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Use of non-steroidal anti-inflammatory drugs in the treatment of ocular allergy

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ABSTRACT

Ocular allergy is a common condition treated by GPs, pediatricians, allergists, and ophthalmologists. The eye is an organ frequently affected by allergic response, as it lacks a mechanical barrier to the entry of allergens. The paper presents the possibilities for using non-steroidal anti-inflammatory drugs in the treatment of allergic conjunctivitis.

KEY WORDS: non-steroidal anti-inflammatory drugs, allergic conjunctivitis, BAK.

INTRODUCTION

The global prevalence of allergic diseases is steadily growing. Ocular allergy is not a single disease, but a group of disorders affecting the eyelids, conjunctiva, and occasionally also the cornea. It is commonly accompanied by systemic symptoms including allergic rhinitis, atopic dermatitis, and bronchial asthma [1].

ALLERGIC EYE DISEASES

There are many classifications of ocular allergy, but in ophthalmic practice the most common classification system is that proposed the European Academy of Allergy and Clinical Immunology (EAACI) in 2001. According to EAACI, ocular allergy can be divided into atopic (IgE-mediated) and non-atopic (non-IgE-mediated) types. The former group of conditions includes seasonal/intermittent allergic conjunctivitis (SAC), perennial/persistent allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC), while the latter comprises contact blepharoconjunctivitis (ConBC), vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC) [2, 3].

The pathomechanism of conditions included in the former group involves the presence of allergen-specific immunoglobulins E (IgE) on the surface of mast cells. The first exposure to an allergen triggers the production of IgE binding to the surface of mast cells. Following a repeated exposure, allergens attach to the surface of mast cells, causing their degranulation and inducing the release of various substances including histamine, heparin, leukotrienes, prostaglandins and cytokines contributing to the onset of symptoms such as itching, tearing, redness, conjunctival injection and swelling, and the development of papillary reaction [1, 2].

In the latter group, the cellular-type response predominates. Immunocompetent cells are dominated by T cells, though fibroblasts and conjunctival epithelial cells also play an important role. The triggering factors and mechanisms are not fully understood. The inflammatory response is associated with an influx of eosinophils, basophils, mast cells, plasma cells, and lymphocytes [2].

DIAGNOSTIC PROCEDURE

The primary examinations laying the groundwork for the diagnosis of ocular allergy include the patient's medical history and slit-lamp evaluation. When examining the patient, the eyelids should be assessed, with a focus on possible redness and swelling, as well as the eyelid margins including Meibomian glands. A characteristic feature of AKC is eyebrow loss or thinning originating in the temporal region, while SAC and PAC are distinct for the presence of long silky eyelashes [3]. Dark circles, i.e. bluish discoloration of the skin of the lower eyelids, resulting from venous congestion, can be observed in SAC, PAC, and AKC [1, 3]. In patients with AD, a distinct feature is the so-called Dennie-Morgan fold, i.e. an extra fold in the skin below the lower eyelid [3]. The conjunctiva of the eye and eyelids require a careful evaluation. Conjunctival chemosis and edema may vary in severity from

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mild to severe (in acute conditions). It is important to examine the conjunctiva of the eyelids, which reveal papillary changes when the upper eyelid is retracted. A mucous discharge is often present in the conjunctival sac. VKC and AKC are associated with the formation of the so-called Trantas dots in the corneal limbus, composed of exfoliated conjunctival epithelial cells, as well as eosinophilia [2, 3].

The next diagnostic step involves performing skin prick tests and determining the levels of total IgE and allergen-specific IgE in blood serum and tears. Other examinations, such as conjunctival provocation test, evaluation of conjunctival scrapings, impression cytology, conjunctival biopsy, and assays of inflammatory mediators and histamine levels in tears, are uncommon in daily medical practice, though they have their applications in clinical trials.

The differential diagnosis of ocular allergy includes dry eye syndrome; bacterial, viral, and chlamydial conjunctivitis; uncorrected vision defects; anterior uveitis; autoimmune diseases; rosacea; sarcoidosis; and glaucoma.

TREATMENT

The diagnosis and treatment of ocular allergy pose a challenge both for allergists and ophthalmologists, and require their close cooperation.

An important role in the treatment of allergic ocular conditions is attributed to non-pharmacological treatment. By limiting patient exposure to allergens and applying non-pharmacological methods to relieve allergy symptoms, the use of pharmacological agents can be reduced. Patients should be advised about proper eye hygiene and care. They should be instructed to avoid rubbing the eyes, reduce exposure to allergens, and apply artificial tears and cold compresses [4, 5]. Non-pharmacological treatments also include specific immunotherapy administered by allergists [4].

Pharmacological treatment of allergic eye diseases is based on topical and systemic antihistamines, mast cell and eosinophil stabilizing agents, topical and systemic glucocorticosteroids, immunosuppressants, and non-steroidal anti-inflammatory drugs (NSAIDs) [4].

