Preservatives – Daily Dose of Benzalkonium Chloride in the Treatment of Glaucoma from the Patient’s Perspective

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Aims of Research

Nowadays, in indication of local anti-glaucoma treatment the physician can choose from several tens of active ingredients and concentrations in eye drops available on the market. We make our choice taking course of the disease, topical clinical record file, and our clinical experience into account, but we also pay attention to the patient’s subjective acceptance of the previous treatment. The objective is to find such a treatment that would guarantee the preservation of visual function as well as the quality of patient’s life. The drug must be well-tolerated and the side effects (either general or local) must not deteriorate the patient’s cooperation in the treatment regime. The presence and composition of excipients play an important role here. We have reckoned with the daily dose of benzalkonium chloride (BAC) in the treatment of glaucoma.

State of the Art

BAC plays a controversial role in the treatment of patients with glaucoma. It is essential in the treatment with the eye drops. However, it causes negative local side effects while used repeatedly. The preservatives-free eye drops packed for multiple usage show the signs of contamination as early as 1 – 2 weeks when applied 2 times a day. [19]

BAC deposits in the ocular tissues and in frequent use it causes damage to the cells. It is toxic, mainly for the cornea and conjunctiva – it can induce the changes on the surface, discomfort, tear film instability, conjunctival inflammation, and apoptosis of epithelial cells. The preservatives can cause allergic or more frequently toxic (90 %) reactions, the detergent effect causes the loss of tear film stability, the direct damage of the corneal epithelium, and the conjunctival immunological reaction.

By deteriorating of the lipid layer of the tear film BAC can increase the evaporation, reduce the number of goblet cells, and secondarily affect the mucin layer of the tear film. BAC can affect the cell proliferation meshwork (0.0002 % BAC), and lens epithelial cells, induce the apoptosis in human trabecular cells in animals post mortem (exposed to BAC 0.00001 % for 15 minutes). [3, 4, 7, 15]

BAC causes: the apoptosis, pro-inflammatory, the damage to the emulsification of the tear film lipid layer, and the loss of goblet cells. [3, 5, 8, 9, 16, 17, 18]

Up to 60 % of patients with glaucoma can be affected by the ocular surface disease (OSD) with the symptoms having impact on the quality of their lives. The most frequent clinical manifestations of OSD accompanying the glaucoma treatment include superficial punctate keratitis, tear film instability, allergic manifestations, pseudopemphigoid, recurrent herpes simplex keratitis, especially after the prostaglandins, corneal decompensation after dorzolamide. Both in animals and humans in vivo the neurotoxic effect of BAC on the ocular surface tissues has been demonstrated. [2]

BAC causes complications especially during the long-term treatment of glaucoma. [11, 13] We can achieve the reduction of the undesired effect on the eye tissue by avoiding preservatives in the further treatment or switching to gentler preservatives. We cannot ignore the fact that a good result of the glaucoma operations depends not only on the surgeon, but on the topical therapy in use before the surgery. The undesired inflammatory effects are more frequent with multiple and long-lasting local treatments.
The inflammations must be reduced to minimum – then there is a chance on a good surgery result.

In a prospective epidemiological study with 249 ophthalmologists and 4,107 patients we carried out a monitoring of the ocular symptoms of glaucoma treatments with the preservatives and without them. We found a lower prevalence of subjective symptoms and the adverse effects on the surface structures of the eye using the eye drops without preservatives. Most of the negative side effects of the treatment with drops with the preservatives disappeared after the treatment discontinuation. [12]

It is necessary to make the difference between â±glaucoma treatment toleranceâ± and â±preservatives toleranceâ±. The eye drops tolerance is influenced by many incorporated components, such as agents which affect pH, viscosity, and specific active substance. When we modify the composition an anti-glaucoma drug by changing the preservative in use, we can achieve better tolerance of the drug. To provide an example we can mention Alphagan P 0.1%. By reformulating the preservative into Purite (stabilized oxychlorine complex) and increasing the pH to 7.8 we achieved better penetration of the drug. It was also possible to decrease the concentration of brimonidine to 50%. In clinical practice, this resulted in a remarkable improvement of treatment safety and tolerance. [3]

