PRESERVATIVE-FREE ALTERNATIVES

Options for decreasing ocular toxicity in patients with glaucoma.

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Topical therapy is typically first-line treatment for patients with newly diagnosed glaucoma. All multidose ophthalmic medications are required to have a preservative to maintain an antimicrobial environment in the bottle, making it important for eye care providers to understand the effects of preservatives on the ocular surface.[1] Unfortunately, most preservatives in ophthalmic medications disrupt the ocular surface and exacerbate preexisting ocular surface disease (OSD).[2,3] Benzalkonium chloride (BAK) is the most widely used preservative in antihypertensive topical medicines, and many studies have clearly demonstrated BAK's toxic effects on corneal and conjunctival epithelium.[4,5] Although most antiglaucoma eye drops are manufactured with very little BAK, doses as small as 0.0001% are toxic to ocular tissue.[5]

Because glaucoma is a chronic disease, the initiation of topical therapy also begins a patient's long-term exposure to preservatives. The prolonged use of BAK-preserved drops is a strong risk factor for OSD in patients with glaucoma.[6] Furthermore, the toxic effect of BAK is additive, and patients who must use two or more medications have worse OSD.[6-8]

> **"The prevalence of ocular surface disease among individuals with glaucoma is high."**

It is no surprise, then, that the prevalence of OSD among individuals with glaucoma is high, with roughly half of all patients on long-term glaucoma therapy reporting adverse ocular symptoms.[7,8] There is thus a clear need for BAK-free glaucoma treatment options to minimize OSD and to improve patients' quality of life. Goldberg at al found that patients who switched to BAK-free medications needed fewer lubricant drops and reported an improvement in dry eye symptoms. The study also showed no significant change in IOP from prestudy levels.[9]

Fortunately, in the past decade, the pharmaceutical industry has sought to address the need for BAK-free options to reduce OSD and improve patients' comfort. These products fall into two categories: BAK-free preserved medicines (using alternative preservatives to BAK) and preservative-free medicines (Tables 1 and 2).

TABLE 1. CHARACTERISTICS OF PRESERVATIVES COMMONLY USED IN GLAUCOMA MEDICATIONS

Preservative	Mechanism	Advantages	Disadvantages	Medications
BAK	Detergent	Excellent broad antimicrobial efficacy, weakens corneal epithelial tight junctions to facilitate drug's entry	Corneal epithelial breakdown and tear film instability	Azopt, Lumigan, Timoptic, Xalatan
Purite	Oxidative stress	Less conjunctival inflammation and corneal toxicity than BAK	Mild cytotoxicity still present	Alphagan P
SofZia	Oxidative stress	Less conjunctival inflammation and corneal toxicity than BAK	Mild cytotoxicity still present	Travatan Z

Abbreviation: BAK, benzalkonium chloride.
Manufacturing information: Azopt (Akorn); Lumigan, Purite, Alphagan P (Allergan); Timoptic (Valeant Pharmaceuticals); Xalatan (Pfizer); SofZia, Travatan Z (Alcon).

TABLE 2. COMMONLY PRESCRIBED GLAUCOMA MEDICATIONS WITH THEIR CORRESPONDING PRESERVATIVE[a]

Medication	Preservative
Xalatan	BAK 0.02%
Lumigan	BAK 0.02%
Azopt	BAK 0.01%
Timoptic	BAK 0.01%
Trusopt	BAK 0.0075%
Cosopt	BAK 0.0075%
Combigan	BAK 0.005%
Travatan Z	SofZia
Alphagan P	Purite
Zioptan	None
Cosopt PF	None
Timoptic in Ocudose	None

Abbreviation: BAK, benzalkonium chloride.
Manufacturing information: Xalatan (Pfizer); Lumigan, Alphagan P, Purite (Allergan); Azopt, Cosopt, Zioptan, Cosopt PF (Akorn); Trusopt (Merck); Combigan, Travatan Z, SofZia (Alcon); Tafluprost; Timoptic , Timoptic in Ocudose (Valeant Pharmaceuticals).
[a] Listed in descending order of BAK concentration.

BAK-FREE PRESERVED MEDICINE

The goal with these products is to maintain an antimicrobial environment in a multidose container while minimizing toxicity to the ocular surface. The two options currently available in the United States are Travatan Z (travoprost ophthalmic solution 0.004%; Alcon) and Alphagan P (brimonidine tartrate ophthalmic solution, 0.1% or 0.15%; Allergan).

Travatan Z is preserved with SofZia, which contains borate, zinc, and sorbitol. SofZia causes microbial death through oxidative damage. When exposed to the tear film, SofZia is inactivated by enzymes.[10] In one study, Travatan Z resulted in less keratopathy and less conjunctival hyperemia than did travoprost preserved with BAK.[11]

Alphagan P is preserved with Purite, a stabilized oxychloro complex that has broad antimicrobial activity through oxidative damage. When the drop is instilled into the eye, light exposure causes the stabilized oxychloro complex to dissociate into nontoxic natural tear components. Noecker et al showed that brimonidine Purite 0.15% produced less conjunctival lymphocytic infiltration than latanoprost, timolol, or dorzolamide.[12]

PRESERVATIVE-FREE MEDICINE

Three topical glaucoma medications completely free of preservatives are available in the United States: Zioptan (tafluprost ophthalmic solution 0.0015%; Akorn), Cosopt PF (dorzolamide-timolol ophthalmic solution 2%/0.5%; Akorn), and Timoptic in Ocudose (timolol maleate ophthalmic solution 0.25% and 0.5%; Valeant Pharmaceuticals). Because of the lack of antimicrobial activity in the solution, all of these products are supplied as a sterile solution in a single-use container. Once it is opened, medication is applied to the eye, and patients should then immediately discard the container and its remaining contents. Zioptan must be stored refrigerated at 2° to 8°C (36°-46°F).

All three preservative-free solutions were better tolerated than their BAK-preserved counterparts. They decreased ocular surface inflammation, improved tear osmolarity, and reduced dry eye complaints.[13,14]

The major disadvantage of preservative-free therapy is its cost. For example, at GoodRx.com as of this writing, a month's

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AT A GLANCE

- The prolonged use of eye drops preserved with benzalkonium chloride (BAK) is a strong risk factor for ocular surface disease in patients with glaucoma.
- In the past decade, the pharmaceutical industry has sought to address the need for BAK-free options to reduce ocular surface disease and increase patients' comfort. These options fall into two categories: BAK-free preserved medicines (using alternative preservatives to BAK) and preservative-free medicines.
- Reducing patients' overall preservative load may improve adherence, quality of life, and the patient-doctor relationship.

WATCH IT NOW

Sheri Rowen, MD, and Steven Vold, MD, discuss identifying and preventing dry eye disease in glaucoma patients in this episode of Glaucoma Today Journal Club.

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supply of generic latanoprost cost roughly $20 cash with a coupon compared to $180 with a coupon for a month's supply of Zioptan. Another potential drawback is that patients with poor dexterity may have difficulty handling the small containers. Finally, the risk of contamination is a concern, especially if a patient saves excess solution for later use.[15]

CONCLUSION

Clinicians encounter patients with burning, watery, irritated eyes all too often. It is therefore important to consider the effect of IOP-lowering drops' preservatives on the ocular surface, especially among patients with a history of dry eye disease (see *Watch It Now*). Reducing the overall preservative load may improve adherence, quality of life, and the patient-doctor relationship. Several BAK-free preserved medicines and preservative-free products are available. These topical solutions have been proven to improve ocular tolerance without a reduction in efficacy. ■

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