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs have been used in ophthalmology in the form of eye drops since the late 1970s. They are among the most commonly prescribed drug groups in the world [6].

Mechanism of action of non-steroidal anti-inflammatory drugs

The mechanism of action of topical and systemic NSAIDs involves inhibition of the stage of conversion of arachidonic acid to prostaglandin H2, which is mediated by cyclooxygenase (COX). There are two isoforms of cyclooxygenase: constitutive (COX-1), which is active all the time, and inducible (COX-2), activated only in certain circumstances, e.g. during inflammatory process. COX-1 is physiologically present in the body, taking part in the conversion of arachidonic acid to prostaglandin E2, I2, and thromboxane A2 [7].

NSAIDs exhibit varying affinities for the COX-1 and COX-2 isoenzymes. Based on their ability to inhibit the activity of specific COX isoenzymes, NSAIDs can be classified into four groups:

- drugs that inhibit both COX-1 and COX-2, with a greater affinity for COX-1,
- drugs that inhibit COX-2 activity with 5- to 50-fold greater selectivity,
- drugs with more than 50-fold greater affinity for COX-2 than COX-1,
- drugs that are relatively weak inhibitors of both isoforms.

All NSAIDs used in ophthalmology in the form of eye drops belong to the first group [7].

Non-steroidal anti-inflammatory drugs used in ophthalmology

At present, six active substances from the NSAID group used in ophthalmology in the form of drops are available on the Polish pharmaceutical market:

- diclofenac (Dicloabak – preservative-free, Difadol, Naclof),
- indomethacin (Indocollyre),
- nepafenac (Nevanac),
- bromfenac (Yellox),
- pranoprofen (Prattack),
- ketorolac (Acular).

The first NSAID that found applications in ophthalmology was indomethacin, in the early 1980s. Then, flurbiprofen and suprofen were marketed globally as ophthalmic drugs, but they were unavailable in Poland. Initially, the therapeutic indications of flurbiprofen and suprofen (which is no longer commercially available) included the prevention of myosis during ophthalmic procedures. The primary indication of diclofenac and pranoprofen was to prevent inflammation after cataract surgery, while ketorolac was used for the relief of itching caused by allergic conjunctivitis [7].

Non-steroidal anti-inflammatory drugs were found to be therapeutically beneficial in inhibiting pupillary constriction during cataract surgery, preventing ocular inflammation after anterior segment procedures, controlling pain after refractive and other anterior segment surgeries, reducing the risk of postoperative macular edema associated with cataract surgery, and alleviating symptoms associated with allergic eye diseases, as well as dry eye syndrome [6, 8].

Dry eye syndrome is a multifactorial disease, with inflammation considered to be an important factor in its pathogenesis. In view of their anti-inflammatory effects, NSAIDs are included among possible therapeutic options for the treatment of dry eye syndrome. Diclofenac has also been found to have cytoprotective effects on cultured human corneal epithelial cells and in a rat model of dry eye syndrome by inhibiting hyperosmolarity-induced apoptosis [9].

None of the NSAIDs in the form of eye drops available in Poland is approved for the treatment of allergic eye condi-

tions. Based on the consensus of Polish allergists and ophthalmologists on the diagnosis and treatment of allergic ocular diseases, topical treatment with NSAID-containing eye drops is an acceptable therapeutic option [4].

Topical NSAIDs are used when, despite treatment with antihistamines and mast cell stabilizers, symptoms persist or the use of topical steroids is contraindicated in a given patient [1]. By blocking the cyclooxygenase pathway, topical NSAIDs inhibit the production of prostaglandins, one of the main mediators of inflammation, easing the symptoms of discomfort associated with the allergic response such as itching, swelling, conjunctival injection, and tearing [1]. Therapeutic agents used in the treatment of ocular allergy include 0.5% tromethamol ketorolac, 0.1% diclofenac, and 0.1% nepafenac [1, 10].

Ketorolac is approved for SAC treatment by the FDA (Food and Drug Administration) [11, 12]. Two multicenter studies have provided evidence for the therapeutic efficacy of 0.5% ketorolac in the treatment of allergic conjunctivitis. In a study with 148 subjects, Ballas *et al*. showed a reduction in itching, foreign body sensation, swelling, and conjunctival injection after treatment with ketorolac administered 4 times a day for 7 days [13]. Another study, conducted by Tinkelman *et al*. in a group of 93 patients, also demonstrated a therapeutic benefit in terms of relieving symptoms of allergic conjunctivitis at this dosage regimen [14]. Similar results were obtained by Tauber *et al*. evaluating the efficacy and safety of 0.1% diclofenac and 0.5% ketorolac in patients with acute seasonal allergic conjunctivitis. The study involving 60 patients confirmed the efficacy of both drugs in lessening the severity of symptoms associated with allergic conjunctivitis. Diclofenac sodium was statistically significantly more effective in relieving pain after 30 minutes and on day 7 of the study. Neither of the drugs studied was found to induce any serious adverse reactions. Only a few subjects experienced a burning and stinging sensation after drop instillation, as well as irritation. Corneal epithelial erosion was noted in one patient in the study group, which was attributed to eye rubbing due to itching [12].

