demands."

All definitions contain two fundamental elements: "fear" and "forcing behavior." Moreover, a definition of a terrorist used by the Oxford dictionary emphasizes that a terrorist act is: "planned, calculated and premeditated" [2].

Due to a growing demand among terrorists for attacks associated with an increasing number of casualties and easier access to materials and technologies used for production of weapons of mass destruction, we should conclude that the probability of using chemical, atomic or biological weapons by terrorists is growing and becomes more and more substantial.

In contrast to chemical substances, biological material (viruses and bacteria) is characterized by the ability to reproduce and mutate. As a result, they become increasingly more dangerous and resistant with time. A single bacteria is capable of dividing every 20 minutes. After 10 hours, we can obtain a billion of daughter cells. It directly follows that it is relatively easy to produce a weapon capable of killing millions of people.

Anthrax bacilli (Bacillus anthracis) attack mainly sheep, cows and goats, which become infected through the oral route. Bacteria is transmitted through water, insects, wild animals or birds and their excretions. Human infections are rare. About 95% of cases constitute lighter forms of the disease involving the skin. When (5% is sufficient) anthrax invades the lungs, patient usually dies. Bacteria are not transmitted from one human to another and patient isolation is not necessary. Vaccines partially protect from anthrax, but they must be administered repeatedly.

On the basis of American simulations regarding the toxicity of anthrax it was concluded, that an airplane drop of 50 kg of bacteria from 2000 m onto a city with a population of 500 thousand people would result in 135 thousand of infected patients, 90 thousand of which would die [3].

Relatively simple equipment, such as ordinary fermenters, is needed for growing bacterial cultures and obtaining pathogens and toxins does not pose any problems.

All of these "qualities" were and are known to terrorists and attempts were made to obtain the resources for bioterrorist attacks. Armed Islamic Group (GIA) conducted experiments in this respect in a biological mini-laboratory in Paris. The AUM sect was preparing for a large-scale attack with, among other things, biological agents. They employed scientists and technicians from Japan and Russia. Professional laboratories were arranged. The sect was partially ready for production of biological weapons, including anthrax, a very contagious disease called Q fever and probably the deadly Ebola virus. Seriousness of the threat is evidenced by the fact that it owned a special, double-turbine helicopter Mi-117 equipped with instrumentation for chemical spraying. It also conducted first biological attacks.

In 1990, using a sprayer of their own construction, terrorists attacked Tokyo downtown with botulin toxin. It turned out to be ineffective, but there were two repeated attempts the same year. The scope of biological weapons used by terrorists includes, beside the previously mentioned anthrax, botulin (also known as "sausage poison"), plague and smallpox. The latter, eradicated around the world in 1980, is still stored in two places: Atlanta (USA) and Kolcovo (Russia).

There are currently several visions of the world threatened by lab-modified microbes. Professors: Claire Fraser from Institute for Genomics Research in Rockville (Maryland) and Malcolm Dando from the University of Bradford in Great Britain are warning on the pages of "Nature Genetics" that rapidly progressing works on decoding microbial DNA can serve development of new varieties of difficult to detect microorganisms, for which there are no vaccines or drugs. It is estimated that as soon as this year or in two years at the latest we should learn the sequence of nucleotides of over 70 viruses and bacteria. Last year, molecular biologists drew a DNA

map of cholera, listeria (causing gastrointestinal infections), leprosy (evoking fear in the antic and medieval times) as well as one of the most dangerous bacteria, Streptococcus pneumoniae – an etiological factor of pneumonia, meningitis, otitis media and peritonitis, which kills over 3 mln children each year and increasingly often becomes resistant to antibiotics [4].

These studies can be used for development of new drugs as well as for better understanding of evolutionary mechanisms. Similar to atomic energy, it can be used both for the benefit of people as well as against them – e.g. development of lethal biological weapons. Such experiments are already being conducted. As early as in 1999, Professor Malcolm Dando cautioned in his book "Biotechnology Weapons and Humanity" that development of a biotechnological bomb directed against specific populations (e.g. Arabs, Serbs, Black men, Kurds or Jews) would become possible during the next 5-10 years. Such microorganisms, like cruise missiles, can be designed for destruction of selected biological targets, e.g. people with particular cell receptors or DNA sequences. It suffices to appropriately remodel genomes of bacteria or viruses causing cholera, plague, flu or hemorrhagic fever to turn the grim visions of science-fiction authors into a real threat.

