Preservative-free Treatment in Glaucoma Is a Sensible and Realistic Aim for the Future

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Abstract

Medical therapy is usually the first-choice option in the management of glaucoma. However, adverse effects of ophthalmic preparations can potentially jeopardise the safety and efficacy of the treatment. Eye-drop bottles contain multiple components, all of which have the potential to cause adverse reactions, although it is the preservatives that are major culprits. The effect of preservatives on the eye has been studied extensively in both human and animal tissues. Benzalkonium chloride (BAC) is a highly effective preservative and the most commonly used in antiglaucoma medications; however, BAC is toxic to ocular tissue, having the potential to cause adverse effects. The use of less toxic preservatives or preservative-free medications has the potential to improve the management of glaucoma.

Keywords

Preservatives, benzalkonium chloride, adverse effects, preservative-free treatment, glaucoma

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Glaucoma is a chronic, potentially blinding condition and one of the leading causes of blindness in the world. The vast majority of patients are asymptomatic until they develop an advanced stage of the disease, at which point quality of life is reduced dramatically by significant visual field loss and potential blindness. The mainstay of therapy for glaucoma is to reduce intraocular pressure (IOP), which is the greatest risk factor in the aetiology of glaucomatous optic neuropathy.

Nowadays ophthalmologists have several treatment options available to offer their patients, the aims of which are to reduce IOP and prevent or delay deterioration: medical therapy, laser or surgical interventions. It is generally accepted that medical therapy is the first-line option of choice in the treatment of glaucoma. However, the adverse effects associated with topical medication can have a negative effect on patient adherence with therapy, the doctor–patient relationship and patient quality of life (see *Figure 1*).

Preservatives

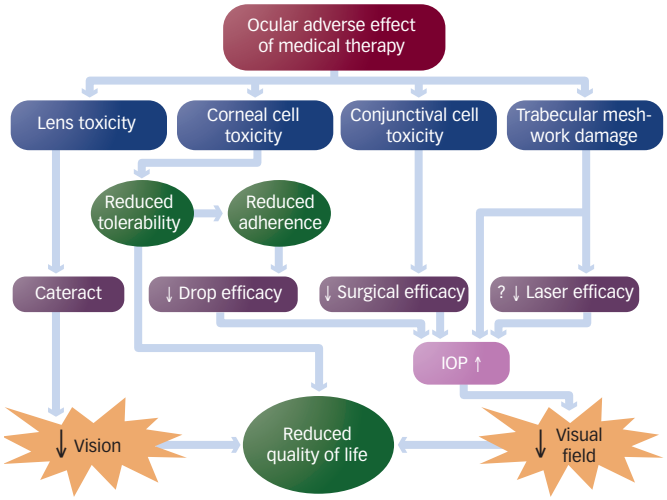
Currently available bottled topical antiglaucoma medications contain numerous ingredients, including the chemically active component (drug), a vehicle for the drug and a preservative. In addition, there are often chemicals preventing the drug from binding to the inner surface of the plastic container, buffers and other stabilising compounds. Development of a preparation must ensure drug penetration into the globe, have adequate efficacy, be acceptable with respect to side effects and include measures to prevent microbial contamination. With respect to the latter issue, there are several antimicrobial agents used in ophthalmic preparations (see *Table 1*).

The preservatives used in eye drops achieve their antimicrobial effect by various means. For example, benzalkonium chloride (BAC) damages cytoplasmic contents after dissolving bacterial walls and membranes, thimerosal precipitates bacterial proteins, chlorhexidine disrupts cytoplasmic membranes, and alcohols (such as chlorobutanol) directly penetrate bacterial lipid layers to exert their toxic effects within. Unfortunately, the ability to damage unicellular microbes is not specific to such cells and the chemicals can exert a toxic effect on human cells.

BAC is the most commonly used preservative in currently available topical antiglaucoma medications, being used in concentrations ranging from 0.004 to 0.02%. Chemically, BAC is a quaternary ammonium that acts as a cationic detergent. Although BAC is a highly effective antimicrobial preservative, it is also toxic to human cells.[1] Finally, BAC can improve ocular surface drug penetration and potentially improve efficacy, at least theoretically.[2,3]

The effect of preservatives (especially BAC) has been studied extensively in humans and in animal models over many years. There is significant evidence that exposure to preservatives such as BAC is a major reason for the development of adverse effects associated with topical glaucoma treatment. Despite the evidence for BAC-induced side effects, the majority of glaucoma patients throughout the world continue to administer BAC-preserved eye-drops. Although ocular side effects are commonly secondary to preservative exposure, an effect of the active ingredient cannot be excluded. In a clinical setting, determination of which drop component is the cause of a side effect can be problematic.

