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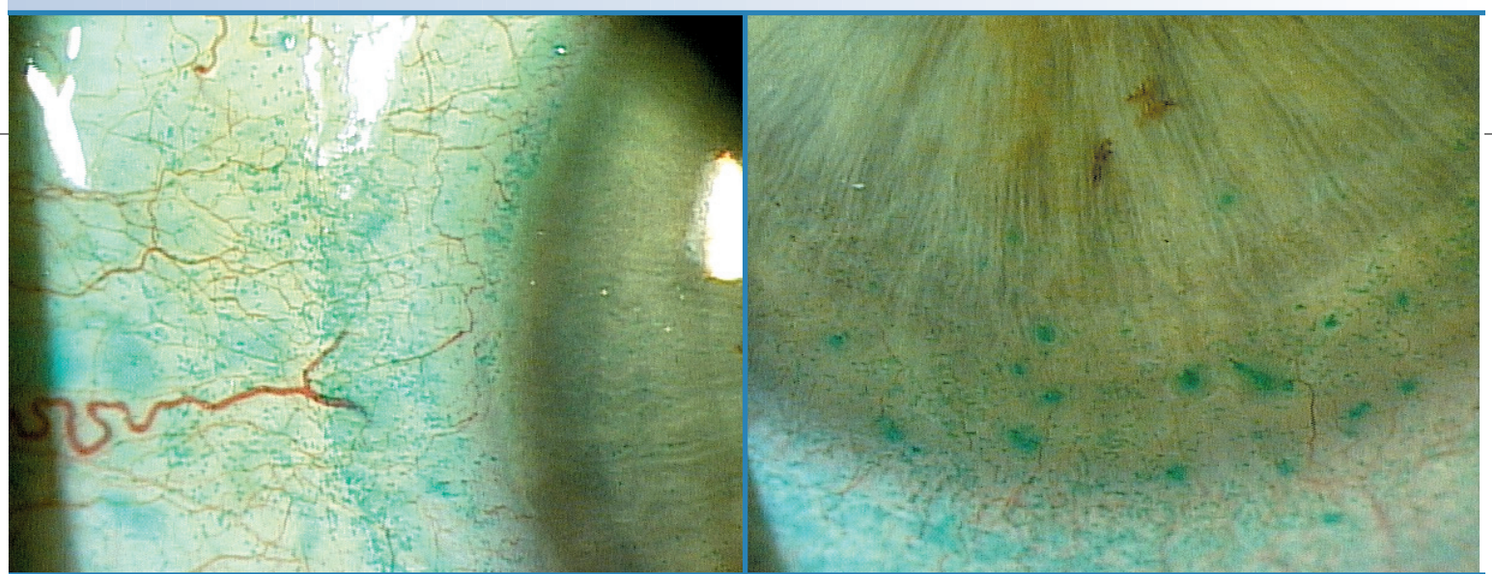
Improving the Safety of Topical Glaucoma Therapy

Learn how the first BAK-free prostaglandin provides efficacy for glaucoma patients while maintaining ocular surface health.



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By Robert P. Wooldridge, O.D.

Dry eye-related ocular surface disease (OSD) is prevalent among glaucoma patients. Both OSD and glaucoma patients tend to be older and perhaps postmenopausal. They may have rosacea and are often treated for concurrent systemic conditions with medications that contribute to OSD. In addition, most glaucoma patients must use one or more topical IOP-lowering drops, the majority of which contain the preservative benzalkonium chloride (BAK), putting them at an even greater risk for developing OSD.

BAK, a quaternary ammonium compound with surfactant (detergent) properties that protects multidose eyedrop containers from microbial contamination, contributes to OSD. This and other effects on the ocular surface as well as conjunctival epithelial cells that may alter the healing process after filtering surgery[1], for instance, may cause enough discomfort to foster poor patient compliance with prescribed glaucoma medications. Given these consequences, we should address OSD as part of glaucoma patient management and consider prescribing BAK-free medications with gentler preservatives whenever possible.