Unfortunately, progress in the field of genetics is increasingly more often used for development of biological weapons. In 1998, David Kelly, a leading United Nations specialist, warned about his suspicions that works on such type of biological weapon had been conducted in Iraq under codename Camel Pox. They were directed at producing pathogens, to which only Arabs would be resistant. Effect of this research is unknown. Wonter Basson, a military biologist from South Africa accused of conducting studies on organisms directed specifically against the black population, gained a nickname "Dr. Death." In this case, the commentators emphasized a clearly emerging threat. There are multiple such causes for concern. Even following the attacks on New York and Washington and in cases of sending anthrax by post, it seems unlikely for the terrorists to have access to more advanced biological technologies. However, it must be a cause for concern that genetic modification of pathogens is easier than anticipated. For years, multiple biological weapons experts argued that the more modifications are introduced, the greater the risk of pathogens becoming less viable and no longer posing a presumed threat. However, it is sometimes sufficient to introduce even small genetic changes to transform a harmless microbe into a lethal pathogen.

Research conducted only several months ago by Australian scientists corroborated that. They accidentally created a particularly dangerous poxvirus following introduction of only one gene into its genome. Scientists from the Australian National University tested a pregnancy vaccine. They used a murine poxvirus transfected with interleukin IL-4 gene. It was supposed to induce formation of ovulation-inhibiting antibodies. Instead, they completely blocked rodents' immunological response protecting them against infections. Until now, it seemed that such manipulations could only weaken microorganisms.

Worldwide arsenals contain 43 types of biological weapons. Viruses, bacteria, rickettsiae (intracellular microorganisms) are used for their production, including genetically modified lethal pathogens, more dangerous than those discovered by scientists in a natural environment. In 1997, anthrax bacilli containing an additional gene were developed in Russia, against which available vaccines do not provide any protection. The most dangerous virus called Ebolapox was also developed by crossing poxvirus with Ebola. This pathogen combines exceptional infectivity and huge mortality. Ken Alibek, the former head of secret Soviet laboratory, Biopreparat, located in 40 cities and employing 70 thousand people, confirmed those facts during his stay in the USA.

Americans conducted similar research during the Cold War. In 1986, as a part of over fifty biological weapon development programs lead by the Pentagon, American scientists induced harmless E. coli bacteria to produce anthrax toxin within the intestine. Journalists from "The New York Times" exposed this fact in a bestseller titled "Germs: Biological Weapons and America's Secret War." It is worth noting that this research is still continued. On that occasion, "Der Spiegel" disclosed that there are experiments conducted on behalf of the Bundeswehr regarding production of Yersinia pestis resistant to antibiotics [5].

A Russian biologist, Siergiej Popov, who emigrated from Russia to Great Britain in 1992 and

later traveled to the USA, revealed that he had conducted research on microorganisms designed to confuse victim's immunological system and lead to central nervous system auto-destruction. He took advantage of the mechanism of multiple sclerosis development, which is one of the most dangerous disorders of central nervous system. It is an autoimmunological disease. Instead of destroying only foreign pathogens, immunological system causes destruction of myelin, which is an important component of nervous sheaths facilitating proper functioning of nerves.

Is it likely that terrorists could blackmail the world with such pathogens? Experts from "British Medical Journal" persuade that biological weapons, similar to chemical weapons, are primarily instruments of inducing fear.

A new stage of bioterrorism expansion was initiated at the end of September 2001. Terrorists began to distribute anthrax bacilli in the USA (Florida, New Jersey) via mail. On the 12th of October, anthrax struck New York. Attacks were directed at people representing the media (employees of NCB, AMI, "The Sun," "New York Times") and the government (offices of United States senators). Thirty-six anthrax infections, including one fatal case, were noted until the 23rd of October 2001. Despite difficulties associated with use of biological weapons as weapons of mass destruction, it evoked panic among American community as well as in Europe. United States government even considered early weaving of patent rights of Bayer Co. – the only producer of ciprofloxacin, an antibiotic effective against anthrax.

Not even the most absurd threat should be ignored nowadays. Bioterrorism grows. The reasons should be traced to the fact that biological weapons are easy to apply and transport. Their low cost can also be encouraging, as mentioned by professor Wieslaw Magdzik from the National Institute of Hygiene in Warsaw, who warned against it as far back as may 2001.

Experiences from previous terrorist attacks noted by the Monterey Institute of International Studies show that incompetent authorities, disorganization of rescue services, panic and poor level of social education are greatest allies of the attackers. To some degree, it is the price we pay for contemporary civilization. In case of ecological disaster, we usually know what substances we are dealing with.

A terrorist attack involves a series of unknowns. Rapid identification of the resources used by the aggressor is crucial to achieving success. Currently, hospitals introduce an electronic disease registration system equipped with special software. Its job is to identify anomalies (e.g. excessive number of infections with particular bacteria or viruses in a given time). A single case of anthrax infection might not arise the vigilance of hospital staff. However, if it appears that similar information flows from several hospitals, the system will alert the crisis management center.

