PRESERVATIVES IN MULTIDOSE TOPICAL OPHTHALMIC DROPS

Recent product recalls emphasize safety concerns.

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The critical need for sterile, topical ophthalmic drops was underscored by recent FDA actions. In October, the agency recalled more than 20 different products owing to bacterial contamination and issued a warning that use of these drops could lead to partial or complete vision loss.[1] Eye drops are integral to the treatment of many ophthalmic diseases. Preservatives in liquid ophthalmic formulations can ward off microbial contamination and significantly prolong the usability of multidose bottles.[2] These preservatives enhance product safety, potentially reducing costs and increasing convenience, for example, by allowing medication to be stored at room temperature. This article explores the preservatives commonly found in topical ophthalmic drops, details their mechanisms of action and safety profiles, and examines reasons why a clinician might opt for a preservative-free eye drop.

FIRST-GENERATION PRESERVATIVES

First-generation ophthalmic preservatives are characterized by broad-spectrum activity and small molecular structure.[3]

Thimerosal

A mercury-based agent, thimerosal disrupts calcium influx into cells. It exhibits efficacy against gram-positive and gram-negative bacteria, fungi, and, to a lesser extent, *Acanthamoeba*.[3] Thimerosal's side effects include stinging, corneal staining, infiltrates, and limbal epithelial cell changes attributed to direct toxicity and delayed immune reactions. This led manufacturers to discontinue the use of thimerosal in topical ophthalmic drops.[3]

Chlorhexidine

This bacteriostatic preservative acts by disrupting cell membranes. It is

effective against bacteria, fungi, and *Acanthamoeba*. Although chlorhexidine does not cause hypersensitivity reactions, it is extremely irritating to the eye, leading manufacturers to phase out its use in ophthalmic drops.[3] There is also evidence suggesting bacterial resistance to chlorhexidine.[3]

Benzalkonium Chloride

This preservative is found in about 70% of available ophthalmic topical drops. The continued popularity of benzalkonium chloride (BAK) can be attributed to its long shelf-life and effectiveness against various bacteria and fungi.[4] As a cationic surfactant, BAK disrupts outer membranes, reduces ocular surface tension, and inhibits DNA synthesis.[4] Its toxicity varies according to its concentration and the frequency and duration of use. The instillation of BAK-containing drops should not exceed four times daily, especially if the duration of treatment is prolonged.[5] Animal research suggests that even short-term dosing of BAK can cause corneal neurotoxicity.[6] Exposure to BAK can cause corneal cell apoptosis, leading to symptoms such as redness, inflammation, discomfort, foreign body sensation, and dryness.[4,5]

MODERN PRESERVATIVES

Modern ophthalmic preservatives typically feature high–molecular-weight molecules that offer both a robust safety profile and broad-spectrum activity against microorganisms. Their larger size is advantageous, particularly in the context of contact lens use, as it reduces the likelihood of absorption into the lenses.[7]

Polyhexamethylene Biguanide

Biguanides, with their high molecular weight, disrupt DNA function, leading to cell death.[3] The acronym PHMB is often used to refer to a group of biguanide-based preservatives that includes variants such as polyaminopropyl biguanide and alexidine.[3] These preservatives are effective against a wide range of bacteria, such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. PHMB-based preservatives typically are not effective against Acanthamoeba, fungi, or yeasts.[3] The correlation between PHMB and corneal toxicity varies by formulation and study, with some indicating potential toxicity.

Polyquaternium-1

This bactericidal preservative is based on quaternary ammonium. Polyquaternium-1 (PQ-1; Polyquad, Alcon) acts by denaturing microbial cell wall proteins.[2,3] As with PHMB, PQ-1 is less effective against *Acanthamoeba*, fungi, and yeasts. This preservative is often used in conjunction with agents such as myristamidopropyl dimethylamine (Aldox, Alcon), which target fungi and amoebae. PQ-1 is generally safe, but has been linked to mild corneal toxicity.[8]

Stabilized Oxychloro Complex

This preservative acts as an oxidating agent. Stabilized oxychloro complex (SOC; Purite, Allergan) may exert its antimicrobial properties by disrupting protein synthesis or intracellular lipids.[2,8] SOC also acts against bacterial and fungal species. It is only a mild ocular irritant, and studies suggest that SOC is well tolerated when administered frequently.[8]