This article explains the short- and long-term ocular surface health implications of BAK and how they affect the clinical value of current glaucoma medications. It also profiles a new BAK-free alternative.

The more the ocular surface is exposed, deprived of its protective tear film and epithelial barrier, the more epithelial breakdown occurs. Each brief period of exposure between blinks adds up over days, weeks and months to a large amount of time when the ocular surface is unprotected.

Effects of BAK

A wealth of research, much of which is from outside the United States, has evaluated the effects of BAK on the conjunctival and corneal epithelium, the corneal endothelium and the trabecular meshwork.

In studies by Guenoun and colleagues,[2,3] human conjunctiva-derived epithelial cells were exposed to three prostaglandin analogues — latanoprost (Xalatan), travoprost (Travatan) and bimatoprost (Lumigan) — in their commercially available forms and to different concentrations of BAK. The researchers found that BAK had an apoptotic effect proportional to its concentration in the commercially available formulations and similar to the corresponding concentration of BAK alone. Toxicity from the prostaglandins themselves was mild.

The researchers also reported two additional findings. By way of measuring inflammatory markers, they concluded BAK is likely the major factor responsible for long-term ocular surface reactions following prolonged medication use but is probably not the main factor in the early onset of hyperemia.

Clinically, researchers observed other effects of BAK, such as a reduction in tear break-up time (TBUT). Baudouin and de Lunardo[4] conducted a crossover, randomized, double-blind study in which they evaluated the effects of BAK-preserved and unpreserved 2% carteolol hydrochloride (Ocupress). Their results showed no significant subjective difference in the level of tolerance between the two formulations. However, the preserved formulation significantly reduced TBUT both at 3 hours and 3 days. They reported that the difference in tear-film stability may not be of much consequence in healthy, young patients, but could pose a problem in those who have ocular surface disorders, are older, or are being treated long-term.

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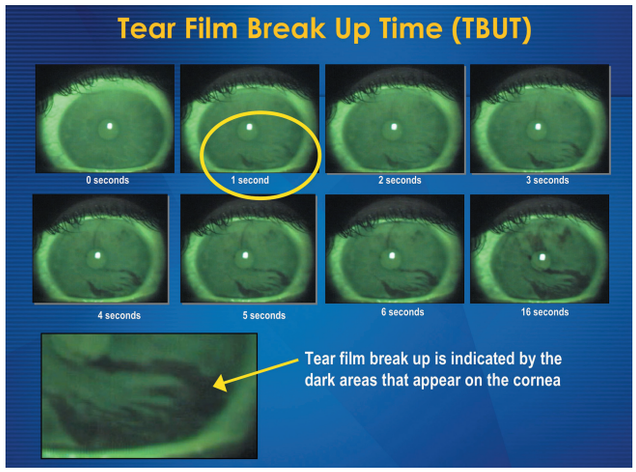
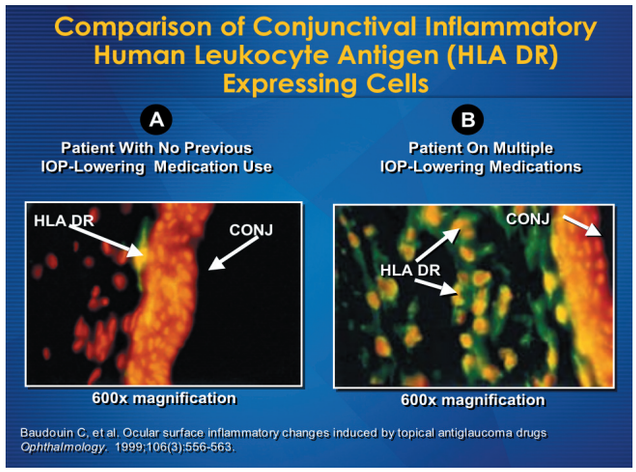


The preservative benzalkonium chloride (BAK) has been shown to adversely affect tear film breakup time (TBUT), a functional measure of tear stability illustrated here. When tear breakup accelerates, the ocular surface is left exposed to external insult.