Words suggesting the use of various bacteria, often implying alleged possession, are most dangerous in the context of this atmosphere. Like toxins, they invade the sense of security in all dimensions. Terrorists' goals are often directed not so much at large numbers of casualties, but at gaining publicity and transmitting their message through the media, which may bring fatal consequences in an era of information society.

References:

1. B. Balcerowicz, Obronność RP a dialektyka wojny i pokoju na progu XXI wieku, cz.I, AON, Warszawa, 2000.
2. Mały oxfordzki słownik historii świata w XXw., Puls, Londyn 1992; Raport (No 2000/02. Chemical, Biologica], Radiological and Nuclear (CBRN) Terrorism, publikacja: Comadian Security Intelligence Service (dost. on-line: www.fas.org).
3. Strach przed bioterroryzmem, "Newsweek Polska", nr 7, s. 151-154.
4. Z. Henisz, Biobomby, „Polityka", nr 46 z 17 listopada 2001, s. 85.
5. TERRORYZM – ZAGROŻENIE GLOBALNE I LOKALNE, Biuro Bezpieczeństwa Narodowego, www.bbn.gov.pl.

Emergency Medicine

Anti-drown ring – a patented drowning protection device (patent no. 197623)

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Summary:

The anti-drown ring is a device that does not restrict the user's movements and, when activated, brings the critical drowning hazard situation under control and allows the user to safely remain in water.

The anti-drown ring, being an inexpensive drowning protection device, should be universally available for water lifeguards, swimming schools, aquatic sports or open-air recreation centers, fishery and other aquatic industries, as well as for military personnel training or operating in areas that require crossing water barriers

Key words: aquatics, equipment, rescue.

Introduction

The beginning of the summer holiday season is always accompanied by media warnings to maintain caution when bathing in open reservoirs. Most cases of drowning are recorded at non-attended beaches. These cases pertain mostly to the youth, but also to adults, oftentimes taking a swim after drinking alcohol in quantities that increase risk-taking, bravado and courage show-off behaviors.

Several hundred drowning cases are recorded every year across the country, with the maximum value reaching as much as 600 drowning cases during a single season.

Methods of aquatic rescue to date

Compared to the development of technical devices that facilitate everyday life in all areas, methods of aquatic rescue used to date should be judged in a very critical manner. Even the most efficient lifeguards are not always able to provide timely rescue aid to the drowning person, as the equipment they have at their disposal is usually limited to the anachronistic life buoys and boats.

This form of rescue is often to no avail, as the time between the alarm and the rescue is too long.

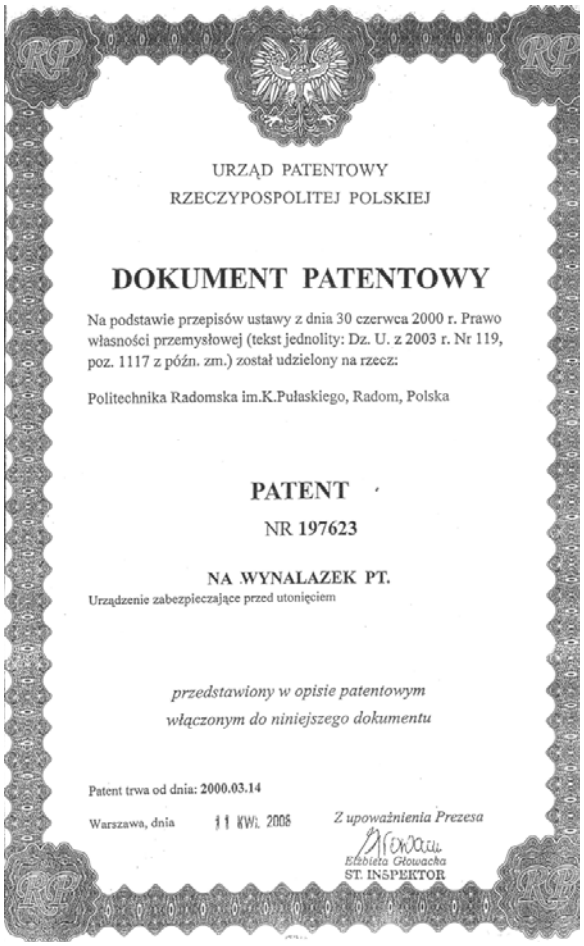
Therefore, there is a need to revise the rescue methods available to date. We should strive to be

able equip the person in water with a device that would allow them to manage the drowning hazard by themselves, without the dramatic wait for rescue. To date, the only device of this type is the life jacket, which restricts the movements and the ease of swimming, and which is used mostly by people working on ships and fishing boats.

