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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.

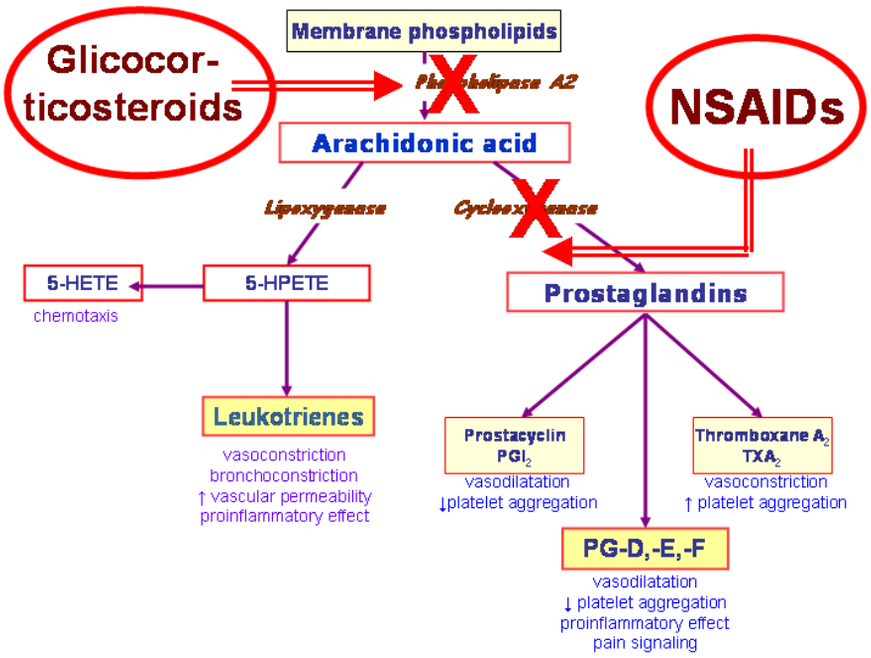


Figure 1: Metabolizm of arachidonic acid (AA) with the aid of cyclooxygenases (COX) and lipoxygenases (LOX) and sites of actions of non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticosteroids in comparison.

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*, *nepafenac*, *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

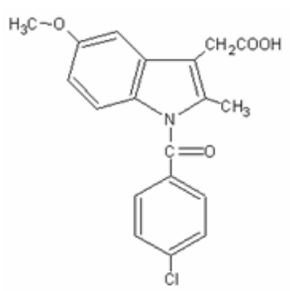
Bromfenak	**Yellox**	0,09% eyedrops; 0.9 mg/ml	Croma/B&L
Diclofenak	**Dicloabak** **Difadol 0,1%** **Naclof**	0.1% eyedrops; 1 mg/ml	Thea Polfa W-wa Novartis
Indomethacine	**Indocollyre**	0.1% eyedrops; 1 mg/ml	Chauvin B&L
Nepafenak	**Nevanac**	0.1% eyedrops; 1 mg/ml	Alcon
Flurbiprofen	**Ocufen** **Ocuflur**	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).

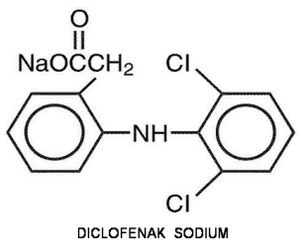


Figure 3: Chemical structure of sodium diclofenac.

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).

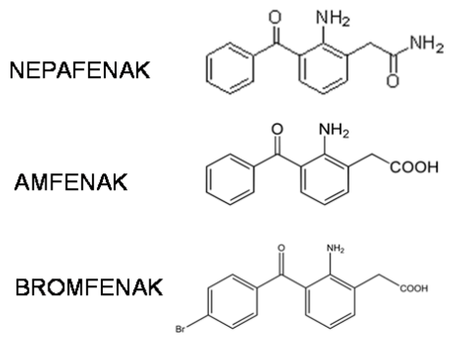


Figure 4: Chemical structure of nepafenac, amfenac and bromfenac.

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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