In a study by Baudouin et al., BAK-preserved topical medications increased the expression of inflammatory cells in conjunctival tissue. HLA DR-expressing cells appear in yellow. Nuclei are counterstained in red.

months to a large amount of time when the ocular surface is unprotected. The resultant signs and symptoms become more prevalent over time.

Baudouin and colleagues[5] also demonstrated histopathologic effects of IOP-lowering medications on the conjunctiva as well as on the trabecular meshwork. They obtained paired specimens of conjunctiva and trabeculum from 61 patients undergoing trabeculectomy. Twenty-six patients had been treated with two or more medications for at least 1 year; 30 had been treated with a beta-blocker for more than 1 year; and five patients had surgery as first-line treatment. The researchers performed immunohistochemistry on all of the specimens.

Among the specimens from patients using multiple medications, researchers found that 24 of 26 conjunctiva specimens and 21 of 24 trabecular specimens were abnormally infiltrated by cells expressing inflammatory or fibroblastic markers or both. In contrast, 19 of 30 conjunctiva specimens and nine of 22 trabecular specimens in the monotherapy group, and only one of five specimens from the primary surgery group were abnormal.

Clearly, the results indicate a cumulative effect. The more medications with BAK that are used and the longer they're used, the more likely inflammation will occur. The same researchers also dosed rats for 1 month with either BAK-preserved 0.5% timolol, non-preserved 0.5% timolol or 0.01% BAK.[4] Both the preserved timolol and the BAK led to infiltrates and toxic

Avoiding the Cumulative Effects of BAK

Research has shown that the effects of the preservative benzalkonium chloride (BAK) on the ocular surface are cumulative and detrimental. The more medications with BAK that patients use and the longer they use them, the more likely inflammation and other damage will occur. Most topical glaucoma medications contain BAK.

In the landmark Ocular Hypertension Treatment Study (OHTS),[1] 40% of patients required two or more medications to control IOP. According to today's updated glaucoma treatment paradigm, in which pressure-lowering goals are more aggressive, that percentage likely is much higher. Therefore, it's in patients' best interests for prescribing doctors to choose medications without BAK whenever possible.

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histopathologic changes compared with the nonpreserved timolol group and the controls. The researchers concluded that BAK was primarily responsible for the toxic and immunoinflammatory effects on the ocular structures.

Similarly, Broadway and colleagues[6] showed inflammatory and cumulative ocular effects of topical glaucoma medications. They used light microscopy to evaluate conjunctival biopsy specimens from 124 patients who were undergoing filtration surgery. Preoperatively, the patients had used either a drug for a brief period, a beta-blocker alone, a beta-blocker in combination with a miotic, or a combination of a beta-blocker, miotic and sympathomimetic.

The conjunctivas in the first two groups were similar, but the most striking changes occurred in the group using the most medications. That group exhibited a significant decrease in goblet cells. In addition, the researchers noted an increase in pale cells, macrophages and lymphocytes in the epithelium and an increase in fibroblasts, macrophages, mast cells and lymphocytes in the substantia propria.

In the same study, the researchers evaluated the effects of different durations of therapy. They found the use of topical medication, regardless of type, caused significant subclinical inflammation if used for 3 years or more.

Current treatments

As a whole, the available body of research shows that decreasing the amount of BAK used in medications is a desirable goal. However, most of the glaucoma medications available today contain BAK in concentrations ranging from 0.005% to 0.02%. Furthermore, prescribing doctors must consider several other factors, including the efficacy, safety, costs and convenience of the medications themselves.

