Advances In Therapy® | Volume 18 No. 5
September/October 2001

Effects of Common Ophthalmic Preservatives on Ocular Health

Robert Noecker, M.D.
Tucson, Arizona

ABSTRACT

Preservatives are an important component of ophthalmic preparations, providing antimicrobial activity in the bottle and preventing decomposition of active drug. Often underrecognized, however, are the significant cytotoxic effects of preservatives associated with long-term therapy and especially use of multiple preserved drugs. The most common preservatives in ophthalmic preparations for glaucoma and surface eye disease—benzalkonium chloride (BAK), chlorobutanol, sodium perborate, and stabilized oxychloro complex (SOC)—were reviewed. Compared with other preservatives, SOC caused the least amount of damage to rabbit corneal epithelial cells. BAK has demonstrated cytotoxic effects in cell culture, as well as in animal and human studies. Physicians should consider treatment with new-generation preparations containing low-risk preservatives such as SOC, especially in patients receiving multiple ophthalmic medications.

Keywords: ophthalmic preservatives; benzalkonium chloride; chlorobutanol; SOC; sodium perborate

INTRODUCTION

The contents of multidose medication containers used twice daily often undergo bacterial contamination within 1 or 2 weeks.[1] As a result, the US Food and Drug Administration and the US Pharmacopoeia mandate that all multidose ophthalmic preparations contain a preservative to ensure a nonhazardous degree of contamination. By providing a level of antimicrobial activity in the bottle, preservatives limit bacterial, mycotic, and amoebal ocular infections caused by contaminated solutions and prolong shelf life by preventing biodegradation and maintaining drug potency. The primary concern with many preservatives is not their efficacy but, rather, their recognized cytotoxic side effects.[2]

©2001 Health Communications Inc.
Transmission and reproduction of this material in whole or part without prior written approval are prohibited.

0639

Address reprint requests to
Robert Noecker, M.D.
655 North Alveron Way, Suite 108
Tucson, AZ 85711

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

High concentrations of some preservatives can damage and irritate ocular tissue. Preservative-free products may prevent the toxic side effects, but they are expensive and the small unit-dose containers can be difficult to use, hindering compliance.[3] Nonetheless, some patients require preservative-free products because of sensitivities or allergies. The goal of the physician should be to prescribe effective agents that contain preservatives with minimal effects on ocular tissues.

CLINICAL RELEVANCE

In chronic diseases, such as glaucoma or dry eye syndrome, high concentrations of preservatives or repeated exposure to preserved medications increases the likelihood of adverse effects. For example, high incidences of endothelial damage, epithelial edema, and bulbous keratopathy characterize patients with glaucoma, dry eyes, infections, or iritis whose use of preservative-containing ophthalmic solutions is frequent and prolonged.[4] Even with infrequent administration, preserved solutions may be contraindicated in the presence of trophic ulcers or other states of severely compromised corneal epithelial integrity.[5] Patients with defective epithelia or corneal ulcers may be most at risk because of increased penetration of the medication and preservatives.[4]

Glaucoma

Long-term use of antiglaucoma drugs has been linked to toxic and inflammatory changes of the ocular surface.[6-8] Conjunctival biopsies from glaucoma patients show a significant increase in immune cells and fibroblasts possibly related to prolonged treatment.[9,10] Repeated doses of preserved eyedrops can have a cumulative effect, and extended contact with the epithelium may lead to chronic irritation and subconjunctival fibrosis, increasing the risk that trabeculectomy will fail.[7,11] Multidrug treatment of glaucoma may also raise the risk for the ocular surface effects of preservatives. Less frequent daily administration, lower preservative concentrations (currently ≤0.01% for most antiglaucoma drugs), and new formulations may help to minimize this ocular surface damage.

Keratoconjunctivitis sicca (KCS)

Patients with severe KCS may need to instill tear substitutes as often as every 20 minutes. Preservatives may worsen the condition by disrupting the precorneal tear film and damaging the epithelial surface.[5] Many corneal specialists believe that KCS may be aggravated by frequent use of preservative-containing artificial tears, especially because these patients may not produce enough natural tears to dilute a harmful preservative.[2,5] Overuse of nonprescription eyedrops can also contribute to adverse effects. When patients with glaucoma or KCS discontinue use of preservative-containing medications, allergic complaints or chronic irritation of the conjunctiva and eyelids also ceases.[4]

Managing Preservative-Induced Ocular Damage

Damage due to ophthalmic preservatives often goes unnoticed because it is difficult to differentiate side effects of an active ingredient from those of the preservative.

