

# Comparison of drugs belonging to the group of ophthalmic non-steroidal anti-inflammatory drugs



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## HIGHLIGHTS

Non-steroidal anti-inflammatory drugs are one of the most widespread classes of drugs in the world. In ophthalmology diclofenac, bromfenac, nepafenac and ketorolac are the most commonly used drugs, which differ in dosage time, form, safety profile and potency.

## ABSTRACT

Ophthalmic non-steroidal anti-inflammatory drugs are non-steroidal anti-inflammatory drugs used to treat or prevent eye inflammation. Their main action is to relieve symptoms such as pain, redness and swelling that can be caused by eye diseases, injuries or eye surgery. Non-steroidal anti-inflammatory drugs used in ophthalmology include substances such as diclofenac, ketorolac, bromfenac and nepafenac. So far, many studies have been published comparing the effectiveness of various systemic and local non-steroidal anti-inflammatory drugs. This work contains a comparative analysis of the above-mentioned substances in terms of their use and effectiveness in ophthalmology.

**Key words:** non-steroidal anti-inflammatory drugs, diclofenac, ketorolac, bromfenac, nepafenac

## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of drugs with analgesic, anti-inflammatory and antipyretic properties, the primary mechanism of action of which is the inhibition of the activity of various isoforms of prostaglandin H<sub>2</sub> synthase, otherwise known as COX cyclooxygenase. NSAIDs can be classified due to their selectivity towards COX isoforms into preferential COX-1 inhibitors or COX-2 inhibitors, or due to their chemical structure into salicylic acid derivatives or arylacetic acid derivatives, which is related to the occurrence of side effects when using a specific group of drugs. In ophthalmology, NSAIDs are used in the treatment of bacterial, viral and fungal infections as well as in the treatment of non-infectious inflammation, relief of inflammation and pain after surgical procedures [1]. Most medications are given topically as eye drops or ointments. The most commonly used drugs are diclofenac, bromfenac, nepafenac and ketorolac, their dosage varies depending on the preparation [2]. So far, many studies have been published comparing the effectiveness of various NSAIDs [3]. NSAIDs are also widely used in treatment age-related exudative macular degeneration [4, 5]. There are also many studies in the literature that confirm that bromfenac, diclofenac or nepafenac reduce postoperative inflammation after cataract surgery [6, 7].

## DICLOFENAC

Diclofenac is a popular and commonly used NSAID in ophthalmology [8]. Applied topically, it penetrates into the anterior chamber of the eye without causing systemic effects. Its effects have been appreciated in many branches of ophthalmology. In the ER (emergency room) diclofenac found its use in the analgesic treatment of corneal erosion. According to randomized trials, it was observed that by giving diclofenac to random pediatric patients with this injury and using oxycodone with acetaminophen on an ad-hoc basis, there was a significant pain relief in patients using diclofenac compared to a control group that didn't use drugs mentioned above. Additionally, in patients using diclofenac the necessity to use oxycodone with acetaminophen on an ad-hoc basis has decreased, comparing to patients in the control group. This confirms the belief in the legitimacy of using this NSAID in this type of disease, especially bearing in mind the quick duration of action and the circumstances of drug administration [9]. An important problem in the first days after cataract surgery is persistent inflammation, eye pain and discomfort. NSAIDs are commonly used in such cases [10]. Studies comparing the effectiveness of diclofenac and bromfenac show that both drugs are effective in reducing inflammation. The difference can be seen in the fact that diclofenac required intensive and prolonged schedules of administration, which can be burdensome for

the patient [11]. On the other hand, bromfenac was better tolerated because it required a lower daily dose and a shorter absorption time to achieve a therapeutic effect. However, when comparing diclofenac with nepafenac, in both cases a high tolerance of drug absorption by the patient can be observed [8]. Pain may also accompany photorefractive keratectomy (PRK). A randomized study showed a difference in the analgesic effect of a solution of 0.1% diclofenac and 0.1% nepafenac. On the second day after PRK surgery, patients using nepafenac experienced less photophobia in the morning and less pain at bedtime. This doesn't change the fact that diclofenac can also be used to alleviate this type of ailment [12]. Like all NSAIDs, diclofenac has its side effects, most often caused by local irritant effect. This causes symptoms of stinging or conjunctival congestion [10]. A burning symptom was also observed after administration of the drug [9].