Research has shown that the effects of the preservative benzalkonium chloride (BAK) on the ocular surface are cumulative and detrimental. The more medications with BAK that patients use and the longer they use them, the more likely inflammation and other damage will occur.

Bimatoprost contains less BAK than latanoprost or preserved travoprost, but it tends to cause the most hyperemia. In this case, the drug itself, not the BAK, may be the issue.

Among the prostaglandins, for example, bimatoprost contains less BAK than latanoprost or preserved travoprost, but it tends to cause the most hyperemia. In this case, the drug itself, not the BAK, may be the issue.

With regard to comfort, which affects patient compliance, the acidity of a medication's formulation, rather than BAK, can be an issue. The carbonic anhydrase inhibitors (CAIs) dorzolamide (Trusopt®[7]) and brinzolamide (Azopt®[7]) are equally efficacious but feel different in the eyes of patients. Dorzolamide tends to sting or burn more, even though it contains less BAK. This particular effect is caused by the lower pH of dorzolamide.

The alpha-adrenergic agonist brimonidine 0.15% (Alphagan P®[7]) is preserved with stabilized oxychloro complex rather than BAK. While it's an effective treatment, it has a substantial peak-trough effect, which diminishes its overall efficacy when used alone. The trough effect is minimized if the medication is used three times per day, a regimen that, in reality, many patients can't or won't follow. Many doctors prescribe brimonidine twice a day specifically for that reason, which means the peak-trough effect can be even more of a concern. Furthermore, an alpha-adrenergic agonist is not as effective in lowering IOP as a prostaglandin.

The beta-blocker timolol maleate (Timoptic-XE®[7]) is preserved with benzododecinium bromide rather than BAK; however, the overall efficacy of beta-blockers is diminished by their relative failure to lower IOP at night, when it tends to be highest. In addition, the potential systemic side effects of topical beta-blockers, the sometimes inconvenient packaging, special ordering requirements and premium cost of single-use formulations must be considered.

New BAK-free option

The detrimental effects of BAK and the limitations of some of the currently available glaucoma medications point to the need for a new therapeutic option. Ideally, any new option would have the following attributes:

- BAK-free formulation
- Well-tolerated
- Excellent IOP-lowering efficacy
- Long-lasting effect
- Multidose bottle
- Preservative with antimicrobial activity that meets regulatory standards
- Same cost as currently available options.

Travoprost 0.004% (Travatan Z) — recently approved by the FDA — meets all of these criteria. It's the same medication in the same concentration as the

Recognizing Dry Eye and Ocular Surface Disease

Several factors predispose glaucoma patients to dry eye and ocular surface disease (OSD). Chief among them are the number of preserved topical medications they typically must use and the duration for which they use them. To protect ocular surface health, doctors should diagnose and treat dry eye and OSD as part of glaucoma patient management. A review of signs and symptoms is presented here.

Features of dry eye and OSD

- Tear instability
- Tear hyperosmolarity, creating a pro-inflammatory condition[1]
- Epithelial cell damage
- Discomfort and visual degradation.

The tear film in a dry eye patient is unstable and incapable of maintaining its protective qualities. Hyperosmolarity has been recognized as a critical attribute of the dry eye tear film. A recent study[1] showed that the hyperosmolar environment is in itself pro-inflammatory. As a result, the ocular surface becomes damaged leading to greater instability. Over time, patients experience this as discomfort, and the ocular surface damage often results in degradation of vision.

Clinical signs of OSD[2]

- Lid margin neovascularization
- Meibomian gland obstruction
- Abnormal tear breakup time (TBUT)
- Corneal and conjunctival staining (lissamine green, rose bengal).

Lid margin disease distinguishes an important subclass of OSD. In meibomian gland dysfunction, meibomian glands produce abnormal amounts of oily secretions that plug ductal openings and decrease lipid volume. It's the leading cause of evaporative dry eye disease.[3]

TBUT is a functional measure of tear stability.[2] If stability is disturbed (as in lipid or mucin deficiency), TBUT can increase rapidly. To measure TBUT, moisten a fluorescein strip with sterile saline and apply it to the tarsal conjunctiva. The time lapse between the last blink and the appearance of the first dry spot on the cornea is the TBUT. Dry spots appearing in less than 10 seconds are considered abnormal.