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

The following sections review the mechanism of action and results of tissue culture and animal studies to compare toxic effects of four preservatives.

COMMONLY USED PRESERVATIVES

A spectrum of preservatives are found in nearly every type of ophthalmic solution. Benzalkonium chloride (BAK) is one of the most commonly used preservatives. Less common are benzododecinium bromide (BDD), cetrimonium chloride, thiomersal, methyl parahydroxybenzoate, sorbic acid, polyquarternium ammonium chloride (PQAC), polyaminopropyl biguanide, and hydrogen peroxide. Tables 1 and 2 list commonly used products and their preservative concentrations.

Table 1. Preservative Composition of Antiglaucoma Medications

Trade Name	Manufacturer	Preservative
Alphagan®	Allergan, Inc.	BAK 0.005%
Alphagan P®	Allergan, Inc.	SOC 50 ppm
Azopt®	Alcon	BAK 0.01%
Betagan®	Allergan, Inc.	BAK 0.005%
Betoptic S®	Alcon	BAK 0.01%
Cosopt®	Merck & Co., Inc.	BAK 0.0075%
Lumigan™	Allergan, Inc.	BAK 0.005%
Propine®	Allergan, Inc.	BAK 0.005%
Rescula®	CIBA Vision	BAK 0.015%
Timoptic®	Merck & Co., Inc.	BAK 0.01%
Timoptic-XE®	Merck & Co., Inc.	BDD 0.012%
Trusopt®	Merck & Co., Inc.	BAK 0.0075%
Xalatan®	Pharmacia & Upjohn	BAK 0.02%

SOC = stabilized oxychloro complex.

Mechanism of Action

Preservatives interfere with microbial organisms by causing lysis of plasma membranes, inhibiting cellular metabolism, oxidizing or coagulating cellular constituents, or promoting hydrolysis.[2] Preservatives can be classified in two main categories as oxidants or detergents.[12] Oxidative preservatives, such as stabilized oxychloro complex (SOC) and sodium perborate, are usually small molecules that penetrate cell membranes and disrupt cellular function by modifying lipids, proteins, and DNA.[13] Their membrane-destabilizing activity is less potent than that of

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

Table 2. Over-the-Counter Products for Ocular Surface Disease and Their Preservative Concentrations

Product Name	Manufacturer	Preservative	Use
GenTeal®	CIBA Vision	Sodium perborate	Artificial tears
Hypotears®	CIBA Vision	BAK 0.01%	Artificial tears
Naphcon-A®	Alcon	BAK 0.01%	Vasoconstrictor
Refresh Tears®	Allergan, Inc.	SOC 50 ppm	Artificial tears
Tears Naturale II®	Alcon	Polyquad 0.001%	Artificial tears
Vasocon-A®	CIBA Vision	BAK 0.01%	Vasoconstrictor
Visine®	Pfizer	BAK 0.01%	Vasoconstrictor

detergent preservatives. At low levels, oxidative preservatives have an advantage over detergent preservatives by providing enough activity against microorganisms while exerting only negligible toxic effects on eukaryotic cells. This occurs because many microorganisms cannot cope with oxidative stress. In comparison, mammalian cells are equipped with antioxidants, oxidases, and catalases to neutralize the effect of a low-level oxidant.