According to the Polish consensus on the diagnosis and treatment of allergic diseases of the eye, the topical medication recommended in the treatment of AKC, VKC and PAC is diclofenac sodium, which significantly reduces the activity of fibroblasts and conjunctival epithelial cells, and stabilizes mast cells and lymphocytes [4].

Laibovitz *et al*. conducted a randomized clinical study, the findings of which were published in the Journal of Ocular Pharmacology and Therapeutics in 1995, to compare the efficacy and safety of 0.1% diclofenac eye drops and placebo in patients with acute seasonal conjunctivitis. The studied NSAID was shown to be effective in alleviating the ocular symptoms of SAC, while the treatment had no impact on visual acuity or intraocular pressure in treated patients. Only 20% of the subjects reported transient burning or stinging during therapy [15].

In their 2015 study in a group of 261 patients with perennial allergic conjunctivitis, Li *et al*. assessed the therapeutic efficacy of eye drops with 0.1% diclofenac sodium diclofenac compared to 0.1% fluorometholone. The NSAID and steroid treatments were shown to have comparable efficacy, and neither of them was associated with serious adverse reactions [16].

Swamy *et al*. reviewed the results of eight studies enrolling a total of 712 patients, comparing the efficacy of topical NSAIDs and placebo in the treatment of allergic conjunctivitis. Topical NSAIDs were shown to be statistically significantly more effective in relieving conjunctival itching compared to placebo, and significantly reduce conjunctival injection. On the other hand, topical NSAIDs exhibited no efficacy in reducing eyelid edema, photophobia, or burning and foreign body sensation in the eyes [17].

In their study of 0.1% diclofenac sodium, 0.5% tromethamol ketorolac, 0.3% napafenac, and 0.07% bromfenac used in a group of 10 patients, Singer *et al*. found that all four NSAIDs significantly decreased corneal sensation. The exact mechanism by which topical NSAIDs reduce corneal sensitivity has not been fully elucidated. Researchers suggest that NSAIDs play an important role in COX inhibition. There are also reports of a direct anesthetic effect of diclofenac sodium on the A-delta and C fibers innervating the cornea [8]. Decreased corneal sensitivity may lead to inadvertent injury resulting from eye rubbing by the patient. It should also be noted that some studies suggest a delay in wound healing when local anesthesia is used [18]. However, a systemic review of five blinded, randomized clinical trials showed no delay in the healing of corneal epithelial erosion and epithelization during NSAID treatment [19].

In view of possible adverse reactions, including eye irritation and burning sensation after administration, and in rare cases also punctate keratitis, corneal ulceration or perforation, it is recommended that NSAIDs are used on a short-term basis [1, 11]. Rare cases of severe complications including corneal thinning have been reported after treatment with 0.1% diclofenac sodium, 0.5% ketorolac, 0.1% nepafenac, and 0.09% bromfenac [20-22].

Flash reviewed a total of 11 cases of patients diagnosed with corneal thinning after using 0.5% diclofenac and found that many other factors might have contributed to the toxicity of the medicine, such as concomitant eye diseases (dry eye syndrome), systemic comorbidities (Sjorgen's syndrome, diabetes mellitus), condition after refractive eye surgeries, long-term use of topical NSAIDs as well as concurrent treatment with other topical drugs, e.g. corticosteroids [23].

Another aspect that needs highlighting is the unfavorable profile of activity of preservatives used in eye drops, particularly in patients with allergic eye conditions. The most widely used ophthalmic preservative is benzalkonium chloride (BAK) [24].

Aside from aggravating the symptoms of allergic inflammation, preservatives can trigger an additional allergic reaction manifesting as eczema and eyelid dermatitis, among other conditions. However, preservative-free NSAID drops (Dicloabak), which do not produce these adverse reactions, are now available on the pharmaceutical market.

SUMMARY

In conclusion, a review of the available literature shows that the use of preservative-free topical NSAIDs on a short-term basis in a carefully selected group of patients represents a safe therapeutic option for the treatment of allergic eye diseases. However, it is advisable to monitor the eye condition both in patients treated with topical and systemic NSAIDs. The current treatment of allergies, including those affecting the organ of vision, is based on numerous drug classes discussed above. Since ocular allergy has an inflammatory component, it seems pertinent to include NSAIDs in the treatment regime to help reduce the inflammatory response before initiating steroids.

It would be beneficial to conduct studies comparing the efficacy and safety profiles of NSAIDs and other drugs indicated for the treatment of allergic conjunctivitis.

DISCLOSURE

The authors declare no conflict of intertest.

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