The prescription of topical ocular agents is a large and central part of the treatment that we offer our patients every day. Drops are the mainstay of treatment for such common conditions as allergy, infection, dry eye, and glaucoma. Even our surgical patients use topical agents pre-, peri-, and postoperatively. One of the great miracles of contemporary medicine is that we are able to use these drops safely, even in compromised eyes with weakened defenses against infection.

What makes this safe use possible is the presence of preservatives. With just a few exceptions, all multiuse topical drop formulations are preserved. And in many cases now there are medication classes with drugs that are preserved in different ways, giving us a choice not only of the therapeutic agent but the preservative system to which our patients will be exposed. This is important because, although preservatives for multiuse topical agents have existed for decades and are generally safe, preservative use is not without consequences.

Indeed, the most common preservative in use today, benzalkonium chloride (BAK), should be considered something of a necessary evil. While it is an effective biocide and is essentially innocuous when used for short periods in low concentration in otherwise healthy eyes, the ocular sequelae of long-term BAK use are sometimes serious and potentially deleterious to long-term compliance. For chronic conditions such as glaucoma, in which many patients use one or more topical agents several times a day, preservative-induced or preservative-exacerbated ocular surface disease can degrade patients’ quality of life to the point of becoming a significant obstacle to effective treatment. Nonetheless, we have asked our patients to persevere and endure the rigors of ocular irritation and toxicity in the name of the greater good of treating a potentially blinding condition.

As the population ages—the 80 million baby boomers began turning 60 in 2006—the number of dry eye and glaucoma patients will increase, making treatment for these conditions an important goal. And to truly reach that goal, treatments must be safe, effective, and as comfortable as possible. Fortunately, the last few years have seen new developments that promise to allow us to offer our patients less toxic topical agents, either through unit-dose vials, which eliminate the need for preservatives, or in newer preservative technologies that deliver the necessary antimicrobial activity without ocular toxicity, allergy, or inflammation.

This supplement reviews the history of preservatives in topical ocular agents to highlight why preservatives are necessary, describe the requirements for ensuring antimicrobial activity, and review some of the most recent advances in preservative technology, as well as future directions in this area. Given these advances, in the future we will not have to ask our patients to endure ocular discomfort in order to obtain the benefits of needed treatment.

Stephen C. Pflugfelder, MD

PRESERVATIVES: A Vital but Sometimes Troublesome Component of Ocular Medication

INTRODUCTION
OPHTHALMIC PRESERVATIVES: The Past, Present, and Future

Stephen C. Pflugfelder, MD

ABSTRACT

The US Food and Drug Administration requires that all topical ophthalmic preparations in multidose containers be able to resist contamination with specific challenge organisms. This means that all such solutions require a preservative, with the exception of two “self-preserved” antibiotics and an antibacterial container. While preservatives enable patients to use convenient and relatively inexpensive multidose containers, preservative use has been a mixed blessing. The history of ocular preservatives reveals numerous cases of ocular toxicity, inflammation, and allergy. This article reviews the history of the preservatives used in topical ocular agents, the requirements for ensuring antimicrobial activity, and some of the most recent advances in preservative technology.

With the exception of agents packaged in unit-dose containers and a few “self-preserved” antibiotics, virtually all premixed ophthalmic drops contain a preservative or a “preservative system” to prevent microbial growth. This includes drops intended for the treatment of glaucoma, dry eye disease, ocular infection, ocular inflammation, and ocular allergy, as well as drops and solutions for contact lens wearers.

Many of these conditions and treatments are chronic, thus magnifying any effects of preservatives. Glaucoma and dry eye disease in particular can be lifelong disorders that require chronic, and often multiple, topical treatments.

Types of Preservative

There are several types of preservatives, but only a few are used frequently in topical ophthalmic agents (Table 1). Preservatives typically work by one of two basic mechanisms: they are either detergents or act through oxidative processes. Detergents (or, more specifically, surfactants) act by dissolving or disrupting lipids. Detergent preservatives kill microorganisms by disrupting cell membranes and causing cell lysis. Examples of detergent preservatives include benzalkonium chloride (BAK, or sometimes BAC), polyquaternium-1 (PQ1), alcohol preservatives, and phenols.

Oxidative preservatives cause oxidative reactions that disrupt cellular metabolism. Small molecules, they can pass through cell membranes and interrupt intracellular cell function. Examples of oxidative preservatives include thimerosal, sodium perborate, sorbic acid, and chlorhexidine.