The search for novel water rescue devices

For many years, various personal rescue devices, oftentimes automatically-triggered devices that could be worn by every individual staying in open reservoirs, have been proposed. Many devices of these type are known from Polish patent descriptions nos. 52602, 105721, 59710, 105722 and 70297

However, the mechanisms to trigger these devices are complex and usually respond only following complete immersion of the drowning person under increased hydrostatic pressure that ruptures the foil surrounding a bag that is then transformed into a life buoy.



URZĄD PATENTOWY
RZECZYPOSPOLITEJ POLSKIEJ

DOKUMENT PATENTOWY

Na podstawie przepisów ustawy z dnia 30 czerwca 2000 r. Prawo własności przemysłowej (tekst jednolity: Dz. U. z 2003 r. Nr 119, poz. 1117 z późn. zm.) został udzielony na rzecz:

Politechnika Radomska im.K.Pułaskiego, Radom, Polska

PATENT
NR 197623

NA WYNALAZEK PT.
Urządzenie zabezpieczające przed utonięciem

przedstawiony w opisie patentowym
włączonym do niniejszego dokumentu

Patent trwa od dnia: 2000.03.14

Warszawa, dnia 11 KWI. 2008

Z upoważnienia Prezesa
Elżbieta Głowacka
ST. INSPEKTOR

Figure 1: Title page of patent no. 197623 regarding the invention titled DROWNING PROTECTION DEVICE, as discussed in the article.

Title page of patent no. 197623 regarding the invention titled DROWNING PROTECTION DEVICE, as discussed in the article.

Anti-drown ring design summary

When not activated, the anti-drown ring in question is a thin ring made of elastic rubber tubing freely placed around the neck and not restricting

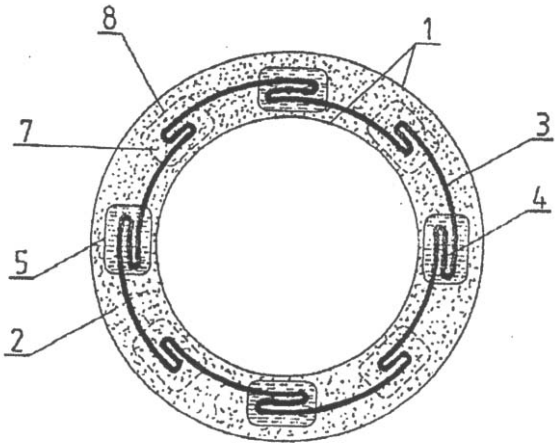


Figure 2:

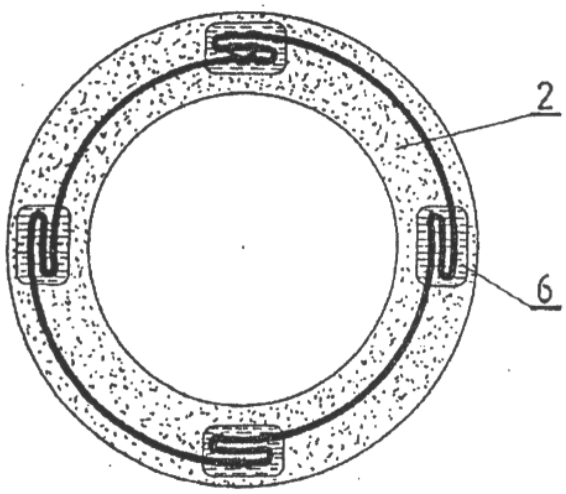


Figure 3: Figures 2-3 present the circular cross-section of non-activated system.

The numbered arrows indicate as follows:
1 – cross-section of the walls of the anti-drown ring;
2 – tubing lumen filled with acidic reagent;
3 – cross-section of ribbon with indicated bends;
4 – ribbon bend inside the container filled with alkaline reagent;
5 – alkaline reagent container wall;
6 – alkaline reagent placed in the container with ribbon bend;
7,8 – free ribbon bends in acidic reagent environment.

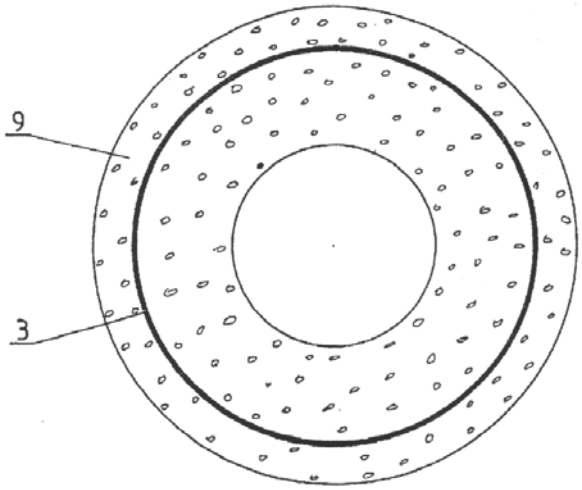


Figure 4: Figure presents a schematic circular cross-section of the anti-drown ring filled with gas. Of note are the wider device lumen and straightened ribbon bends.

