ORIGINAL ARTICLE

Preservative Substances – the Daily Dose of Benzalkonium Chloride in Glaucoma Treatment from the Patient's Point of View

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SUMMARY

The author calculated the daily dose of Benzalkonium Chloride (BAC) in eye drops used in glaucoma treatment from the patient's point of view, which means the real amount of BAC applied in the conjunctival sac. The information about BAC concentration in 1 milliliter (mL) do not offer sufficient picture about real circumstances, because the size of the drop, especially after the introducing of the use of generic products in clinical practice in specific anti-glaucomatic drugs, differs significantly. The daily dose of BAC may have substantial significance in the patient's treatment tolerance. The overview of BAC daily dose in single therapeutic groups and drugs follows: betablockers: Timo-COMOD 0, Arutimol 2.6, Vistagan 2.8, Timolol-POS 3.0, Arteoptic 3.7, Betoptic S 4.8, Timoptol MSD 6.3, Betoptic 10.0; alpha-mimetics: Alphagan 3.5, Luxfen 3.5, Aruclonin 7.1; derivates of prostaglandine, prostamides: Taflotan 0, Monopost 0, Lumigan 1.4, Unilat 3.1, Travatan 3.9, Latanoprost Apotex 4.3, Rescula 5.8, Latanoprost POS 5.9, Xalatan 6.0, Latanoprost Ratiopharm 6.0, Latanoprost Actavis 6.0, Latanoprost Arrow 6.0, Arulatan 5.4, Latalux 6.0, Glaucotens 6.0, Xaloptic 6.0, Solusin 6.1; carboanhydrase inhibitors: Batidor 3.8, Azopt 4.8, Trusopt 5.4,Oftidor 8.1; fixed combinations: Ganfort 1.4, Dorzolamid/timolol TEVA 2.8, Combigan 3.2, Duotrav 4.3, Cosopt 5.6, Xalacom 6.0, Glaucotima 6.0, Latanoprost/timolol Apotex 6.3, Azarga 6.4, Dorzogen Combi 6.5, and Dozotima 8.8 µl.

Key words: glaucoma, antiglaucomatic treatment, preservatives, Benzalconium Chloride, BAC, daily dose of BAC

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INTRODUCTION

At present, in the case of indication of local anti-glaucoma therapy, the doctor has the option of choosing from several dozen effective substances and concentrations in eye drops which are available on the market. The choice is subject to the indication criteria, the course of the disease, the current clinical finding and the doctor's own clinical experience, but we also take into account how the patient has subjectively evaluated the medication hitherto. The aim is to find a treatment which would guarantee the preservation of visual functions without causing a deterioration of the patient's quality of life. The medicament must be well tolerated by the patient, general or local adverse reactions must not reduce the patient's co-operation within the therapeutic regime. A significant role is played here by the presence and composition of adjuvant substances, in particular concentrations of preservative agents. We refer to our previous statement, in which we calculated the daily dose of benzalkonium chloride in glaucoma therapy for the available anti-glaucoma drugs. Here we present an overview updated on the basis of changes in the therapeutic portfolio.

METHODOLOGY

Depending on the concentration, the presence of preservative agents in eye drops may have a cytotoxic effect on the cells of the cornea and conjunctiva, and thus cause patients subjective complaints backed up by an objective finding (1, 5, 7, 9, 18).
As a result, a comparison of the concentration of benzalkonium chloride (BAC) in the particular drugs used in glaucoma therapy is of great interest. The most significant criterion in this observation is a calculation of the daily dose of BAC for individual anti-glaucoma drugs based on the size of the drop and the concentration of BAC in the drug. The data was obtained using the methodology described in our previous study on this topic (2006, 2011), thus not only with the use of the data presented in the medicinal product SPC, package leaflet, in documentation of the pharmaceutical company, the distributor or the marketing authorization holder, but also by the help of our own calculation based on verification of the current average content in three packages of eye drops. Taking into account the official data, we determined the daily dose of BAC in glaucoma therapy according to the current situation, i.e. by calculating from the point of view of the patient who collects a specific package of the pharmaceutical in the pharmacy and applies it according to the recommended method.
As was the case before the publication of the data in 2006 and 2011, when updating the data we first of all selected the form of consultation of the results with the distributors or marketing authorization holders of the pharmaceutical product. This time also the response was not as problem-free as we would have expected from subjects whose representatives continually visit doctors in their surgeries and