Figure 1: Ocular Adverse Effects of Medical Therapy



IOP = intraocular pressure.

Table 1: Preservatives Commonly Used in Ophthalmic Products

Benzalkonium chloride (BAC)
Benzododecinium bromide (BDB)
Purite®
SofZia®
Polyquaternium-1 (PQ-1)
Cetrimide
Chlorhexidine
Chlorobutanol
Disodium edetate (EDTA)
Methylparahydroxybenzoate
Phenylmercuric nitrate
Polyhexamethylene biguanide hydrochloride
Sodium perborate
Sorbic acid
Thimerosal

Benzalkonium-chloride-induced Cell Toxicity

Champeau and co-workers[4] found that a significant proportion of BAC accumulates in the corneo-conjunctival epithelium and stroma and to a lesser extent in the iris, lens, choroid and retina. BAC was identified in ocular tissues up to one week after exposure, having a half-life of around 20 hours. It was suggested that the epithelium acts as a reservoir and gradually releases the agent into the eye. Debbasch and co-workers[5] reported that BAC-induced cell toxicity was a dose-dependent event.

In vitro studies[6,7] have identified that even at a low concentrations BAC causes trabecular meshwork cell toxic changes and apoptosis. Theoretically, therefore, long-term use of BAC-preserved topical antiglaucoma therapy could be a basis for reduced trabecular function and potential worsening of any glaucomatous process within the trabecular meshwork. Furthermore, BAC has been implicated in the aetiology of cataract. Goto and co-workers[8] found that BAC was toxic to cultured human lens epithelial cells in experiments where preservative-free antiglaucoma drugs were used in control cultures. Furthermore, it was concluded from a large, long-duration, prospective, randomised control trial (The Ocular Hypertension Treatment Study) that the incidence of cataract was higher in eyes exposed to preserved topical antiglaucoma therapy.[9]

Ocular surface toxicity has been investigated in more detail. Pisella and co-workers[10] investigated the prevalence of ocular side effects in more than 4,000 patients using antiglaucoma medications. It was found that the frequency of side effects was related to the number of preservative-containing eye-drops used. The preservatives appeared to be directly responsible for poor tolerance of the treatment since this improved after switching therapy to preservative-free preparations.

Symptomatic ocular surface disease (OSD), either caused or exacerbated by antiglaucoma therapy, is almost certainly more prevalent than many clinicians believe. Nordmann and co-workers[11] undertook a survey to quantify the problem. It was determined that 62% of 173 glaucoma patients were complaining of at least one significant ocular surface side effect related to their topical treatment. Among them, 19% reported at least four simultaneous such side effects. The most frequently identified problems were burning, tearing, itchiness and blurred vision. Furthermore, poor adherence with therapy was directly correlated with poor quality of life, indicating that, understandably, the occurrence of side effects reduces adherence to therapy, potentially jeopardising the efficacy of treatment. In an even larger study, Jaenen and co-workers[12] surveyed almost 10,000 patients and found that patients using preservative-free drops were about 50% less likely to develop ocular surface side effects.

There are several ocular surface sites upon which preservatives can act to induce adverse effects: the pre-corneal tear film (PCTF), the cornea, the conjunctiva and adnexal tissues.

The Pre-corneal Tear Film

Preservatives acting as detergents, such as BAC,[13,14] create a low surface tension by disrupting the superficial lipid layer of the PCTF, resulting in a decreased PCTF break-up time (BUT), allowing subsequent evaporation of the middle aqueous layer and precipitation of mucin layer components. Moreover, the toxic effect on conjunctiva reduces the number and function of conjunctival goblet cells,[15] resulting in impairment of mucin production and subsequent failure of corneal epithelial wetting. The long-term use of BAC-preserved eye drops can therefore result in significant PCTF thinning and malfunction, the development of superficial punctate epithelial erosions and an increased risk of vision-threatening corneal ulceration.

