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Do preservatives enhance corneal permeability and thus the effectiveness of ophthalmic drugs?

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HIGHLIGHTS

The preservatives contained in ophthalmological drugs increase the corneal permeability and can affect the effectiveness of therapy.

ABSTRACT

Preservatives used in ophthalmic preparations are chemical compounds with an antibactericidal effect. They ensure the sterility of the drug, preventing accidental contamination with microorganisms and the development of microorganisms in the bottle, which may cause infection of the eye tissues, and additionally change the physicochemical properties of the active substance. The most commonly used preservative in ophthalmology is benzalkonium chloride which, by acting as a surfactant, unseals the connections between corneal epithelial cells, facilitating the penetration of the drug. Studies in rabbits using benzalkonium chloride which, by acting as a surfactant, unseals the connections between corneal epithelial cells, facilitating the penetration of the drug. Studies in rabbits using benzalkonium chloride have shown a significant increase in corneal penetration. Studies comparing the same effectiveness of drugs without preservatives in relation to drugs with preservatives have been carried out many times, showing similar effects of preparations in most studies. Some studies, however, describe better effect of preserved drugs, which will be presented in the article.

Key words: corneal permeability, preservatives, drug penetration, therapeutical efficacy

INTRODUCTION

Preservatives in ophthalmic preparations are designed to keep the drug sterile and prevent microbial contamination of the eye. Therefore, they are indispensable in multi-dose packaging without sterile dispensers because repeated use of the same drug may contaminate the bottle with bacteria, fungi or other microorganisms [1]. Thanks to their antimicrobial properties, preservatives can significantly enhance safety of multi-dose eye formulations and extend the shelf life after the first opening [1].

Preservatives used in ophthalmology belong to several chemical groups, so their effects on tissues and cells may vary. Overall, preservatives can be classified into four groups [2]:

- surfactants
- agents containing mercury and alcohol
- oxidizing agents
- ionic buffer systems.

BENZALKONIUM CHLORIDE AND INCREASED CORNEAL PENETRATION

Surfactants are the most used group of preservatives, with benzalkonium chloride (BAK) being their main representative. They reduce the surface tension and can thus affect the physicochemical properties of the cornea and other tissues. By breaking down permanent intercellular connections and reducing the integrity of the corneal epithelial layers, surfactants can increase permeability of the corneal epithelium. Thus, they improve drug penetration into the eyeball [3].

Benzalkonium chloride is a cationic quaternary ammonium salt with both hydrophilic and hydrophobic elements found in more than 70% of topical ophthalmic medications [4]. In most ophthalmic drops, the concentration of BAK ranges from 0.004% to 0.02%. Benzalkonium chloride demonstrates high antimicrobial efficacy, which ensures eye drops stability and limited epithelial permeability. It is effective against both Gram-positive and Gram-negative bacteria, as well as against fungi and viruses [5]. Bactericidal activity of BAK occurs through its interaction with bacterial cell membranes that depolarizes cytoplasmic membranes inducing their instability and, consequently, cell lysis [4, 5].

In 2008, Majumdar et al. proved that BAK can significantly enhance corneal permeability of acyclovir. After application of BAK at 0.01%, corneal permeability increased more than tenfold, and at half of the concentration – more than threefold. The study was performed on a New Zealand rabbit model. Additionally, authors found that other substances (e.g., chitosan, EDTA) did not increase corneal permeability [6].

After this publication, the fact that BAK enhances corneal permeability began to be widely described in ophthalmology textbooks, guidelines and statements published, among others, by the European Medicines Agency (EMA) [2, 5]. Moreover, this is one of basic information on BAK provided in introductions to many review articles [7].

Benzalkonium chloride is a frequently used preservative not only in ophthalmic preparations. It can be used to treat throat and mouth infections accompanied by sore throat and bad breath, and topically in eczematous skin diseases. In higher concentrations, BAK is used as an antiseptic for wounds, abrasions, and minor cuts.

EFFICACY OF MEDICINES CONTAINING PRESERVATIVES

Many clinical trials have been conducted to compare the efficacy of preservative-free and preservative-containing drugs. Some of these studies have shown systematic errors due to, e.g., lack of randomization or blinding. Over the past 20 years, many preservative-free formulations have been introduced into the drug market thanks to single-dose packaging or special systems that prevent the drug from going back into the package. Registration of these preparations was preceded by a number of clinical trials. Most studies have focused on IOP-lowering medications for the treatment of glaucoma. Active substances included drugs from different groups, including latanoprost, a prostaglandin analog, and/or a β-blocker (timolol). Latanoprost is an inactive isopropyl ester prodrug that becomes biologically active after hydrolysis to the acid form during passage through the cornea.

Most frequently, the research hypothesis was formulated as follows: preservative-free formulations are as effective as preservative-containing formulations at reducing IOP. Accordingly, study groups involved patients using preservative-free medications, and control groups patients using formulations containing preservatives. Therefore, to prove higher efficacy of preservative-containing preparations, research hypothesis should be stated the other way round. If preservative-free formulations (the study group) are not as efficient as preservative-containing formulations, then, since the active ingredient is the same, drug efficacy depends on the presence of the preservative.