Lissamine green and rose bengal are dyes used for staining cells that are devitalized or have lost their normal mucin surface.[2,4] They reveal abnormal epithelial cells and ocular surface changes associated with insufficient tear-film protection. The nasal conjunctiva tends to stain first and the most. The two dyes are considered equally efficacious, although rose bengal is more likely to cause tearing.[4]

Common symptoms of OSD

- Painful or sore eyes
- Foreign body sensation
- Discomfort, especially in windy or dry conditions
- Blurred or poor vision
- Photophobia.

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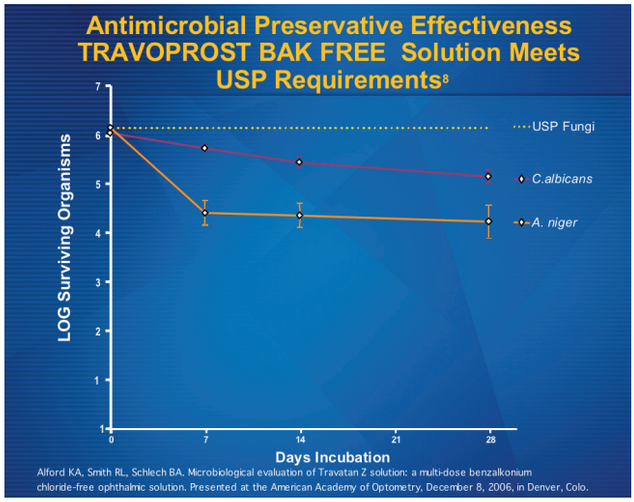
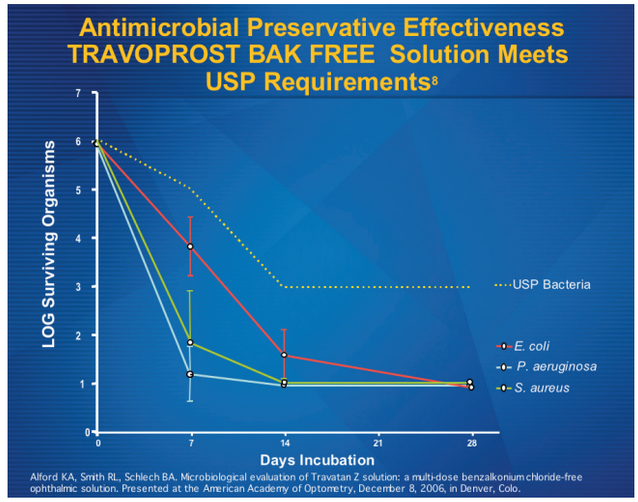




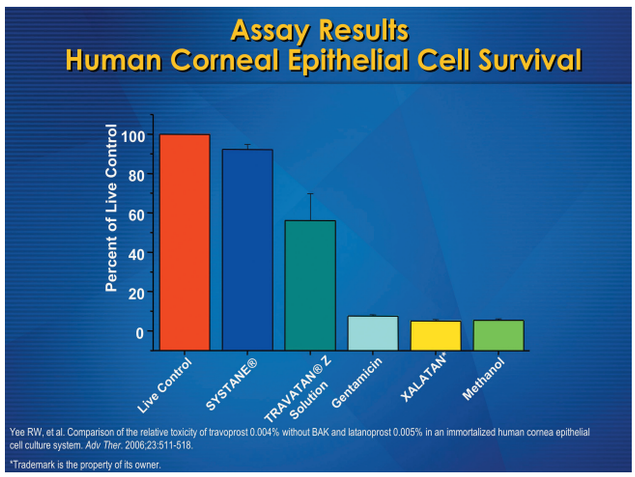
The sofZia preservative system used in travoprost 0.004% (Travatan Z) meets the standards of effectiveness required by the United States Pharmacopoeia. In the studies illustrated here, the bottle was inoculated with approximately 1 million organisms. A reduction of 99.999% of the organisms is achieved at the value of 1 LOG surviving organisms on the Y axis.

