

The issue of preservatives in the light of evidence-based medicine

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HIGHLIGHTS

Applying the drug directly to the eyeball carries a risk of bacterial infection and, consequently, serious eye damage. Therefore, all ophthalmic preparations are strictly sterile thanks to the presence of preservatives.

ABSTRACT

Glaucoma is the leading cause of irreversible blindness worldwide. Most patients will require drug therapy for the rest of their lives. Preservatives play a key role in the development of topical medications whose primary role is to provide antimicrobial activity to maintain sterility. The most common preservative is benzalkonium chloride, which has antibacterial, antifungal, and antiviral properties. This article was written based on the latest research in MEDLINE and other major bibliographic databases for studies published in English by August 1st, 2021. Our meta-analyses confirm that eye drops side effects are not caused solely by the presence of preservatives, and the effectiveness of anti-glaucoma drugs containing benzalkonium chloride and those without preservatives is comparable. During the COVID-19 pandemic, studies showed the protective effect of preservatives against SARS-CoV-2.

Key words: glaucoma, SARS-CoV-2, preservatives, eye drops, benzalkonium chloride

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide. It is strongly associated with an increase in intraocular pressure (IOP), and progression is inhibited by lowering IOP, which most often occurs after the administration of eye drops. As glaucoma is a chronic disease, most patients will require treatment for the rest of their lives. Patients with glaucoma may require topical treatment much longer than previous generations due to the increasing life expectancy of the population. Glaucoma treatment can only be effective when used by patients, so adherence is very important. Satisfaction with treatment has been identified as an important factor in improving adherence [1].

Preservatives play a key role in the development of topical ophthalmic drugs for the treatment of a wide variety of eye conditions, their primary role being to provide antimicrobial activity to maintain sterility and thus cost-effectively extend shelf life [1]. The most common preservative is benzalkonium chloride (BAK), which is used in approximately 70% of ophthalmic formulations [2, 3] and is therefore the focus of this article. BAK is a quaternary ammonium compound containing both hydrophilic and hydrophobic elements, thanks to which it is highly soluble in water [2, 4]. The bactericidal effect occurs through the interaction of BAK with bacterial cell membranes, which leads to membrane instability and cell lysis [2]. BAK is effective against both Gram(+) and Gram(-) bacteria, and also against fungi [4]. BAK may also act as a corneal penetration enhancer, which could enhance penetration into the eye of active ingredients in BAK-preserved preparations [4–6].

However, there were concerns about the use of preservatives with regard to the efficacy and safety profile. This has led to the development of new classes of preservatives including polyquaternium-1 (Polyquad) which is a detergent, oxidizing preservatives such as stabilized oxychloride complex (Purite) and sodium perborate (GenAqua), and the ion-buffered preservative SofZia. Thanks to the dosing mechanisms, and thus extending the life of bottles in preparations such as COMOD and ABAK, it was possible to use drops without preservatives (PF) [7].

MATERIAL AND METHODS

The studies were identified by searching MEDLINE and other major bibliographic databases for studies published in English up to August 1st, 2021. Additional information was obtained from a search of conference materials for the 2 years prior to August 2021 and a targeted search of health economics databases. Gray literature such as unpublished reports from disease registry websites is not covered. Studies based on the same dataset were systematically excluded to avoid reporting the same data multiple times.

RESULTS

Laboratory and animal studies on the effects of BAK on the eye structures were the driving force against preservatives [8]. There are no randomized studies that would confirm the toxicity of BAK in humans (so far reported *in vivo*, animal, and *in vitro* studies), further randomized studies evaluating the effect of BAK on eye tissues are necessary [1]. When using glaucoma drops, many patients report side effects such as redness, burning, and irritation of the eyes. It is assumed that preservatives may cause damage to the eye surface and thus intensify side effects and complications associated with the local treatment of glaucoma [8]. Experimental studies have shown that BAK has a detrimental effect on many eye structures, including conjunctival tissue and corneal epithelium, as well as trabecular meshwork and lens epithelium [9]. The introduction of drops without preservatives was to reduce the occurrence of side effects. However, PF drops are often produced in small single-dose vials, which may be difficult for some patients to administer. The cost of these drops is often higher than those containing preservatives, and more plastic is used to make them [8].