## KETOROLAC

Of the compared NSAIDs, ketorolac is the strongest COX-1 inhibitor and the strongest PGE<sub>2</sub> inhibitor, reaching much higher concentrations in the aqueous humor of the eye [13]. This may result in minor systemic effects after administration of the drug. The effect of ketorolac is used in reducing inflammation after cataract surgery. Researchers in a meta-analysis compared the effectiveness of nepafenac with ketorolac. Both medicines were effective in reducing inflammation and macular swelling. However, there were differences in drug tolerance. Nepafenac was more effective in alleviating discomfort along with symptoms of congestion. However, the above information doesn't change the fact that both drugs can be used after this type of surgery [14]. Ketorolac is also used in refractive corneal surgery for pain relief after operations. This is an important aspect of postoperative management in PRK. Both diclofenac and ketorolac are drugs used in such cases [15]. On the other hand, ketorolac was observed to control better lacrimation and photophobia, which may lead to the choice of this drug by the physician. A randomized study compared solutions of 0.1% nepafenac and 0.4% ketorolac. Two factors were taken into account: effect on corneal reepithelialization and pain. In both cases, healing time was an average of 4 days, and pain relief was effective. No effect on corneal healing was observed [16]. In contrast, nepafenac was more tolerable. Considering only the patient's sense of comfort after PRK surgery, nepafenac will be a better choice. Different results have been observed with epi-laser assisted in situ keratomileusis (epi-LASIK) refractive laser surgery. The two factors tested were pain and the time of eye healing. Nepafenac showed a slower healing time (average 8 days) compared to ketorolac (average 6 days), but the results were not statistically significant. Significant corneal opacity

was also observed in patients taking nepafenac, prompting the discontinuation of further studies. In this case, the results were statistically significant [17]. When considering the benefits of using this NSAID, side effects should also be taken into account. Studies comparing diclofenac, flurbiprofen, ketorolac and indomethacin show that itching symptoms were most frequently reported by patients using ketorolac. In more severe cases, corneal ulceration and thinning may be observed [18]. The side effects presented were isolated and don't affect the general use of ketorolac.

## BROMFENAC

Bromfenac is another drug belonging to the group of NSAIDs. It is similar in structure to amfenac except for the bromine atom in position C4. This modification increases the penetration of bromfenac into the eye tissues, increasing its anti-inflammatory effect. It strongly inhibits the enzyme cyclooxygenase, especially the type 2 (COX-2), and only minimally inhibits COX-1 [19]. Clinical studies on bromfenac consistently confirm the potency of the compound, both in terms of penetration into the eyeball, safety profile and anti-inflammatory effect. Bromfenac in a solution of 0.07% compared to 0.09% once daily has been shown to be more effective in anti-inflammatory and analgesic in patients after cataract surgery [20]. In a pilot study of bromfenac 0.07% and nepafenac 0.3% once daily in phacoemulsified cataract surgery patients, similar benefits were demonstrated with respect to postoperative inflammation, visual acuity and retinal thickness. It should be noted, however, that bromfenac showed a faster onset of anti-inflammatory activity than nepafenac [21]. The efficacy, tolerability and safety of bromfenac 0.09%, nepafenac 0.1% and diclofenac 0.1% in the prophylaxis of cystoid macular edema after phacoemulsification was also studied. Studies have shown that among the three drugs, bromfenac showed the best tolerance and effectiveness [22].

## NEPAFENAC

Nepafenac, unlike other NSAIDs, is a prodrug, i.e. a pharmacologically inactive drug derivative, which makes it an inert molecule. This unique property that allows for rapid penetration of the cornea. In addition, nepafenac is converted by intraocular hydrolases to the more active amfenac [23]. Nepafenac and amfenac work by strongly inhibiting COX-1 enzymes and COX-2. The use of nepafenac is mainly based on prophylactic activity and medicinal. Studies have shown that nepafenac in the form of a solution of 0.3% and 0.1% in the case of eye drops, it is safe and effective in preventing and treating inflammation and pain associated with cataract surgery [24]. Compared to other NSAIDs, nepafenac may be more preferred and chosen by patients because it only needs to be administered once a day, while diclofenac and ketorolac must be taken several times a day [25]. Studies comparing ketorolac and topical nepafenac showed that nepafenac was more effective in terms of tolerability in cataract surgery patients. Both drugs are equally desirable in the treatment of anterior chamber inflammation, vision rehabilitation and intraoperative mydriasis [23]. The efficacy of topical nepafenac has also been studied in a 0.1% solution and diclofenac in a 0.1% solution in inflammation of the anterior segment of the eyeball after cataract surgery. They showed that nepafenac provides better control of inflammation than diclofenac in the first month after surgery [13].