original travoprost except it doesn't contain BAK. Instead, it's preserved in the bottle with a novel ionic-buffered system called sofZia. SofZia consists of carefully selected concentrations of ions and buffers, which are also used in artificial tears. The ions and buffers include boric acid, propylene glycol, sorbitol and zinc chloride. When these components are instilled into the eye, they are neutralized by the positive ions in the tear film, making the system very gentle on the eye.

This preservative system meets the standards of effectiveness required by the United States Pharmacopoeia. It's been shown to withstand high levels of ocular pathogens, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans* and *Aspergillus niger*.[8] Other in-use testing with high-levels of *Fusarium solani*, *Ralstonia pickettii*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* demonstrated that the preservative is effective.[8]

FDA approval of the new formulation was based on a double-masked, randomized, parallel group, multicenter study involving 690 patients.[9] The researchers reported that BAK-free travoprost 0.004% is equivalent to travoprost 0.004% in both safety and efficacy. Researchers randomized study participants to receive travoprost 0.004% (n=346) or BAK-free travoprost 0.004% (n=344) once a day in the evening. Patients were followed for 3 months. IOP was measured at 8 a.m., 10 a.m. and 4 p.m. during study visits at week 2, week 6 and month 3.

Mean reduction in IOP across all nine study visits and times ranged from 7.3 mm Hg to 8.5 mm Hg in the BAK-free travoprost group and from 7.4 mm Hg to 8.4 mm Hg in the travoprost group. The study also showed statistical equivalence for the comparison of mean IOP changes. Adverse events and the number of patients discontinued due to adverse events were similar for both treatment groups. In the BAK-free group, 6.4% of patients experienced hyperemia compared with 9.0% in the original travoprost group. In addition, the IOP-lowering endurance of BAK-free travoprost was shown to be equivalent to that of the original formulation.[10]



Yee and colleagues exposed tissue culture plates containing human corneal epithelial cells to BAK-preserved latanoprost 0.005%, BAK-free travoprost 0.004%, negative-control compounds and live-control compounds. Compared with latanoprost, travoprost 0.004% without BAK showed significantly less cell toxicity.

Travoprost 0.004% (Travatan Z) ... [is] the same medication in the same concentration as the original travoprost except it doesn't contain BAK. Instead, it's preserved in the bottle with a novel ionic-buffered system called sofZia.

Preclinical toxicity studies

Preclinical toxicity studies compared the BAK-free formulation of travoprost 0.004% with the latanoprost formulation preserved with 0.02% BAK in rabbit corneas and immortalized human corneal epithelial cells.

Whitson and colleagues[11] used confocal microscopy to assess corneal epithelial morphology and cell size in two groups of New Zealand white rabbits. One group of eyes was then bathed for 3 minutes in the BAK-free formulation of travoprost or the latanoprost formulation preserved with 0.02% BAK, rinsed with balanced salt solution and reexamined. Another group of eyes was reexamined after receiving 1 drop of each medication per minute for 3 minutes.

The BAK-free formulation of travoprost didn't cause corneal epithelial toxicity; however, the latanoprost formulation preserved with 0.02% BAK induced superficial cell loss. Surface cells were significantly smaller and brighter and exhibited less distinct borders. Larger, more mature cells on the surface sloughed off, revealing smaller, less mature cells. The researchers reported the loss of superficial cells was presumably due to latanoprost's relatively high concentration of BAK.