inform them not only about the company's current offer, but also about the qualitative differences between the specific products, in the sense of their advantages in comparison with the competition. What is the balance? The responses of the addressed subjects varied – from agreement to lack of interest, and in one case we even received a hostile statement. This state of affairs strengthened our conviction that this represents an important issue, which receives little attention and in certain cases is perhaps even intentionally overlooked.

RESULTS

The authors determined a dose of BAC in 1 drop of each observed product. Upon the calculation of the daily dose, attention was paid to the frequency of daily application according to SPC. Anti-glaucoma drugs were divided according to groups (beta-blockers, alpha-mimetics, prostaglandin derivates and docosanoids, carboanhydrase inhibitors and fixed combinations), and classified according to the determined daily dose of BAC. They determined significant differences in the values of the daily dose of BAC between the groups and between the individual anti-glaucoma drugs within the particular group – beta-blockers 0-10.0 μg, alpha-mimetics 3.5-7.1 μg, prostaglandins 0-6.1 μg, carboanhydrase inhibitors 3.8-5.5 μg, fixed combinations 1.4-8.8 μg (Table 1).

DISCUSSION

BAC plays an inconsistent role in the treatment of patients with glaucoma. It is essential in treatment with eye drops upon using packages for multiple applications but it causes local adverse reactions. Packages of eye drops designated for multiple application without preservative agents manifest signs of contamination after only 1-2 weeks upon application twice daily (19). BAC accumulates in eye tissues, and upon frequent use causes damage to cells. It has a toxic effect mainly on the cornea and conjunctiva – it can cause changes to the surface, discomfort, instability of the lacrimal film, inflammations of the conjunctiva and apoptosis of the epithelial cells. Preservative agents may be the cause of allergic or more frequently toxic reactions (90%) – the detergent effect causes loss of stability of the lacrimal film, direct damage to the epithelium of the cornea and conjunctiva, as well as immunoallergic reactions. By influencing the lipid layer of the lacrimal film they increase evaporation, reduce the number of cup cells and secondarily negatively influence the mucin layer of the lacrimal film. Preservative agents may influence the proliferation of cells of the trabecular meshwork (0.00002% BAC) and the cells of the epithelium of the lens, induce apoptosis of human trabecular cells in animal post mortem (exposure for period of 15 min BAC 0.0001%) (3, 4, 7, 15).

BAC acts apoptotically, inflammatorily, causes damage to the lacrimal film, emulsification of the lipid layer and loss of cup cells (3, 5, 8, 9, 16, 17, 18). As many as 60% of patients with glaucoma may be afflicted with an ocular surface disease (OSD), with manifestations of a negative influence on quality of life and compliance. The most common clinical manifestations of OSD in connection with glaucoma therapy include keratitis superficialis punctata, instability of the lacrimal film, allergic manifestations, pseudopemphigoid, recurrent herpes simplex keratitis especially in reaction to prostaglandins, decompensation of the cornea in reaction to dorzolamide.

In both animals and humans, a neurotoxic effect of BAC on the tissues of the ocular surface has been demonstrated by in vivo studies – a significant reduction in the density of the stromal nerve fibres, axonopathy, a reduction of sensitivity of the cornea and damage to DNA (2).

BAC causes complications especially in the case of long-term therapy, which is the case of glaucoma treatment (11, 14).