Detergent preservatives, such as BAK, are usually monomeric or polymeric compounds that have surfactant effects and alter cell membrane permeability by causing lipid dispersion and lysis of cytoplasmic contents.[14] Some may have a similar action on eukaryotic cells and cause cytotoxic effects. Mammalian cells cannot neutralize detergent preservatives, which can be incorporated into the cell by liposomes or other intracellular vacuoles and cause cellular damage.[15]

Purite®* (SOC)

SOC destroys many types of bacteria as well as the fungus *Aspergillus niger*.[16] Introduced in 1996, it consists of an equilibrium mixture of oxychloro species—99.5% chlorite (ClO_2), 0.5% chlorate (ClO_3), and trace amounts of chlorine dioxide (ClO_2)—that have bactericidal and viricidal activity.[17] In saline solution, SOC generates chlorine dioxide free radicals in the presence of microbial contamination. However, SOC is an oxidizing, not a chlorinating, agent.[12] The free radicals provide the antimicrobial activity by oxidizing unsaturated lipids and glutathione in the cell.[12] When SOC is administered in the eye, it is converted into natural tear components, such as sodium and chloride ions, oxygen, and water. This conversion occurs by way of cascade-type reactions between SOC and tear-film components and photolytic reactions between SOC and light.[16,17]

Mild cytotoxic effects and an excellent safety record have earned SOC a US Environmental Protection Agency category II rating as a mild eye irritant on the basis of rabbit studies. Although exposure to 2% SOC can produce slight irritation of

*Registered trademark of Allergan, Inc., Irvine, Calif, USA.

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

the conjunctiva, cornea, and eyelid, this concentration is higher than that used in most commercial products. Efficacy at low concentrations (0.005% w/v) that are benign to the eye makes SOC an ideal ophthalmic preservative. Safety and tolerability were established in a study of 62 patients with mild to moderate dry eye who were treated with an SOC-containing product four to eight times per day for 4 weeks.[18] No evidence of in vivo or in vitro mutagenicity or carcinogenicity has been found.

Chlorine dioxide has been used since 1944 to purify water, and conventional doses appear to be safe for that indication.[17] Mild cytotoxic effects make it a common ingredient in toothpaste, mouthwash, and antacids. Chlorine dioxide destroys microorganisms in fish, fruit, and vegetables without altering the food's nutritive and organoleptic qualities.[17]

Sodium Perborate

One of the first oxidative preservatives, sodium perborate is converted to hydrogen peroxide when combined with water. Sodium perborate oxidizes cell walls or membranes, affects membrane-bound enzymes, and disrupts protein synthesis. On entering the eye, it is rapidly decomposed to water and oxygen by catalase and other enzymes in the conjunctival sac.[16] Sodium perborate is bactericidal and can kill *A. niger*.[16] Low levels retain antimicrobial activity and are comfortable in the eye. However, hydrogen peroxide levels between 30 and 100 ppm, normally produced by ophthalmic preparations containing sodium perborate, can cause ocular stinging.[19,20] Limited testing has also identified sodium perborate as a direct-acting in vitro mutagen.[21] It can also destabilize cell walls and membranes, albeit to a lesser degree than other types of preservatives.

BAK

The quaternary ammonium compound BAK is the most common antimicrobial preservative,[3,5] found at an average concentration of 0.01% (range, 0.004%–0.02%)[3] in topical multiuse ophthalmic preparations. Nearly all antiglaucoma medications contain BAK. Highly efficacious against numerous microbes, BAK denatures proteins and causes lysis of cytoplasmic membranes. The surfactant effect of quaternary ammonium compounds, including BAK, can solubilize the intercellular cement of the corneal epithelium, thereby increasing the compound's penetration.[4,14] Moreover, because BAK can accumulate and remain in ocular tissue for relatively lengthy periods,[4,15] it can induce different types of cell death in a dose-dependent manner: growth arrest at low concentrations, apoptosis at 0.01%, and necrosis at higher concentrations.[21]

In an antiglaucoma preparation, BAK does not alter the drug's ability to lower intraocular pressure but can modify the ocular surface with long-term use.[22] For example, timolol maleate, which contains 0.01% BAK, rapidly decreased cell viability and numbers in a human conjunctival cell line.[23] Similarly, patients treated with timolol maleate 0.5% containing 0.01 g/100 mL of BAK exhibited ocular surface damage attributed to a reduced rate of aqueous layer production and impairment of the tear-film mucus layer.[24] In another study, 127 patients instilling various antiglaucoma drugs containing BAK had significant conjunctival metaplasia compared with patients not using topical treatment.[25] There was no significant difference on cytologic examination between those using any of the medications for less or more than

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.