Preservatives and Ocular Surface Disease

Preservatives play a vital role in the safe use and availability of multidose topical ophthalmic agents. Inclusion of preservatives in these products is so important that it is required by the US Food and Drug Administration (FDA). However, preservatives have been encumbered by tolerability issues, and they can cause or exacerbate ocular surface disease in glaucoma patients (Figure 1). Ocular surface disease co-occurs with glaucoma in a high proportion of patients. Those of us who treat glaucoma patients with ocular surface disease have heard the typical symptoms: “It feels like there’s something in my eye;” “My eyes feel like they’re on fire.” Table 2 lists the characteristic signs and symptoms of ocular surface disease.

Molecular entities other than the preservative may be involved in tolerance problems; some studies suggest that the active ingredients may also contribute to ocular irritation. However, it is clear that until the recent development

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Table 1

<table>
<thead>
<tr>
<th>Compound Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quaternary ammoniums</td>
<td>Benzalkonium chloride (BAK)</td>
</tr>
<tr>
<td></td>
<td>Polyquaternium-1 (PQ1)</td>
</tr>
<tr>
<td>Mercurials</td>
<td>Thimerosal</td>
</tr>
<tr>
<td>Alcohols</td>
<td>Chlorobutanol</td>
</tr>
<tr>
<td></td>
<td>Benzyl alcohol</td>
</tr>
<tr>
<td>Carboxylic acid</td>
<td>Sorbic acid</td>
</tr>
<tr>
<td>Phenols</td>
<td>Methyl/propyl paraben</td>
</tr>
<tr>
<td>Amidines</td>
<td>Chlorhexidine</td>
</tr>
<tr>
<td>Other</td>
<td>Disodium EDTA</td>
</tr>
</tbody>
</table>

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Table 2  
Signs and Symptoms of Ocular Surface Disease*

<table>
<thead>
<tr>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Ocular discomfort described as:</td>
</tr>
<tr>
<td>- Scratchiness/grittness</td>
</tr>
<tr>
<td>- Sore or tired eyes</td>
</tr>
<tr>
<td>- Burning or itchiness</td>
</tr>
<tr>
<td>- Stinging</td>
</tr>
<tr>
<td>- Foreign body sensation</td>
</tr>
<tr>
<td>▶ Blurring/fluctuation of vision</td>
</tr>
<tr>
<td>▶ Impaired vision</td>
</tr>
<tr>
<td>▶ Light sensitivity</td>
</tr>
<tr>
<td>▶ Superficial punctuate corneal staining</td>
</tr>
<tr>
<td>▶ Conjunctival staining (lissamine green or rose bengal)</td>
</tr>
<tr>
<td>▶ Reduced tear volume</td>
</tr>
<tr>
<td>▶ Shortened tear film break-up time (TFBUT)</td>
</tr>
<tr>
<td>▶ Debris in the tear film</td>
</tr>
<tr>
<td>▶ Low Schirmer test score</td>
</tr>
<tr>
<td>▶ Tear film instability</td>
</tr>
<tr>
<td>▶ Conjunctival hyperemia</td>
</tr>
<tr>
<td>▶ Viscous precorneal tear film</td>
</tr>
<tr>
<td>▶ Thickened lid margins</td>
</tr>
</tbody>
</table>

* Presence and severity of symptoms will vary with the severity level of the disease.
**THIMEROSAL IN OCULAR SOLUTIONS**

Thimerosal was at one point widely used in contact lens solutions, where it caused an epidemic of problems. Considered to be one of the most allergenic of preservatives, thimerosal acts as a hapten (partial antigen) and induces delayed hypersensitivity. In ophthalmic solutions at concentrations of 0.004% to 0.005%, thimerosal induced delayed ocular hypersensitivity reactions, including superior limbic keratoconjunctivitis, conjunctival hyperemia, limbal follicles, giant papillary conjunctivitis, corneal infiltrates, superficial punctate keratitis, pseudo-dendritic corneal lesions, epithelial opacities, and neovascularization.

Thimerosal was clearly the inciting agent, as studies showed that the signs of allergic conjunctivitis resolved when the thimerosal-containing solution was removed. In the vast majority of cases, challenge with a thimerosal-containing solution reinstituted the conjunctivitis, and many patients also showed a positive skin patch test to thimerosal, although the latter test results were not always in concordance with the presence of ocular allergic reactions.

Effects of BAK

Numerous studies have measured the toxic effects of BAK on the cornea. These effects are both direct and indirect. Direct toxic effects involve modifying the structure and physiology of the epithelium, which affects both epithelial barrier function and optical properties. Numerous in vitro and in vivo studies have examined the impact of BAK on corneal health; with findings of decreased epithelial cell integrity (in which the barrier is compromised and healing is impaired); increase in conjunctival inflammatory cells; loss of goblet cells; effects on the contractility of corneal fibroblasts, which can alter the shape of the cornea and measurement of intraocular pressure; dose-dependent disruption of cytoplasmic membranes and cell detachment; dose-dependent swelling and desquamation of superficial epithelial cells; and apoptosis.

