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Eye-drops in therapy – facts and myths about preservatives

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HIGHLIGHTS

The paper describes the substances contained in eye drops and their effects.

ABSTRACT

Drugs in ophthalmology are most often applied topically in the conjunctival sac. All preparations administered through this route must meet specific requirements and, therefore, not just a simple solution or suspension of the drug in water. In addition to the therapeutic substance, eye drops contain various additives: buffers, preservatives, stabilisers, antioxidants, and isotonic substances to increase solubility and viscosity. Excipients are essential components of drugs that determine their quality and properties and can increase the effectiveness of treatment, e.g. by increasing the penetration of the drug through biological barriers. However, because of the high demands placed on ocular medicines, the choice of excipients is very limited.

This article discusses the facts and myths surrounding the use of excipients, including preservatives, in eye drops.

Key words: antibiotics, preservatives, eye drops, benzalkonium chloride, side effects

INTRODUCTION

In the treatment of eye diseases, the most commonly used forms of medication are eye drops, ointments, and gels that are applied topically to the conjunctival sac. Over the years, many myths and controversies have arisen regarding the excipients contained in these medications. The following are some of the most common.

THE SHORTER THE FORMULATION, THE BETTER

It would be ideal to use only a solution of the drug suspended in water or saline. Unfortunately, it is possible that the drug in such a solution may not sufficiently penetrate the tissues or may irritate the eye, for example, due to an inadequate pH. Such a drug would have a very short shelf life, even before opening the package, it could not be stored for long in pharmaceutical wholesalers or pharmacies. Once opened by the patient, it would have to be used quickly and there would be a risk of microbiological contamination [1].

All drugs administered into the conjunctival sac must meet certain requirements. Eye drops are not simply a solution or suspension of a drug in water. In addition to the active ingredient, ophthalmic drugs contain several other substances, of which preservatives and their role have been the most controversial in recent times, probably because it would be easiest to eliminate this group in the future [2].

PRESERVATIVE-FREE EYE DROPS CONTAIN ONLY THE ACTIVE SUBSTANCE AND WATER

Even preservative-free eye drops contain a variety of substances with different functions. These include isotonicants, buffers, antioxidants, and solubility and viscosity enhancers [3–5].

Isotonic additives regulate the osmotic pressure of ocular medications and hydrating eye drops. Iso-osmosity prevents ocular irritation due to the difference in osmotic pressure between the administered drug and the cellular fluid. The most commonly used salt for this purpose is sodium chloride.

It is important to regulate the pH of eye drops to ensure optimal efficacy. This is typically accomplished by adding alkaline and acidic buffers to the solution. Some buffers may also modify the osmotic pressure of the solutions or have antibacterial properties. Examples of alkaline buffers include phosphate and boric acid, while acidic buffers include citrate and acetate.

Antioxidants are used to ensure the stability of drugs by protecting them from oxidative degradation. Notable antioxidants include α-tocopherol, butylhydroxytoluene, butylhydroxyanisole, and sulfur compounds. The efficacy of antioxidants can be enhanced by using chelating compounds, whose role is to bind trace amounts of heavy metal ions. One of the most commonly used chelating agents is disodium edetate.

A serious problem with drugs in solutions is their poor solubility, which makes it impossible to achieve the appropriate drug concentration. Therefore, substances that increase solubility are added to ophthalmic solutions, including glycerol, propylene glycol, macrogols and micellar solubilizers.

Moreover, eye drops contain viscosity enhancers that increase the contact time of the drug, thereby maximizing its therapeutic effect. These substances are often polymers, which are used in higher concentrations to form eye gels.

In addition, polymers have a coating and moisturizing effect that reduces the risk of irritation. Cellulose derivatives (mainly hypromellose), carbomer, polyvinyl alcohol and tyloxapol are the most common polymers used in ocular formulations [2, 4, 6, 7].

ARE PRESERVATIVES HARMFUL?

Harmfulness depends on various factors, the most important of which are the dose or concentration and, consequently, the frequency of administration and the duration of treatment. Paracelsus, a 16th century physician, said that "everything is poison and nothing is without poison," and these words are still relevant in medicine. This rule also applies to preservatives. Because the tissues of the ocular surface are very sensitive (the presence of a mucous membrane and the unique structure of the transparent cornea), there are few substances that can be safely administered into the conjunctival sac. The task of the scientists who develop the drug, and then the manufacturers who produce and market it, is to obtain such a formula and select the appropriate concentrations so that the drug is safe for the eye during the specified period of use and so that it works effectively. Therefore, the drug is thoroughly tested before and after it is introduced to pharmacies. Once the drug or supplement is available in pharmacies, it is subject to safety controls by the appropriate agencies and manufacturers.