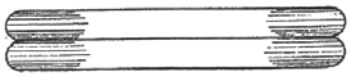


Figure 5: Figure presents a transverse cross-section of an anti-drown ring consisting of two parallel tubings.

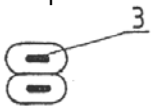


Figure 6: Figure presents a transverse cross-section including the ribbon cross section indicated by arrow 3

the user's movements in water. The diameter of the ring is slightly smaller than the diameter of human head, which prevents the device slipping off neck and head while making rapid movements in water.

Inside the tubing, there is a loose-fitted ribbon made of material characterized by high resistance to tear and to various ambient conditions.

Besides the ribbon, the inside of the tubing is filled with reagent 1, which is a solution of an acidic substance. The ribbon includes several tightly insulated bends comprising containers filled with reagent 2, which is a powdered alkaline substance.

The walls of containers filled with reagent 2 are made of material impenetrable to both materials, albeit relatively easy to tear.

Explanations to figures 2-5: Figures presenting schematic cross-sections of the anti-drown device of the invention.

The principle of operation

The anti-drown ring is slightly extended and placed on the neck by sliding it over one's head. When at risk of drowning, the user holds on to the device and tears it so as to unfold the folds of the ribbon inside the containers filled with reagent 2. Unfolding the ribbon leads to the container walls being ruptured, leading to the release of the alkaline reagent (reagent 2) from the containers into the acidic reagent (reagent 1) that fills the tubing.

Mixing both reagents leads to an instantaneous chemical reaction with the release of gas which automatically transforms the tubing into a pumped bladder. The quantities and rations of both reagents should be matched so as the formed gas extends the tubing to a diameter of ca. 10 cm. Thus, the bladder buoy formed around the neck provides displacement sufficient to maintain one's head above water while allowing to maintain free movements of entire body.

Loose fitting of the ribbon inside the tubing is provided by ribbon bends not placed in containers with reagent 2 (free bends). This solution allows for slight expansion and multiple putting on and removing the anti-drown ring without damaging the walls of containers with reagent 2 and thus triggering the unwanted chemical reaction generating gas when putting on the device.

Such a design solution allows the resistance to be felt twice: the first time when the ribbon is straightened out at free bends, and the second involving the rupture of container walls, leading to contact between both reagents and generation of gas.

Leak protection

The anti-drown ring made of thin rubber tubing may be at risk of accidental puncturing. In order to avoid such risk, the ring may be made of two parallel tubings fitted with identical ribbons and identical reagents.

The benefits of the anti-drown ring

The anti-drown ring is characterized by the simplicity of technical solution, capability of being put on and removed multiple times before a

critical situation is encountered that requires the device to be activated.

The incentives to start production of the anti-drown ring should with no doubt include low costs of materials required for production (rubber tubings, ribbons, reagents) and, as a consequence, low prices that would make the device available to everyone.

Production and marketing of the anti-drown ring

Design preparation, production of a prototype batch and initiation of production would require efforts to obtain funds from state or European Union budget allocated to water rescue, or from private sponsors.

The prototype series should be made in order to raise interest of sponsors so as to acquire funds required for the development of technical solutions for serial production of the anti-drown rings. Semi-technical scale implementation works should be made in institutes (plants) developing rubber industry machinery.

The next marketing stage would involve the promotional campaign, mostly in the media as well as in the water industry aquatic sports and recreation centers, the military, the police and public schools of all levels.

The promotional campaign should include presentations in shopping centers and at the aquatic sports and water rescue equipment trade fairs.

After the anti-drown rings are well accepted by the general public, technical solutions should be developed so as to allow automated mass production of the devices.

Mass marketing of anti-drown rings

With mass-production capabilities available, promotional campaigns should be organized at the national and international aquatic sports and water rescue equipment trade fairs.

Likewise, long-term educational campaign should be started to promote the benefits of such a simple drowning protection device. Trainings should be provided mostly to individuals spending free time at or working on open water reservoirs.

Strategic goals of the promotional campaign

Dissemination of social awareness of the benefits of using the anti-drown rings.

Introduction of legal obligation to use anti-drown rings by individuals staying in open water reservoirs.

The ultimate goal would be to reduce the annual number of statewide drowning cases from several hundred to not more than several dozen accidents (wintertime and flood drowning).