Table 1 lists NSAIDs i.e. diclofenac, ketorolac, bromfenac and nepafenac by their mechanism of action, mode of penetration, forms, effects of lipophilicity, appearance of the next and half-life.

## CONCLUSIONS

Comparison of the above mentioned NSAIDs made it possible to show their common features and differences. The literature on the subject doesn't suggest a single drug from the group of ophthalmic NSAIDs that would be used uni-

TABLE 1

Comparison of NSAIDs (based on [26–28]).

NSIADs	Diclofenac	Ketorolac	Bromfenac	Nepafenac
<b>Effect</b>	inhibits COX-1 and to a lesser extent COX-2	the strongest COX-1 inhibitor, to a small extent COX-2	the strongest COX-2 inhibitor, to a small extent COX-1	strong inhibitor COX-1 and COX-2
<b>Drug penetration</b>	enters the anterior chamber of the eye	highest concentration in the aqueous humor of the eye	highest concentration in the cornea	greatest corneal penetration
<b>Form</b>	drug	drug	drug	prodrug
<b>Lipophilicity</b>	yes	no	yes	yes
<b>Maximum drug concentration [%]</b>	0.1%	0.4%	0.09%	0.1%
<b>C<sub>max</sub> [min]</b>	30 min	20–60 min	150–180 min	60 min
<b>T<sub>½</sub> [h]</b>	1–2 h	4–6 h	1.4 h	0.85 h

versally in most clinical cases. It may seem that the use of nepafenac has a theoretical advantage over other NSAIDs because it works by penetrating the cornea. However, the expected therapeutic benefit of nepafenac isn't fully visible in a comparative assessment of clinical anti-inflammatory efficacy. Therefore, a wide spectrum of symptoms occurring in the patient and his medical history should be taken into account in order to select the appropriate drug in the therapeutic process. Medical knowledge combined with the patient's preferences makes it possible to choose the

right drug. Table 2 summarizes the most important pharmacokinetic and pharmacodynamic properties of NSAIDs. When choosing the right type of substance, its duration of action and application should be taken into account. Knowing the patient's medical history, it is possible to determine the possible advantages of using a given substance and predict possible side effects. Therefore, medical knowledge combined with the patient's preferences makes it possible to choose the right drug.

TABLE 2

Summary of the most important features of NSAIDs (based on [26–28]).

Type of drug	Operation time	Application	Drug penetration	Advantages of use	Disadvantages of use
<b>Diclofenac</b>	6 h	pre- and post-operative relief of inflammation in patients after cataract surgery and refractive corneal surgery	enters the anterior chamber of the eye	temporary relief of pain and photophobia prophylaxis of pre- and postoperative cystic macular edema application in inflammation after injury, in the wound, without penetration of the eyeball well tolerated by patients systemic absorption is part if enabled	risk of eye irritation after use
<b>Ketorolac</b>	4–6 h	pre- and post-operative relief of inflammation in patients after cataract surgery	highest concentration in the aqueous humor of the eye	prevention and treatment of macular edema after cataract surgery good penetration into the aqueous humor and very low systemic absorption of the drug	after administration, common side effects are eye pain and irritation
<b>Bromfenac</b>	1.4 h	post-operative relief of inflammation in patients after cataract surgery	greatest penetration	temporarily reduces the swelling and pain of the eyeball systemic absorption is limited, if any	common side effects are eye pain and irritation
<b>Nepafenac</b>	4–6 h	post-operative relief of inflammation in patients after cataract surgery	greatest penetration	analgesic and anti-inflammatory effect after cataract surgery in diabetic patients, it reduces the risk of postoperative macular edema systemic absorption is limited, if any	adverse effects on corneal epithelial healing have been observed

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