Wirta et al., in a study published in 2022, did not confirm the bioequivalence of a BAK-free latanoprost with latanoprost containing BAK at 0.05% concentration [8]. In the study, patients were randomly assigned in a ratio of 1 : 1 to either a group without BAK or to a reference group with BAK. For 12 weeks, patients self-administered 1 drop of the medication nightly to the affected eye(s). The primary efficacy endpoint was IOP measured at 8.00 a.m., 10.00 a.m. and 4.00 p.m., at the baseline and on days 7, 28, 56 and 84.

To confirm the bioequivalence of BAK, the following three criteria had to be met for IOP differences between the study group and the control group:

1. A 95% confidence interval of the mean IOP difference between the two groups includes 0 mmHg for all time points (i.e., the difference in IOP should be about zero, the interval cannot be shifted one way or the other).
2. The upper limit of 95% confidence interval is less than 1.5 mmHg at all time points.
3. The upper limit of 95% confidence interval is less than 1 mmHg at minimum 7 of 12 time points.

The first criterion was met in 7 of 12 measurements, the second one in all measurements, and the third one only in 4 of 12 measurements. The authors concluded that the bioequivalence of the formulations was not achieved. They reported a greater reduction in IOP in the group of patients using BAK-containing formulations [8].

The same formulations were studied again in July 2022 by Lee et al. The authors noted a similar hypotensive effect of the two formulations; however, BAK-containing latanoprost was slightly more effective in lowering IOP. The difference was not statistically significant, but the graph presented by the authors showed a higher decrease of IOP in patients using BAK-containing preparations [9].

In 2021, Skov et al. published a meta-analysis that evaluated studies comparing the hypotensive effect of β-blocker timolol with and without preservatives. The β-blocker was used as a separate preparation or in combination with other drugs (prostaglandin analog or a carbonic anhydrase inhibitor). In their meta-analysis, the authors included 7 clinical trials. The difference in mean IOP changes between preservative-free and preservative-containing formulations was statistically significant, but of no clinical importance (MD 0.29 mmHg; 95% confidence interval 0.07–0.51 mmHg; p = 0.010). In 6 out of 7 studies, slightly lower IOP was reported in patients using preservative-containing formulations [10].

ADVERSE EFFECTS

Authors of the studies [8, 9] examining the efficacy of IOP-lowering medications, evaluated their safety by assessing the number of adverse effects during their use.

Wirta et al. found that patients using preservative-free formulations reported more adverse effects, including significantly more serious adverse ones (18 vs. 8) [8]. Similarly, authors of the second study reported more adverse effects in patients using BAK-free formulations (893 vs. 827). Therefore, it can be concluded that preservatives in ophthalmic drops do not affect their safety or the number of adverse effects [9]. In the meta-analysis, the level of evidence for all ocular surface outcomes was low or very low and reported in only a few studies. No significant difference was observed in ocular surface symptoms [10].

It is also worth noting that, according to current European Glaucoma Society guidelines [11], not all patients are sensitive to preservatives in eye drops and not all adverse reactions to eye drops can be attributed to preservatives. Therefore, most patients do not have to start treatment with preservative-free ophthalmic formulations.

CORNEAL BARRIER VERSUS DRUG ABSORPTION

It is well-known that the cornea is a significant mechanical and chemical barrier to drug delivery. Due to the lack of studies of other substances and on how preservatives affect their efficacy, corneal absorption was also analyzed. Due to tear drainage, systemic drug absorption and biological barriers (primarily the corneal epithelium) only a small fraction of the applied dose (less than 5%) reaches the intraocular tissues [12, 13]. Benzalkonium chloride increases corneal penetration by affecting the corneal epithelium, which is the main barrier limiting drug absorption into the eye. If only less than 5% of the active ingredient reaches intraocular tissues, even the slightest increase of the drug concentration in the anterior chamber is highly desirable.

CONCLUSIONS

The discussed studies prove that preservatives in ophthalmic formulations increase corneal penetration and slightly increase drug efficacy. The studies evaluated hypotensive drugs used in the treatment of glaucoma. There is a strong need for similar studies conducted on other ophthalmic formulations. Further studies on preservatives should be conducted in patients using antibiotics, glucocorticosteroids and other topical ophthalmic medications.

It is recommended to start ophthalmic treatment with preservative-containing formulations since they have similar or fewer adverse effects and slightly better efficacy. Treatment should be changed only in the case of drug intolerance. Adverse reactions affecting the eyes are most often transient and occur only during drug administration.

Slightly higher efficacy of preservative-containing formulations may contribute to better treatment results. Regardless of whether we use antibiotics, glucocorticosteroids or hypotensive therapy, increased concentration of active ingredients inside the eyeball due to better corneal penetration provided by preservatives is extremely desirable.

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Marta Misiuk-Hojło: research concept and design, critical revision of the article; final approval of article.
Martyna Tomczyk-Socha: collection and assembly of data; data analysis and interpretation; writing the article.

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