The Cornea

There is some evidence that preservatives alter corneal fibroblast contractility,[16] with a potential effect on corneal shape and reduced reliability of IOP measurements, although the clinical significance of this is questionable. However, corneal surface toxicity is much more relevant and has been studied extensively in animal models. In one rabbit study, increasing concentration of BAC correlated with the number of corneal microlesions and the amount of lactate dehydrogenase and albumin (known markers of corneal distress) released into the tears.[17] The effect of preservatives on the healing process within the cornea has also been studied in rabbits. Even small concentrations of BAC (0.01%) caused rupture of the epithelial barrier.[18,19] The same concentration of BAC or 0.1%

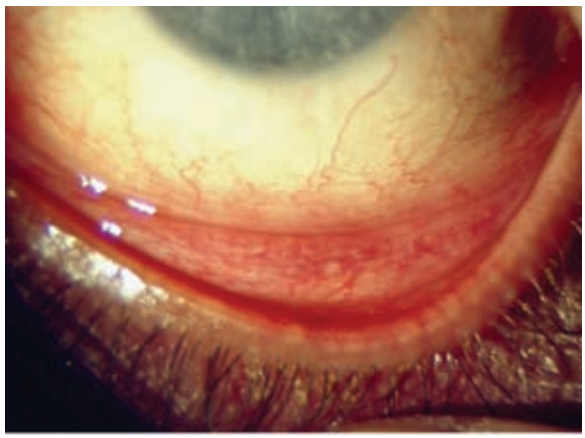
ethylene diamine tetra-acetic acid (EDTA) caused a delay in corneal healing, whereas 0.02% BAC completely inhibited the healing process post-keratectomy in rabbit eyes.[20] In dog studies, 0.0025% BAC or 0.025% thiomerosal have been reported to inhibit epithelial cell pseudopod growth and impair epithelial regeneration.[21] For humans there are several published case reports where BAC-related corneal toxicity has been reported in contact lens wearers,[22] in patients in the early post-operative course following cataract surgery[23] and in those suffering from dry eye,[24,25] the important point being that patient symptoms resolved after the implicated preserved topical treatments were replaced with preservative-free preparations.

The Conjunctiva

Clinically adverse conjunctival reactions to preserved antiglaucoma therapy can be classified into four groups: allergic, toxic, cicatricial or subclinical. Immunologically allergic conjunctivitis[26] is a type IV hypersensitivity response and is most commonly due to mercurial preservatives (e.g. thimerosal), although it has been suggested that the increasing use of BAC in household products (e.g. soaps and disinfectants) may be resulting in sensitisation and an increased prevalence of allergy. Most commonly, allergic conjunctivitis presents as a non-specific hyperaemia, but the specific feature of an allergic reaction is papillary conjunctivitis, which if left untreated may result in a more widespread dermato-blepharo-conjunctivitis. Patients with allergic conjunctivitis tend to complain of itchiness and mucoid discharge.

However, toxic conjunctivitis is more common than the allergic type and is frequently mis-diagnosed as an allergic reaction, particularly in the early stages when patients present with non-specific hyperaemia and non-specific symptoms (see *Figure 2*). Unfortunately, toxic conjunctivitis is sometimes treated inappropriately with preserved antiallergy drops and when the preservative itself is the cause, the condition is exacerbated rather than cured. Morphologically the toxic reaction results in loss of microvilli on surface epithelial cells within 10 minutes of exposure to BAC, with subsequent loss of contact with adjacent cells and cell death peaking at two to three hours, resulting in cell desquamation and ulceration.[27,28] Toxic conjunctival changes induced by BAC occur by means of several mechanisms. The detergent effect of the positively charged hydrophilic head and uncharged tail of the BAC molecule enables insertion into cell membranes and gap formation. The gap development results in reduced ionic resistance and an osmotic influx of water and ions with subsequent oedema and cell damage.[29,30] There is also evidence that damage induced by low concentrations of BAC can occur due to apoptosis, whereas in high concentration the preservative can induce necrosis.[1,4] In addition, BAC-containing drops generate superoxide anions, O_2^-, the level of which correlates with the loss of cell-membrane integrity and apoptosis.[4,29] Another mechanism involved in BAC-induced toxicity is an immuno-inflammatory process involving Langerhans antigen presenting cells, the outcome of which is eventual subconjunctival fibrosis.[30] As a result of the drop-induced conjunctival fibrosis following long-term use of preserved antiglaucoma treatment, some patients can develop foreshortening of their inferior fornices and pemphigoid-like changes.[31,32] There is strong evidence to indicate that prolonged exposure to multiple preserved antiglaucoma therapy induces subclinical inflammatory pathological changes in sub-epithelial conjunctival tissue.[14,33] Moreover, the drop induced subclinical conjunctival inflammation has been implicated as a risk factor for potential filtration surgery failure.[34]