The obligation to use the anti-drown rings would lead to a great change in the profile of water rescue activities by limiting the latter to educational and preventive activities, including the control whether individuals staying in open water reservoir wear the rings.

The planned strategic goals may be achieved by convincing entrepreneurship-supporting institutions and decision makers about the attractivity of the device, obtaining funds for prototyping, promotion, trainings and initial production stages.

Depending on the societal interest and demand for anti-drown rings, mass-scale production should be undertaken so as to meet the market demands.

As the experience in using the anti-drown rings would grow, the proposed model might be modified provided that the general principle of operation and use remain unchanged.

History of medicine

Speech made by Commandant of the Military Centre for Pharmacy and Medical Technology in Celestynów, Colonel DMSc Radosław Ziemba

Radosław Ziemba

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Ladies and gentlemen!

We have an honourable opportunity to attend the ceremony of Mr Colonel Krzysztof KONDRACKI parting with the uniform of the Polish Army. This ceremony is all the more solemn as it falls on 29 November – Day of Officer Cadet, which

Figure 1: Col Radosław ZIEMBA, M.D., Ph.D., the Commander of the Military Center for Pharmacy and Medical Technique, awards a saber on behalf of the staff of the Center to Col Krzysztof Kondracki, M.Sc. (Pharm.), as a symbol of bravery of the Polish army and of military duty and loyalty.

Figure 2: Col Krzysztof Kondracki, distinguished by the Commander with a photo against the background of the Banner of the Military Center for Pharmacy and Medical Technique.

Figure 3: The Commander of the Military Center for Pharmacy and Medical Technique awards an encyclopedia to Col Krzysztof Kondracki.

Figure 4: The retiring Col Kondracki gives a speech to the guests attending the event.

is a special day for every officer. The officer cadet period is an introduction to an officer epic, and Mr Colonel started the latter on 31 June 1978 with studies at the gen. Bolesław Szarecki Medical Military Academy in Łódź at Pharmaceutical Faculty. It's worth adding that he simultaneously studied pharmacy at the then existing Medical Academy (civilian university) in Łódź.

He began the studies after obtaining a certificate of secondary education at Frédéric Chopin Secondary School in Sochaczew.

I wish to add that Mr Colonel Kondracki has continued the traditions of the officer ethos, as he was born into the family of an officer who served in 32nd regiment of fighting and reconnaissance air forces in Sochaczew. It is with this town that Mr Krzysztof bound his life from his birth, through Primary School, until he obtained his certificate of secondary education.

On Łódź Soil he made important decisions of his life, as in January 1982 he married Wanda, here his son Maciej was born, now also a holder of an MPharm degree. From 10 May 2010 to 6 May 2011, his son participated in the 7th change of Polish contingent in Afghanistan. Thus, Mr Kondracki's son is also continuing the family traditions in some way.

As far as the children are concerned, the hero of today's celebrations adopted gender parity a few years ago, as in April 1985 his daughter Agata was born in Celestynów – now as a physiotherapist.

It is with Celestynów, or the Military Centre for Pharmacy and Medical Technology to be precise, that he bound his first eight years after completing the studies and gaining the rank of an officer on 26 June 1983. In 1986, he was commissioned as a lieutenant (as a section manager), and in 1989 – as a captain. From 18 November 1991 he bound his life with the Central Clinical Hospital of Medical Military Academy at the post of a senior pharmacist where in 1993 he was promoted to the rank of major at the post of deputy manager of the pharmacy and from 23 February 1996 he

took up the post of the manager of the pharmacy and was promoted to the rank of lieutenant-colonel in 1998.

On 12 May 2003 he became the Manager of the Base at the already existing Military Institute of Medicine. Then, on 1 April 2007 he joined the Inspection Office of Military Health Care at the post of deputy Chief Pharmaceutical Inspector of Polish Army and was commissioned as colonel. At this post, at this pace and with this rank, he served until 15 October 2012.

Mr Colonel earned high recognition and respect through his self-discipline, tact, loyalty, authority among colleagues, principled attitude to his service, tactful style of behaviour among co-workers. Always modest, genuine, without excessive pretensions or elation. He always showed helpfulness and responsibility, fulfilling a discursive approach to the idea of officer and pharmaceutical ethos. You are, Mr Colonel, a Paracelsus in the uniform for us.

Mr Colonel, a specialist in many areas of pharmacy – especially military one – we have immortalized you in a photograph against a background of the banner of the Military Centre for Pharmacy and Medical Technology in Celestynów. It is there that you started your initiation into the service.