The indirect toxic effects of BAK involve its ability to modify the tear film, causing reduced tear production and shortened tear break-up time. Studies have also shown reduced tear film stability with topical medications preserved with BAK, even in short-term studies. Several clinical studies have documented significantly reduced tear break-up time in solutions preserved with BAK compared to preservative-free solutions.

The corneal toxicity observed with BAK is dose dependent: slowed cell growth is observed with BAK at 0.0001%; apoptosis is triggered at concentrations of 0.01% BAK, and necrosis is observed with BAK 0.05%—concentrations above or close to those found in BAK-preserved commercial drug preparations. Use of BAK-preserved glaucoma treatments have also been reported to have deleterious effects on glaucoma filtration surgery.

Whether the harmful corneal effects of BAK are due to allergy or toxicity has been a subject of debate. Recently, Baudouin et al showed, via the expression of CCR5 and CCR4 (two chemokine receptors that act as markers of Th1 and Th2 pathways) that both allergic and toxic processes are involved.

It is important to remember that preservatives such as BAK and PQ1 are safe and effective for short-term use in topical agents; it is their long-term use that can no longer be recommended in light of the evidence of corneal changes. If multidose agents are to continue to be used, an alternative to quaternary ammonium preservatives is needed.

**Alternative Preservation**

When considering newer alternatives to BAK and PQ1, physicians should remember that there are several goals that must be met in creating a preservative (beyond simple antimicrobial activity). Any topical formulation that uses a preservative should have the same (or greater) efficacy and endurance of effect as the nonpreserved agent. The formulation should be well tolerated and meet or exceed the US Pharmacopeia standards for antimicrobial activity (see box). The new formulation should also be available at the same or lower cost than the nonpreserved form and, when used in a glaucoma treatment, it should not inhibit or interfere with the future success of surgical treatment for glaucoma.

There are a few preservative-free, unit-dose commercial agents (some artificial tears, cyclosporine, and timolol for glaucoma). Unit-dose application is convenient for some patients but more expensive or even cost-prohibitive for other patients. For many older patients, especially those with dexterity problems, the small vials can be difficult to handle. This is a relatively common problem in older patients with glaucoma or dry eye disease.

There are also two “self-preserved” agents used to treat ocular infections, but the agents themselves are antibiotics: moxifloxacin 0.5% (Vigamox®) and levofloxacin 1.5% (Iquix®). Purite® is a stabilized oxychloro complex (sodium chlo- rite) with a long history of use in water purification systems. It is used by one manufacturer (Allergan) in its bromidine tartrate preparation for glaucoma (Alphagan P®) and in its Optive™ artificial tear preparation. Purite is relatively innocuous because it degrades to chloride ions and water upon exposure to UV light.

**sofZia®: A New Preservative System**

sofZia® (Alcon) is a relatively new, proprietary, ionic, buffered solution consisting of zinc, borate, propylene glycol, and sorbitol, chemical entities that are themselves not significantly toxic to the ocular surface. sofZia, however, maintains an antimicrobial environment in the bottle, such that it meets the US Pharmacopeia standards for antimicrobial activity (see box). sofZia produces more than a 3-log reduction in its Optive™ artificial tear preparation. Purite is relatively innocuous because it degrades to chloride ions and water upon exposure to UV light.
Ophthalmic preservatives: the past, present, and future

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The US Pharmacopoeia Standards for Preservatives in Ocular Topical Agents

The US Pharmacopoeia preservative effectiveness test (PET) involves inoculating a solution containing the preservative with Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli, as well as Aspergillus niger and Candida albicans. Samples of the preserved solution are inoculated with 10^6 colony-forming units/mL at Day 0 with each organism (tested separately), and survivors are counted at Days 7, 14, and 28. Requirements to pass the PET include a 1-log reduction in bacteria by Day 7, a 3-log reduction in survivors by Day 14, and no increase in survivors from Days 14 to 28. For fungi there can be no increase in survivors from Day 0 to Day 28.

(99.9% kill) in surviving organisms after 8 days of incubation. sofZia is the preservative system used in Alcon’s prostaglandin analog Travatan Z.

In addition to its biocidal activity against the five required challenge organisms, sofZia was tested against Ralstonia pickettii, Staphylococcus epidermidis, Streptococcus pneumoniae, Hemophilus influenzae, and Fusarium solani. The fungal challenge test showed a steady decrease in surviving organisms over 14 days. Moreover, “real-life” conditions were simulated using low but continuous exposure to bacteria (ie, 10^5 colony-forming units per mL, eight times [at 3- to 4-day intervals] over 28 days). The Travatan Z solution preserved with sofZia reduced the number of viable organisms with increasing efficacy over the study period.