Figure 2: Toxic Blepharo-conjunctivitis – Subtle but Symptomatic Conjunctival Hyperaemia with a Follicular Reaction



Fortunately, there is some evidence that the newer antiglaucoma prostaglandin analogue therapies are less 'toxic' to the conjunctiva with respect to inducing changes that might compromise the outcome of any subsequent filtration surgery.[35] Furthermore, there is some evidence that the subepithelial inflammatory changes induced by chronic use of antiglaucoma therapy may be reversible, thus reducing the adverse effect on the outcome of filtration surgery.[36,37]

Preservatives and Dry-eye Syndrome

Glaucoma and dry-eye syndrome are both very common age-related conditions and thus both are of ever increasing importance to most ophthalmologists. Furthermore, patients with OSD represent a large proportion of those with glaucoma. The reported prevalence of dry eye in adult populations varies from 5.5 up to 33.7%,[38–44] whereas Tsai and co-workers reported the prevalence of glaucoma in patients with significant OSD to be 66%.[45] Prevalence data such as those presented by Tsai and co-workers provide further evidence suggesting that antiglaucoma therapy causes or exacerbates dry-eye syndrome. Recently published data from Fechtner and co-workers have identified a similar high prevalence of OSD in patients exposed to topical antiglaucoma therapy: approximately half of their 630 patients suffered from OSD. The severity of symptoms correlated directly with the number of topical medications used and was, unsurprisingly, significantly higher in patients with known dry-eye syndrome.[46] It is therefore important to highlight the fact that management strategies for both glaucoma and OSD have to be considered together.

Alternatives to Benzalkonium Chloride Preservatives

Having identified the adverse effects attributed to use of BAC-preserved eye-drops, it is important to consider the alternatives. There are several problems that have to be solved in the development of new topical therapy products to ensure adequate drug penetration into the eye, efficacy, tolerability, stability, sterility and affordability. Two recently introduced preservatives (Purite® and SofZia®)[47,48] have been utilised in topical antiglaucoma products, and the published evidence indicates that these are less toxic to the eye than BAC, being well tolerated and as efficacious as their BAC-preserved

Table 2: Currently Available Preservative-free and Benzalkonium-chloride-free Preparations

Beta-blockers: timolol, carteolol, betaxolol, levobunolol
Carbonic anhydrase inhibitors: dorzolamide
Combination: Cosopt® (timolol + dorzolamide)
Miotic: pilocarpine
Alpha-agonists: apraclonidine, brimonidine (Purite-preserved)*
Prostaglandins: tafluprost, travoprost (SofZia-preserved; experimental only)*

**Benzalkonium-chloride-free Purite- and SofZia-preserved glaucoma medications are not available in Europe.*

equivalents. However, neither Purite nor SofZia preservatives have yet been approved by the European Medicines Agency (EMEA) for use in Europe.

Purite is a stabilised oxychloro complex that exerts its preservative action by oxidising unsaturated lipids and glutathione within microbes. The breakdown products of Purite are sodium ions, chloride ions, oxygen and water (salt water and oxygen being unlikely toxic suspects).[49] Noecker and co-workers[50,51] have demonstrated that Purite induces less corneal epithelial damage than BAC.

SofZia is an ionic buffer solution composed of boric acid, propylene glycol, sorbitol and zinc chloride. In comparison with BAC, SofZia has been shown to be less toxic to corneal epithelial cells both *in vitro*[52] and *in vivo*.[53]

Polyquaternium-1 (PQ-1), another potential alternative preservative for use in topical antiglaucoma medication, has been used successfully in contact lens solutions[54] and artificial tears. Polyquaternium-1 is a quaternary ammonium compound, and in an *in vivo* rat model has been shown to be less toxic than BAC.[55] Although PQ-1 has been used to preserve brimonidine, this was in an experimental situation only,[56] and PQ-1 is not currently used in a commercially available antiglaucoma product.

The use of preservative-free single-dose units (SDUs) allows total avoidance of preservatives and the associated adverse effects of their usage. However, SDU manufacturing and packaging makes them expensive and, for certain patients (i.e. those with significant arthritis of the hands), difficult to use.[51] Based on recent data, there is no difference between the ease of handling of SDU and multidose containers.[57]

A list of the currently available preservative-free and BAC-free drops is presented in *Table 2*.