We also have the great honour to hand this piece of cold steel called a sabre. Having different patterns, through centuries it lighted with the flash of the blade often heroic deeds of the Polish army, accompanied cavalry troops, and today adds colour to parades, state and military celebrations. So let it be in your hands the symbol of fulfilling a soldier's duty and loyalty in the officer community.

Let the motto engraved at its handle:

"A reliable friend is recognized in an uncertain situation…" determine your acts in this stage of life.

IMĆ Panu Pułkownikowi Krzysztofowi KONDRACKIEMU idącemu w nowy seans życia „pod kapeluszem”

Akt one, scena pierwsza

Przez dyskretny otwór w kurtynie
wejrzeć tylko w zakulisy wiersza
z historii losu spojrzeć o pustej godzinie
kiedy widownią są oczy, a uszy słuchowiskiem
i cienie rzęs na uboczu
więc rozprawimy się z jednym nazwiskiem
za którym stoi ten oto…

Krzysztof zawinął bieg swojej historii
choć wszystko w niej bywa odmienne.
Tak pewien dzień października
w tysiąc dziewięćset pięćdziesiątym dziewiątym
wyłonił go nam na tę ziemię.
Waga mu rysy rzeźbiła na twarzy
kiedy wodził oczyma po sochaczewskim niebie.

Tamte twarze szkolnego ornamentu
tamta pamięć ust jak pieczęci,
grona pedagogów, edukacji momentów.
W cenzurze świadectw różne uczniowskie chęci,
Tropem w czasy dojrzałe, lato ciała,
spokój pajęczany, krzewy obute w kiści
kołysały beztrosko – niebieskie lata młodości.

W szkolnych wierszach bagnetów strome błyskawice
tam nasza chluba i naszych możliwości granice,
co noc pośród latarni szukało się srebrnych kawiarni
w dzień nad biurkiem trzeba było się zgiąć,
pod kluczem szopenowskich nut ksiąg…

Przyszedł dzień, kiedy strugi mazowieckiego świtu
wysłały w misję wyroku Dioskurydesa przesłanie
na łódzkim bruku podchorążacko — studenckie ślubowanie
słowa Gaudeamus, żołnierskiej przysięgi
cyzelowały drogę do etosu oficerskiej wstęgi.
W panteonie dwudziestego wieku.

Powroty z balów, dyskotek, klęsk, wypraw krzyżowych
skacząc przez Pietrynę jak po kolorowych krach,
unosząc potem drewniane powieki,
przechodząc niebieską granicę w alchemii farmaceutycznych praw.
Od Hipokratesa idei do Farmakopei
Przy egzaminie – Panie Boże zbaw.

Akt two, scena druga

Na ozłoconym przez bliskość balkonie
Pani Wanda założyła dłonie
niech mnie Krzysztof z nadziei wybawi
w przestworzach mojego świata się zjawi
zimowego stycznia szesnastego
złotych obrączek ikona
oświetlała marsza Mendelsona…

W sierpniu zszedł z niebiosa
Maciej, syn łaskawy, pociecha rodziców
jako w maju rosa co pada na trawy,
cicho zszedł w objęcia do komnaty matki
jak majowa rosa co pada na kwiatki
nazwisko jak totem utrwalone potem.

Nie zapominaj jaka to siła
w czerwcowe słońce gwiazdki zdobyła
etos olśniła i animuszu do farmacji
dodała Panu od wtedy co chwila.
Z tego posłania od łódzkiej ziemi
w Celestynowie między nowemi.

Akt three, scena trzecia

Taki to czas był, co dzierżył w swej treści
młodości radości i dobytek mnogi
dziecięciom płaci w lasach mazowieckich
odtąd z Agatką przechodziłeś wszystkie drogi.
Czasy edukacji, tym razem dla dzieci
co troską ojcowską trzeba było cieszyć.

Można by wieczność zobaczyć wśród nocy
kiedy się z wojskową farmacją połączył
jak wielki pierścień życia nieskończonej mocy
na tło ogromnych cieni do tej właśnie sprawy
rzucono kapitana w konszachty Warszawy.
Jak u światłych ludzi czasem bywa,
przyszła kariera nawet całkiem błyskotliwa.

Czasem tony przedziwne bezrozumnej skargi,
obok nich jak z lutni fantazje i fraszki
różnej cierpkości dowcipnego lotu igraszki.
Obok nich pokłony i uciech zasadzki wszelakie,
cierpkie lecz drogie, jakby skarby jakie
rozpraszają człowieka , z doświadczeń bogaty.