Benzalkonium chloride (BAK) is the most popular preservative used in eye drops today, having been known and used since 1910. In addition, it has been used as a preservative for drugs and cosmetics since 1982, when it was approved by the U.S. Food and Drug Administration (FDA). Other derivatives of quaternary ammonium salts used to preserve ophthalmic products are cetrimide (trimethyltetradecylaminium bromide) and benzododecinium and lauralkonium chloride, but they are used less frequently than BAK. Chlorhexidine acetate, chlorhexidine gluconate and nipagin M are also used. Sodium benzoate and sorbic acid ensure sterility of preparations containing vitamin A and sodium diclofenac. Also used are: Octoxynol 40, phenylmercuric borate, phenylmercuric nitrate, thiomersal,

polyquaternium-1, Purite (stabilized oxygen and chlorine complex) and SofZia (combination of boric acid, zinc, sorbitol and propylene glycol), sodium perborate (GenAqua™), ethylenediaminetetraacetic acid (EDTA), polyhexamethylene biguanide (PHMB) [3, 5, 8, 9].

In recent years, a number of studies have highlighted the potential adverse effects of preservatives, including ocular irritation, chronic conjunctivitis, keratitis and blepharitis, and worsening of dry eye symptoms [3]. As the role of preservatives is currently being debated, researchers and physicians are reconsidering the reasons for their introduction and continued use as eye drop additives. It is necessary to consider whether the current composition of the drugs can be modified: reducing the concentration of the preservatives previously used, introducing a newer generation of preservatives, or changing the packaging if the physicochemical properties of the drug allow it [9].

PRESERVATIVES ENSURE MICROBIOLOGICAL SAFETY AND DO NOT CAUSE ANTIBIOTIC RESISTANCE

A healthy, intact ocular surface is adequately protected from infection by the impermeable corneal epithelium and the tear film, which washes away infected dust particles or liquid droplets. Unfortunately, these defense mechanisms may not be sufficient if the corneal epithelium is damaged (e.g., as a result of injury, surgery, or contact lens wear).

All ophthalmic drugs are subject to strict sterility requirements. This applies both to the stage of drug production and the time of its use by the patient. Due to direct contact with the ocular surface, eye drops must not only contain an active ingredient that reaches a therapeutic concentration in the conjunctival sac after instillation, but must also not pose a risk of microbial infection that could lead to serious eye damage.

Preservatives are active against all microorganisms, unlike antibiotics or antifungals which are active only against certain groups of microorganisms [5].

PRESERVATIVE-CONTAINING EYE DROPS ARE SAFE

Before a new drug is introduced to the market, studies are conducted to determine the concentration of the drug that will produce an effective therapeutic or irritating effect on the mucous membranes. Such observations are made during preclinical and clinical studies, even after the drug has been marketed. If there are doubts about the safety of a drug already on the market, it can be quickly withdrawn, for example by announcing in the press or on the Internet that the drug should not be taken, for example because of a detected contamination. The patient can then return the drug to the pharmacy where it was purchased. Today, many drug manufacturers are introducing modern solutions to enhance safety, including drug additives such as special media or preservatives with unique, patented compositions. One notable example is Purite preservative, a stabilized oxocloro-complex consisting of a mixture of chlorite, chlorate and chlorine dioxide. It has been shown to have antimicrobial activity against bacteria, viruses and some fungi [10, 11]. In solution, Purite generates reactive chlorine dioxide that imparts an oxidizing antimicrobial effect to the preservative. When applied to the eye, this preservative is an oxidizing agent for organic matter, including bacteria and viruses, while simultaneously transforming into many compounds (including sodium and chloride ions) that are also naturally present in the tear film [12].

PRESERVATIVES IMPROVE CORNEAL PENETRATION WHICH CONTRIBUTES TO INCREASED DRUG EFFICACY

In a study of β-blockers used to treat glaucoma, it was found that the penetration of this group of drugs into the eye was enhanced by substances similar to BAK. BAK allows more drug to enter the anterior chamber of the eye by acting on the intercellular junctions in the cornea and conjunctiva. It increases the concentration of the drug in the aqueous humor, which increases its effectiveness. This effect has encouraged companies to keep the BAK in the drug preparations [8].