By the elimination of BAC from Travatan P we prepared Travatan Z, in which the drug concentration and the pH remained the same while the drug effectivity and tolerance was equivalent. Nevertheless, a sole change of the preservative (SoFZia – buffer containing borate, sorbitol, polyethylene glycol, and zinc – instead of the BAC) has no major effect on the overall drug tolerance. [10] The percentage of living cells of cornea and conjunctiva is significantly higher when using POLYQUAD or SoFZia instead of the BAC. [1] Latanoprost with the BAC, however, has a significantly higher antimicrobial protection than travoprost (SoFZia). [13] In abroad, a large number of anti-glaucoma drugs has their gentler versions, however, these are not registered in our country. Such a discrepancy in the treatment possibilities in the Czech Republic and abroad may be viewed as a depth of the pharmaceutical companies and distributors.

We obtained the data from the SPC of the drugs, package instructions leaflets, from the materials published by pharmaceutical companies, distributors, or registration holders, as well as from our own calculations based on the topical average amounts of content in three packages of the eye drops. With regard to the official data we determined the daily dose of BAC in the treatment of glaucoma from the patient’s point of view, i. e. in the situation when they collect the drug at a pharmacy and follow the usage instructions.

Before the publication we sought to consult our research results with the distributors or registration holders. However, they were not very responsive – their reactions varied from the agreement to the indifference, even with a case of offensive attitude. This situation confirmed our opinion that these issues are important, not enough monitored and sometimes maybe even deliberately ignored.

We determined the dose of BAC in a droplet of each product. When calculating the daily dose of BAC we took a daily frequency of usage according to the SPC into account. The anti-glaucoma drugs were sorted into groups (beta-blockers, alpha-mimetics, prostaglandin derivatives and doxycyclines, carbonic anhydrase inhibitors, and fixed combinations). And then we sorted them according to the observed daily dose of BAC. We found significant differences in the values of BAC daily dose among the groups as well as among individual anti-glaucoma drugs within each group: beta-blockers 0 – 10 µg, alpha-mimetics 3,5 – 7,1 µg, prostaglandins 0 – 6,1 µg, carbonic anhydrase inhibitors 3,8 – 5,5 µg, fixed combinations 1,4 – 8,8 µg.

The daily dose of BAC is one of the factors that may play an important role in the tolerance of the long-term anti-glaucoma treatment. The data are not readily available. The concentration of BAC in 1 ml of the product referred to in the drug materials does not say enough about the amount of BAC that the patient actually applies to the conjunctival sac in a daily therapeutic regimen.

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Keywords

Glaucoma

Definition: Is a term describing a group of ocular disorders with multi-factorial etiology united by a clinically characteristic intraocular pressure-associated optic neuropathy.


UMLS: –

SNOMED CT: 23986001

MeSH: C11525381

Application in Biomedicine and Healthcare

The presence of preservatives in the eye drops can have a negative effect on the cells of cornea and conjunctiva. It can cause patients the subjective symptoms supported by the objective findings. [1] [6] [7] [9] [18] Therefore, it is very interesting to compare the BAC concentrations in the individual products used in the treatment of glaucoma. The most important criterion in our monitoring was to count the daily dose of BAC for individual anti-glaucoma eye drops based on the measurement of a droplet and the BAC concentration in the drug.
Conservative Treatment

**Definition:** A treatment, that doesn’t include any operation or intervention.


**UMLS:** –

**SNOMED CT:** no matching results found

**MeSH:** no matching results found

Benzalkonium Chloride

**Definition:** A yellow white powder prepared in an aqueous solution and used as a detergent, fungicide, bactericide, and spermicide. Benzalkonium chloride is a mixture of the chlorides of various organic compounds having a benzene ring attached to an ammoniated alkane.


**UMLS:** –

**SNOMED CT:** 64686009

**MeSH:** D0267527608

Preservative

**Definition:** Is a substance that is added to products such as foods, pharmaceuticals, paints, biological samples, wood, etc. to prevent decomposition by microbial growth or by undesirable chemical changes.


**Antiglaucoma**

**Definition:** A medicine used to treat glaucoma.


**UMLS:** –

**SNOMED CT:** 386757008

**MeSH:** C536824

References