Nadziejo święta, pokoro wysoka
jak szczyt niebios wśród planet pochodu
Twój wielki szlak jest wskazany dla oka
Ty znajdziesz gniazdo jak ptak opierzony
wyfruniesz łatwo, sam to dostrzec zdołasz.
Powracaj znów zatem w Celestynowskie strony…

Krzysztof Barczewski
Anno domini 29 listopada 2012

Editorial policy and general information

Military Pharmacy and Medicine is an international, peer-reviewed scientific journal that publish original articles based on own research, as well as review articles and case reports in the field of pharmacy and military medicine, and modern solutions in the field of military and civilian healthcare based on the latest national and international achievements.

Military Pharmacy and Medicine is quarterly interdisciplinary journal of Military Centre of Pharmacy and Medical Technique in Celestynów, Poland, published in English on scientific, socio-professional and training issues of Military Pharmacy and Medicine. Journal appears continuously and systematically in printed (primary version) and on-line version since 2008 at: *http://military.isl-journals.com/* and information contained therein are continuously updated, but not less frequently than quarterly.

The editors endorse the principles embodied in the Declaration of Helsinki and expect that all investigations involving humans will have been performed in accordance with these principles. For animal experimentation reported in the journal, it is expected that investigators will have observed the Interdisciplinary Principles and Guidelines for the Use of Animals in Research, Testing, and Education issued by the New York Academy of Sciences Adhoc Committee on Animal Research. All human and animal studies must have been approved by the investigator's Institutional review board. It is recommended to enclose a copy of that document to a submitted manuscript.

Editors *Military Pharmacy and Medicine* in the daily practice refer to the guidelines of the Committee on Publications Ethics concerning Code of Conduct and Best Practice Guidelines for Journal Editors (*http://publicationethics.org/resources/guidelines*).

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Editors consider only submissions in English. Manuscripts are evaluated on the basis that they present new insights to the investigated topic, are likely to contribute to a research progress or change in clinical practice or have the desirable teaching/training value. The correctness ensures Editor-in-Chief, Deputy Editor, Section Editors, Statistical Editor, reviewers and Linguistic Editors.

The signature of the corresponding author on the letter of submission signifies that:

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Received manuscripts are first examined by the *Military Pharmacy and Medicine* editors due to preparation of the manuscript, photographic documentation, and all authors consent to publication. Manuscripts with insufficient priority for publication are rejected promptly. Incomplete packages or manuscripts not prepared in the advised style will be sent back to authors without scientific review.

The authors are notified with the reference number upon manuscript registration at the Editorial Office. The registered manuscripts are sent to at least two independent experts for scientific evaluation. Competent reviewers designate Editor-in-Chief. Reviewers prepare opinions that contain reasoned recommendations and suggestions of corrections and additions to content and form of the article. In case of papers written in a foreign language at least one of the reviewers is affiliated to a foreign institution. Reviewed paper and reviewers did not come from the same institution.

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Submitted papers are accepted for publication after a two positive opinion of the independent reviewers, who agreed that the paper can be published in present form. If the reviewers differ in their opinions, or feel that the manuscript should be accepted only after the corrections, editors may take a decision to send paper to another reviewer in order to settle or return it to the authors for correction.
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Editorial Board of *Military Pharmacy and Medicine* takes under consideration for publication original articles in experimental and clinical medicine and related disciplines with the understanding that neither the manuscript nor any part of its essential substance, tables or figures have been published previously in print form or electronically and are not taken under consideration by any other publication or electronic medium. Copies of any closely related manuscripts should be submitted to the Editor along with the manuscript that is to be considered by the *Military Pharmacy and Medicine*. The Editor discourages the submission of more than one article dealing with related aspects of the same study.

Each submission packet should include the statement signed by the first author that the work has not been published previously or submitted elsewhere for review and a copyright transfer.

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Accepted manuscripts are published in the following journal sections:

1) Original articles: reports of previously unpublished results from scientific experiments conducted by the authors in order to confirm or refute a clearly identified hypothesis. Most of the articles published in a given issue will belong to this category.

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Antoni Penc MD PhD, Department of Radiology, University Hospital, Dobra 22, 01-153 Warsaw, POLAND; phone (+48) 227786734, fax: (+48) 227776671; e-mail: *antoni.penc@wp.pl*;

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Papers published in journals:

12. Pui CH, Behm FG, Raimondi SC et al: Secondary acute myeloid leukemia in children treated for acute lymphoid leukemia. N Eng J Med, 1989; 321(3): 136–42.

Book chapters:

3. Kowalczyk JR: Cytogenetics of secondary leukemias. In: Becher R, Sandberg AA, Schmidt CG (eds.): Chromosomes in Hematology. W. Zuckschwerdt Verlag, Munchen, 1986,pp. 125–45.

Electronic materials (Internet):

6. Martin JM: A software for the description of workplaces in the PRS system. http://www.matforsk.no/ola/fisher.htm (accessed 29.08.2002).

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