Due to continued concerns about BAK-preserved preparations, there is a need to review clinical trials comparing the efficacy and possible side effects of intraocular pressure-lowering drops containing both preservatives and PF. According to the current guidelines of the European Glaucoma Society (EGS Guidelines 5th Edition), not all patients are sensitive to the presence of preservatives in eye drops, and not all side effects associated with the use of intraocular pressure-lowering drops can be attributed to the presence of preservatives in the preparation. The recommendations emphasize that special attention should be paid to patients with existing ocular surface diseases (OSD), such as dry eye syndrome or Meibomian Gland Dysfunction (MGD), when using preservatives [10].

DISCUSSION

In a meta-analysis by Hedengran et al. [8], an extensive analysis was performed based on 16 randomized controlled clinical trials comparing the efficacy and safety of glaucoma eye drops preparations containing benzalkonium chloride (BAK), drops containing alternative preservatives (AP, including PQ1 – polyquaternium-1) and preservative-free (PF). Based on 10 included studies, BAK agents were compared to PF agents, another six to AP agents. A meta-analysis for the primary endpoint (IOP changes) was planned according to the protocol and a random inverse variance meta-analysis was used for the pooled data. A difference greater than or equal to 2 mmHg was considered clinically significant. Secondary endpoint meta-analyses were performed when possible *post hoc*. Secondary

endpoints included adverse reactions reported, ocular surfaces and all measures of visual acuity, disease progression, quality of life, patient preference, adherence, and the need to interrupt or change treatment. For each meta-analysis, subgroup analyzes for AP and PF vs. BAK were performed [8]. The general tolerance of the eye drops active substances of which were prostaglandin analogues or β -blockers, both with preservatives and without preservatives, is good. No statistically significant differences in terms of safety and efficacy have been demonstrated. There were no statistically or clinically significant differences in lowering the intraocular pressure between the groups of drugs containing BAK and the control group (PF or AP preparations). Conjunctival hyperemia was analyzed in nine of the studies (among 3,800 patients), no statistically significant differences were observed; 14.9% in the BAK group and 14.2% in the compared group. The next analysis of ocular hyperemia was carried out on the basis of five studies (2,268 patients), where the incidence of its occurrence in the BAK group was 7.7% and 5.7% in the compared group, the difference was not statistically significant. All ocular adverse reactions were analyzed in the five included studies (1,906 patients), with a frequency of 24.5% in the BAK group and 23.12% in the comparator group. The tear film break time (TBUT) was studied in three studies (130 patients), the meta-analysis showed no statistically significant differences [8]. A study by Goldberg et al. showed a statistically significantly more frequent occurrence of hyperpigmentation after the use of preparations without preservatives vs. Containing BAK [11].

Steven et al. conducted a study to collect and analyze the results of randomized, double-blind studies on the use of drops containing an intraocular pressure-lowering substance with and without preservatives in patients with glaucoma [1].

A randomized clinical trial (Shedden et al.) conducted on 261 patients compared the efficacy and safety of the dorzolamide/timolol preparation in two groups divided 1 : 1 (1 – preparation containing BAK; 2 – preparation without preservatives) [12]. Efficacy was assessed on the basis of intraocular pressure (IOP) measurements taken after a 3-week pretreatment with timolol alone, followed by 2.6 and 12 weeks after treatment with PF or a conserved dorzolamide/timolol combination. Tolerance was assessed on the basis of reported adverse events by patients and an objective clinical assessment. It was shown that the efficacy of the preparation in both groups was identical, and both variants of the drug were well tolerated. No statistically significant differences in the incidence of side effects were found. Moreover, a similar percentage in each study group had point erosions of the corneal epithelium (23.8% preparations with BAK vs. 16.8% without preservatives) [12].