One of the studies was a 12-week follow-up of 578 patients treated for glaucoma with BAK-containing and preservative-free latanoprost eye drops. Patients receiving BAK and preservative-free latanoprost achieved significant and clinically meaningful reductions in IOP compared to baseline. Adverse events observed were mild and occurred with similar frequency in both groups. The IOP reduction from baseline at all time points for BAK-free latanoprost was approximately 6–7 mmHg; the mean (95% CI) difference in IOP reduction from baseline between BAK-containing and BAK-free latanoprost ranged from a mean of 0.29 mmHg with extreme values (-0.27–0.85 mmHg) to 0.91 mmHg (0.36–1.47 mmHg). In addition, BAK-containing eye drops lowered IOP slightly more than preservative-free eye drops [13].

This is the same reason that explains the difference in the concentration of BAK in other eye drops. For example, moxifloxacin eye drops do not contain preservatives, while gatifloxacin eye drops contain BAK. This is because moxifloxacin has been shown to penetrate ocular tissue better than other fluoroquinolones, including gatifloxacin [8].

PRESERVATIVES EXTEND EYE DROPS SHELF LIFE BEFORE AND AFTER OPENING THE CONTAINER

Eye drops with a longer shelf life can be stored by wholesalers or pharmacies for several or a dozen months. They can

usually be used for a month after opening the container. For comparison, magistral eye drops usually have a maximum shelf life of 2–3 days, and minims (sterile single-dose eye drop containers) should be used the same day. Unlike magistral medications, ready-to-use multi-dose eye drops are available to patients at any pharmacy. The availability of pharmacies preparing prescription drugs is reduced in Polish conditions [14].

BOTTLES CONTAINING EYE DROPS WITH PRESERVATIVES ARE EASY TO USE

Multi-dose eye drop containers are often more convenient for patients than single-dose containers, especially for older patients with impaired manual dexterity [9].

Eye drops with a built-in antimicrobial system or single-dose containers are an alternative to standard multi-dose containers. Unfortunately, many elderly patients, the group most likely to use eye drops, have problems with self-administration. This may be due to general illnesses or degenerative changes in the cervical spine or hands that make it difficult to administer medications. In the case of single-dose containers (minims) with a tip that is mechanically torn off before use, the sharp plastic edges of the tip can injure the corneal or conjunctival surface. Minims are also a problem for older patients with poor vision who are more likely to misplace these small, transparent packages [5, 15].

MOST PATIENTS TOLERATE PRESERVATIVES WELL

A large proportion of patients tolerate preservative eye drops well and report no adverse effects. In addition, preservatives are often used because potential ocular surface problems do not manifest themselves in every patient. Many people who have been using preservative eye drops for years seem to tolerate them very well, as IOP control and good tolerability of long-term treatment are important in the management of glaucoma.

Because it is known that the risk of side effects increases with the length of time a medication is used, ophthalmologists are paying more attention to possible side effects in their examinations and discussions with patients [10, 15].

In a review published in 2020, the authors analyzed 433 articles describing randomized controlled trials on the efficacy and safety of glaucoma eye drops containing prostaglandin analogues or β-blockers. The trials evaluated the differences between two groups of eye drops: one containing BAK and another containing an alternative preservative (referred to as the AP group) and a group without preservatives (referred to as the PF group). Of the 433 articles reviewed, 16 trials were included. A meta-analysis of IOP was performed on 13 studies (4201 patients) covering a period from 15 days to 6 months.

There were no significant differences in IOP between BAK and PF and AP. Meta-analyses revealed no significant differences between BAK and AP and PF in terms of conjunctival hyperemia, ocular hyperemia, total ocular adverse events or tear break-up time. However, the authors concluded that there were no clinically significant differences in efficacy and safety between the 3 groups compared: BAK, AP, and PF. However, there were significant safety concerns, including the fact that patients were using the product for longer than the study period [16].

CONCLUSIONS

Additives to ophthalmic medications are often essential ingredients that are critical to the proper quality and properties of the medications. In addition, they have the ability to enhance the efficacy of drugs by increasing their penetration across biological barriers. However, due to the high demands placed on ophthalmic products, the choice of additives is very limited. Each additive must play a strictly defined role in the formulation. Both the active ingredients in eye drops and the additive have their beneficial effects, but they are not free of side effects.

Chronic use of eye drops, for example in the treatment of glaucoma or dry eye syndrome, can lead to side effects, often affecting the anterior segment of the eye. It is up to the physician to decide whether the benefits outweigh the risks. Biotechnology and biomedical engineering are expected to make significant advances, facilitating the introduction of increasingly effective drugs through innovations in developed formulations and delivery systems. The development of observational studies allows the assessment of the efficacy and safety of their use.

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