Efficacy and Tolerability of Benzalkonium-chloride-free Drops

It has been suggested that through its detergent activity BAC can aid drug penetration into the eye and thus aid efficacy. With respect to low-dose (0.01%) bimatoprost, for example, unpublished dose–response experiments in rabbits have shown that the highest concentration of active ingredient in aqueous humour was obtained with 200ppm BAC.[2] In another rabbit study, epithelial permeability was higher in corneas exposed to latanoprost preserved with 0.02% BAC compared with travoprost with SofZia.[3] Although a low dose of prostaglandin might induce less hyperaemia, this might come at the cost of a greater degree of BAC-induced adverse effects as implied by the results of a recently published rabbit study.[58]

Furthermore, human studies comparing the efficacy and tolerability of BAC-preserved with alternative BAC-free or unpreserved preparations have demonstrated equal efficacy, together with either equal or improved tolerance. For example, preservative-free timolol has been reported to be equally effective and as safe as BAC-preserved multidose timolol.[59] Both preservative-free carteolol and BAC-free/SofZia-preserved travoprost have been found to have identical efficacy, safety and tolerability profiles to their BAC-preserved equivalents.[60,61] In addition, the toxic effect of preservative-free carteolol on tear film stability was significantly lower,[60] and the incidence of hyperaemia in BAC-free/SofZia-preserved travoprost-treated patients was less prominent.[61,62] The efficacy of preservative-free tafluprost has been shown to be no different to a BAC-preserved preparation of the drug in human eyes[63] and, in an *in vivo* rabbit study, the effect of preservative-free tafluprost on the conjunctiva and cornea was minimal and very similar to buffered phosphate solution.[64] No human studies comparing the tolerability of BAC-preserved tafluprost with preservative-free tafluprost have yet been published. However, it has been reported that preservative-free tafluprost maintained IOP at the same level as latanoprost, but was better tolerated in patients having signs or symptoms while on preserved latanoprost.[65] With respect to brimonidine, the incidence of allergic reaction in Purite-preserved brimonidine-treated patients has been reported to be 40% lower than to the BAC-preserved preparation, whereas efficacy was determined to be equal.[66] Furthermore, there was no difference found in terms of safety and efficacy between Purite- and PQ-1-preserved brimonidine eye-drops.[56]

The Future

In current practice, clinicians and their patients are fortunate to have increased choice with the introduction of BAC-free or preservative-free topical antiglaucoma medications. However, preservative-free preparations remain expensive and, for some, inconvenient to use. In the future there is hope for the introduction of topical antiglaucoma medication supplied in multidose preservative-free bottles, the presumed high price of which, one would hope, would fall with increasing sales.

At present, several preservative-free multidose bottle designs are used to ensure long-term sterility of certain ocular lubricants and anti-allergy eye drops: the ABAK® patented filter system,[67] the COntinuous MOno Dose system (COMOD®),[68–70] the Airless Antibacterial Dispensing System (AADSTM)[71] and the VISMED® multi system.[72] The ABAK system provides up to two months of sterility and uses a 0.2µ nylon fibre membrane to prevent bacteria from entering the bottle. The ABAK and COMOD systems have been used to package timolol (Timabak®/Timolabak®/Timo-comod®) and carteolol (Carteabak®), but these products are not readily available in all countries.[67,73] The COMOD and AADSTM bottles provide three months of sterility due to a silver coil within the tip (which has antibacterial properties) together with multiple valves combined with an airless pump and collapsing internal walls, designed to prevent air contact with the contents of the bottle when a drop is administered. The VISMED multi system guarantees up to three months of sterility by means of a specially designed top with an active carbon filter.

The development of preservative-free, multidose systems for supplying ocular lubricants provides hope that a similar or identical

system will soon allow more patients to administer preservative-free antiglaucoma medications from easy-to-use multidose bottles. The introduction of new delivery systems is a seemingly simple and sensible approach, but will have to undergo full testing and then approval from the various international drug authorities before commercialisation in all countries. However, the growing hope is that glaucoma patients will soon have medications that are easily administered, less toxic and better tolerated, all of which factors will improve adherence to therapy. Preservative-free treatment in glaucoma is thus a sensible and realistic aim for the future. ■

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