A reduction of the adverse effect of glaucoma therapy on the ocular tissue and an improvement of the patient's compliance may be achieved by switching from therapy containing preservative agents to therapy without preservative agents, or switching to preservative agents which are less harmful to the eye. It is also not possible to overlook the fact that a good result of glaucoma surgery depends not only on the surgeon, but also on local therapy in the preceding period. In the case of multiple and long-term local therapy, adverse inflammatory manifestations are more frequent, and there is a stronger tendency to healing which degrades the effect of the filtration operation. Inflammatory manifestations must be reduced to a minimum – there is then a better chance

Table 1 Daily dose of BAC (μg) – frequency of application of pharmaceuticals according to SPC

BETA-BLOCKERS	
Timo-COMOD	0
Arutimol	2.6
Vistagan	2.8
Timolol-POS	3.0
Arteoptic	3.7
Betoptic S	4.8
Timoptol MSD	6.3
Betoptic	10.0
APHA-MIMETICS	
Alphagan	3.5
Luxfen	3.5
Aruclonin	7.1
PROSTAGLANDIN DERIVATES, PROSTAMIDES	
Taflotan	0
Monopost	0
Lumigan	1.4
Unilat	3.1
Travatan	3.9
Latanoprost Apotex	4.3
Rescula	5.8
Latanoprost POS	5.9
Xalatan	6.0
Latanoprost Ratiopharm	6.0
Latanoprost Actavis	6.0
Latanoprost Arrow	6.0
Arulatan	5.4
Latalux	6.0
Glaucotens	6.0
Xaloptic	6.0
Solusin	6.1
CARBOANHYDRASE INHIBITORS	
Batidor	3.8
Azopt	4.8
Trusopt	5.4
Oftidor	8.1
FIXED COMBINATIONS	
Ganfort	1.4
Dorzolamide/timolol TEVA	2.8
Combigan	3.3
Duotrav	4.3
Cosopt	5.6
Xalacom	6.0
Glaucotima	6.0
Latanoprost/timotol APO	6.3
Azarga	6.4
Dorzogen Combi	6.5
Dozotima	8.8

of attaining a good effect of the surgical procedure.
In a prospective epidemiological trial involving 249 ophthalmologists and 4107 patients, observing ocular symptoms of glaucoma therapy with and without preservative agents, a lower prevalence of subjective complaints and adverse effects on the superficial structures of the eye was determined upon the use of eye drops without preservative agents. The majority of adverse reactions upon therapy with drops containing preservative agents disappeared following discontinuation of their application (12).
It is necessary to differentiate the terms "tolerability of glaucoma therapy" and "tolerability of preservative agents". Tolerability of eye drops is influenced by a number of ingredients added to them – agents influencing pH, viscosity, as well as the particular active ingredient. Upon modifications in the composition of already used anti-glaucoma drugs, it is possible to achieve better tolerance to the pharmaceutical with a change of preservative agent. Alphagan P 0.1% is an example. Through reformulating of the preservative agent to Purite (stabilized oxychloro complex) and increase of the pH to 7.8, better penetration of the drug was achieved, thus enabling a reduction of brimonidine concentration to 50%. The result in clinical practice is a pronounced improvement in safety and tolerability of the therapy (6).
Removal of BAC from Travatan has enabled the creation of Travatan Z, in which pH and concentration of the drug remained identical; efficacy of the drugs and tolerability is equivalent. However, a mere change of preservative agent (SofZia – a buffer containing borate, sorbitol, polyethylene, glycol and zinc instead of BAC) does not have a pronounced effect on overall tolerability of the pharmaceutical here (10). Upon use of polyquad or SofZia as a replacement for BAC, the percentage representation of live cells of the cornea and conjunctiva is significantly higher (1). However, Latanoprost with BAC demonstrates considerably higher anti-microbial protection than travoprost (SofZia) (13).
Modified, more sparing variants of drugs are available abroad for a large number of anti-glaucoma medications, but these are not registered in the Czech Republic. This discrepancy in the options of therapy abroad and in the Czech Republic can be regarded as a certain shortcoming on the part of pharmaceutical firms and distributors.

CONCLUSION

The daily dose of BAC is one of the factors which can play an important role in tolerability of a long-term glaucoma therapy. Data is not generally available. The concentration of BAC in 1 ml of pharmaceutical product stated in the pharmaceutical documentation does not give a sufficiently accurate account of the quantity of BAC which the patient actually applies to the conjunctival sac in the daily therapeutic regime.

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