Sodium Perborate

When mixed with water, sodium perborate (GenAqua, Alcon) transforms into water and hydrogen peroxide.[2] The resulting hydrogen peroxide oxidizes microbes by altering the permeability of their cell membranes.[3] Sodium is a mild ocular irritant, but is generally well tolerated.[8]

PRESERVATIVE-FREE OPTIONS

Spurred on by the recognition of preservatives' potential ocular side effects, the trend toward preservative-free ocular drops has gained momentum in recent years.[9] One alternative is single-use vials, which are disposed of immediately after application, thus eliminating the need for preservatives. Multidose preservative-free drops are another option, which was recently introduced. Innovative cap designs help

AT A GLANCE

- Eye drops often include preservatives to fend off microbial contamination, but these additives can lead to adverse ocular effects, necessitating the evolution of safer alternatives.
- The recent recalls by the FDA of multiple eye drop brands due to contamination underscores the imperative of sterility and effective preservation in eye care products.
- The market is seeing a surge in demand for preservative-free eye drops, driven by the desire to avoid preservative-induced ocular side effects, with innovations such as single-use vials and advanced multidose bottles enhancing user safety.

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avert microbial contamination. Patient feedback suggests both delivery systems are user-friendly and efficient, but multidose bottles are preferred because they can be recycled.[9]

CLINICAL GUIDANCE

Each year, approximately 30,000 cases of microbial keratitis occur in the United States and require ophthalmic drops for treatment.[10] A nuanced understanding of patient characteristics, medical conditions, and treatment adherence is pivotal to the selection of topical therapy. Patients with a history of poor adherence to prescribed medical therapy are at increased risk of drug contamination.

Preserved drops are recommended if dosing will be infrequent (< four times daily) or therapy will be short term.[5] Preservative-free options may be preferable for the treatment of chronic conditions such as dry eye disease and glaucoma.

Current limitations in nonpreserved options suggest that preserved drops will remain a mainstay in eye care for the foreseeable future. ■

1. Food and Drug Administration. FDA warns consumers not to purchase or use certain eye drops from several major brands due to risk of eye infection. Updated November 15, 2023. Accessed November 20, 2023. www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-purchase-or-use-certain-eye-drops-several-major-brands-due-risk-eye#eyedrops
2. Steven DW, Alaghband P, Lim KS. Preservatives in glaucoma medication. *Br J Ophthalmol*. 2018;102(10):1497-1503.
3. Bradley CS, Sicks LA, Pucker AD. Common ophthalmic preservatives in soft contact lens care products: benefits, complications, and a comparison to non-preserved solutions. *Clin Optom (Auckl)*. 2021;13:271-285.
4. Coroi MC, Bungau S, Tit M. Preservatives from the eye drops and the ocular surface. *Rom J Ophthalmol*. 2015;59(1):2-5.
5. Pucker AD. A review of the compatibility of topical artificial tears and rewetting drops with contact lenses. *Cont Lens Anterior Eye*. 2020;43(5):426-432.
6. Sarkar J, Chaudhary S, Mamavari A, et al. Corneal neurotoxicity due to topical benzalkonium chloride. Cornea. 2012;53:1792-1802
Pucker AD, McGwin G, Franklin QX, Nattis A, Lievens C. Application of Systane Complete for the treatment of contact lens discomfort. *Cont Lens Anterior Eye*. 2021;44(5):101399.
7. Kaur IP, Lal S, Rana C, Kakkar S, Singh H. Ocular preservatives: associated risks and newer options. *Cutan Ocul Toxicol*. 2009;28(3):93-103.
8. Pucker AD, Lievens C, McGwin G Jr, Franklin QX, Logan A, Wolfe GS. Quality of life in digital device users who are treated with Systane Hydration PF. *Clin Optom (Auckl)*. 2023;15:45-54.
9. Wilhelmus KR. Review of clinical experience with microbial keratitis associated with contact lenses. *CLAO J*. 1987;13(4):211-214.

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