Yee and colleagues[12] exposed tissue culture plates containing human corneal epithelial cells to 100 µl of the BAK-free formulation of travoprost or the latanoprost formulation preserved with 0.02% BAK and performed assay tests after 25 minutes.

They used two groups of cells (exposed to methanol and gentamicin) as negative controls and two groups (exposed to corneal epithelial culture media and a gellable lubricant eye drop) as live controls. They quantified the effects of each medium on the cells by counting the live and dead cells. Compared with the latanoprost formulation preserved with 0.02% BAK, the BAK-free formulation of travoprost 0.004% showed significantly less cell toxicity.

Elusive condition

OSD, despite its prevalence, remains an underdiagnosed and, therefore, undertreated condition. This is especially true among glaucoma patients, where the doctor's main goal is to lower IOP. The necessary, chronic use of BAK-containing topical medications exacerbates OSD and creates conjunctival and corneal epithelial inflammation and damage.

With FDA approval of the BAK-free formulation of travoprost 0.004%, doctors can eliminate at least one complicating factor, a toxic preservative. I believe the data suggest that this new formulation will provide the unsurpassed IOP-lowering power of a prostaglandin and a gentle, yet effective, preservative system. This new formulation also may provide convenience and comfort, both of which lead to better patient compliance and the best possible outcomes, at the same cost as previously available medications. **OM**

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1. **According to Robert Wooldridge, O.D., which of the following increases a glaucoma patient's risk for ocular surface disease (OSD)?**
   a. Family history
   b. Uncontrolled IOP
   c. Use of topical IOP-lowering drops containing benzalkonium chloride (BAK)
   d. Hypertension

2. **Guenoun and colleagues concluded that BAK is likely the major factor responsible for long-term ocular surface reactions following prolonged medication use but is probably not the main factor in the early onset of what condition?**
   a. Glaucoma
   b. Conjunctivitis
   c. Hyperemia
   d. Trichiasis

3. **In a crossover, randomized, study by Baudouin and de Lunardo, the preserved formulation of 2% carteolol (Ocupress) significantly reduced tear breakup time at how many hours and days?**
   a. 2 hours and 2 days
   b. 3 hours and 3 days
   c. 4 hours and 4 days
   d. 5 hours and 5 days

4. **In the landmark Ocular Hypertension Treatment Study, what percentage of patients required two or more medications to control IOP?**
   a. 40%
   b. 30%
   c. 20%
   d. 10%

5. **Most of the glaucoma medications available today contain BAK in which concentration range?**
   a. 0.005% to 0.02%
   b. 0.004% to 0.01%
   c. 0.003% to 0.01%
   d. 0.002% to 0.03%

6. **Which glaucoma medication contains less BAK than latanoprost 0.005% or preserved travoprost 0.004% but tends to cause the most hyperemia?**
   a. Brimonidine 0.1%, 0.15%
   b. Brinzolamide 1%
   c. Bimatoprost 0.03%
   d. Dorzolamide 2%

7. **Of the following carbonic anhydrase inhibitors, which one tends to sting, or burn, more than brinzolamide even though it contains less BAK?**
   a. Sezolamide
   b. Methazolamide
   c. Acetazolamide
   d. Dorzolamide

8. **The beta-blocker timolol maleate (Timoptic-XE) contains which preservative?**
   a. Stabilized oxychloro complex
   b. Benzododecinium bromide
   c. Benzalkonium chloride
   d. Sodium perborate

9. **The time lapse between the last blink and the appearance of the first dry spot on the cornea is the tear breakup time. Dry spots appearing in less than how many seconds are considered abnormal?**
   a. Four
   b. Six
   c. Eight
   d. Ten

10. **According to research by Yee and colleagues, the BAK-free formulation of travoprost 0.004% showed significantly less cell toxicity than which of the following medications?**
    a. Brimonidine 0.1%, 0.15%
    b. Dorzolamide 2%
    c. Latanoprost 0.005%
    d. Bimatoprost 0.03%