With respect to the therapeutic agent, travoprost, clinical data show equivalent efficacy between Travatan Z and travoprost preserved with BAK. In a large study, 661 patients were randomized to receive daily doses of either travoprost 0.004% preserved with BAK (n = 322) or Travatan Z (n = 339). Itraoculoc pressure was measured 3 times per day at Weeks 2, 6, and 12. The extent of intraocular pressure lowering was equivalent between the two preparations.

In another short-term (2-week) study of 106 patients comparing travoprost with BAK to Travatan Z, both treatments produced statistically significant and comparable decreases in intraocular pressure (>6 mm Hg). Drug-related side effects were uncommon and also comparable between the 2 groups. Animal studies comparing Travatan Z with latanoprost (a glaucoma drug preserved with 0.02% BAK) and artificial tears showed that Travatan Z produced fewer corneal changes and less conjunctival inflammation than the latanoprost with BAK solution. In fact, the corneal and conjunctival changes with Travatan Z were similar to those induced by preservative-free artificial tears.

For glaucoma patients in particular reduced inflammation, toxicity, and/or allergic reaction will also likely increase adherence (Figures 4A-4C). Adherence (ie, compliance with a prescribed regimen) is a serious issue in the medical management of glaucoma. Glaucoma is a chronic disease in which medical treatment is awkward to administer, the patient sees no immediate treatment effect, and the ocular-surface side effects of many glaucoma medications are unpleasant to the patient. Hopefully, reducing symptoms by reducing the load of BAK to which glaucoma patients are exposed will increase their willingness to stay on their medications.

The Future of Preservatives

For many years, eye physicians have had to use topical treatments that clearly caused corneal damage and unpleasant symptoms because no other options were available. Faced with the choice between ocular irritation (that could be fairly severe) and glaucoma progression, physicians understandably chose the lesser of the two evils.

We now have preservatives, such as the “vanishing preservatives” sofZia, Purite, and sodium perborate (which converts to water and oxygen on contact with the tear film). Other options, such as multiuse bottles that prevent contamination and remove the necessity for preservatives, are available or in the pipeline.

Even though it may not be blinding, corneal toxicity is an important issue to patients and is not to be dismissed for the “greater good” of treating glaucoma. This is especially true because glaucoma is a chronic condition in which the adverse effects of the preservatives are likely to affect adherence. The development of preservatives that reduce or eliminate ocular symptoms is an important step forward for patients and physicians.

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References


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OPHTHALMIC PRESERVATIVES: The Past, Present, and Future

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STATEMENT OF NEED AND PROGRAM DESCRIPTION
Almost all multiuse topical ophthalmic agents are preserved to prevent microbial contamination. As preservatives evolved from the highly toxic thimerosal to quaternary ammonium compounds such as benzalkonium chloride (BAK), toxicity diminished. BAK and similar preservatives have an acceptably low level of toxicity when ocular exposure to them is limited.

However, chronic use of preserved medication to treat glaucoma and other chronic ocular conditions can have serious sequelae in a significant number of patients.1-3 This point was essentially moot while there were no alternatives to BAK- or similarly-preserved medications.

In recent years, however, several manufacturers have introduced alternative preservative systems that reduce still further the toxic effect of long-term instillation of topical antihypertensive medication.

This CME activity reviews the history of ophthalmic preservatives, describes the toxic effects of common and novel preservative systems, and suggests evidence-based strategies for lowering exposure to toxic ocular preservatives.

A literature search reveals that while the prevalence of ocular surface disease is approximately 15%, in patients on long-term topical antihypertensive medications, the prevalence is as high as 50%.1-3 Now that it is possible to reduce patients’ exposure to more toxic medications, there is a need to educate physicians on effective means for accomplishing this end, especially among patients whose medical therapy requires daily dosing with antihypertensive agents.

LEARNING OBJECTIVES
Upon completion of this activity, physicians should be able to:

1. State why almost all topical multidose medications for ocular application are preserved.
2. Name the most common preservatives and describe their potential for ocular toxicity.
3. Describe two novel preservatives and state how they might be used in a regimen designed to lower the overall toxic burden placed upon a medically managed glaucoma patient’s eye.

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FACULTY AND DISCLOSURE STATEMENTS

Stephen C. Pflugfelder, MD is a professor of ophthalmology and James and Margaret Elkins chair in the department of ophthalmology at Baylor College of Medicine and a member of the Center for Cell and Gene Therapy at Baylor College of Medicine. He is a consultant for Allergan and Bausch & Lomb. He has received research support from Alcon and Allergan.

References