Another randomized, double-blind clinical trial by Day et al. compared bimatoprost without preservatives and contain-

ing 0.005% BAK. 597 patients with OHT and various types of glaucoma were randomized [13]. Persons taking other medications chronically or with changes to the surface of the eye were excluded. Treatment duration was 12 weeks, as assessed at baseline and after 2, 6, and 12 weeks. The results of the studies showed that both preparations were equally well tolerated by the patients during the study, and their effectiveness was identical. Ocular side effects occurred in 32% of patients taking the unpreserved variant and in 35% of the bimatoprost group with BAK. The incidence of hyperemia, pruritus, and punctate keratitis was virtually identical in both groups, and “foreign body sensation” in the eye was more frequently recorded in the unpreserved bimatoprost group (2.3%) vs. BAK (0.7%) [13].

The work of Goldberg et al. analyzed two variants of bimatoprost 0.03% + timolol 0.5% in the version without preservatives and with 0.005% BAK [11]. 561 patients with OHT or POAG were randomized. This was a double-masked RCT that was performed for 12 weeks following a washout period of 4–28 days. Safety was assessed based on reported adverse events, slit lamp study, and conjunctival hyperemia assessments based on the Oxford hyperemia scoring system. Both the BAK version and the unpreserved version were well tolerated by the patients. The frequency of adverse reactions resulting from the use of the preparations was as follows: 28.8% in the bimatoprost/timolol group without preservatives vs. 28.7% in the bimatoprost/timolol group with BAK [11].

In a study by Aptel et al. similar efficacy was found for the preservative-preserved and preservative-free prostaglandin analogue – both types of drops reduced IOP to a similar degree. Good patient compliance was reported in both groups. There were also no statistically significant differences in side effects (i.e. pruritus) between the groups using BAK drops and drops without preservatives [14].

In randomized, double-blind studies Katz et al. it has been shown that in patients with moderate OSD, some symptom relief can be obtained by switching from preservative-free drops to preservative-free drops. A similar corneal discoloration was found in both groups, however, in the group without preservatives (PF), more pain symptoms, congestion, and irritation were reported than in the group with preservatives [15].

In all of the above studies, the IOP lowering effect was comparable. At the moment, there is no evidence of differences in the effectiveness of preparations without preservatives and containing BAK in the treatment of glaucoma.

It has been suggested that the use of BAK in intraocular pressure-lowering drops causes poor tolerability and side effects that may affect drug use and disease control. It is very difficult to replicate the negative impact of BAK data published in clinical trials, often the results obtained are unique and even contradict previous results. For example, a French

study on a group of 4,000 patients (Pisella et al.) [16] emphasizes that patients who use drops without preservatives have half the symptoms of ocular surface disease (OSD). On the other hand, other clinical studies [17] show that different concentrations of BAK used in preparations have little or no effect on corneal toxicity. Additionally, eye drops containing BAK did not induce corneal toxicity in the vast majority of patients. There is also no evidence of differences in the degree of corneal discoloration depending on the amount of the daily dose of BAK [1].

In addition, the protective effect of BAK against SARS-CoV-2 has been demonstrated in a clinical study by Ryohei Hirose et al. The effectiveness of BAK disinfection against SARS-CoV-2 and IAV (influenza virus) on human skin was relatively high and showed a similar trend to that observed in the in vitro evaluation results [18].

CONCLUSIONS

The term *glaucoma* describes a group of diseases whose main feature is progressive neuropathy of the optic nerve, which, if left untreated, leads to the development of irre-

versible blindness. The main risk factor for its development is increased intraocular pressure. Treatment of glaucoma consists of a regular intake of drops that lower intraocular pressure. This requires discipline on the part of patients who usually do not notice the symptoms of their disease but observe common local side effects of the drops such as conjunctival hyperemia and dry eye syndrome. The article presents meta-analyses confirming that the side effects of eye drops are not only caused by the presence of preservatives in them, and the effectiveness of anti-glaucoma drugs containing BAK and without preservatives is comparable. In the case of patients undergoing polypharmacy or with OSD, a cumulative higher dose or concentration of BAK in the tear film may mean that preparations without preservatives are preferred in this group of patients. Based on current evidence, there is no justification for the routine use of PF medications in people without significant OSD, especially those requiring only a small amount of medication (1–2) per day. During the COVID-19 epidemic, studies appeared showing the protective effect of preservatives against SARS-CoV-2. However, confirmation of antiviral activity is required in subsequent randomized trials.

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