DO WE REALLY NEED PRESERVATIVES FOR EFFICACY OF GLAUCOMA MEDICATIONS?

A Critical Approach

Prof. Dr. Murat Irkec
Director, Glaucoma Unit
Department of Ophthalmology
Hacettepe University School of Medicine
Ankara-Turkey

47th Panhellenic Ophthalmological Congress, Thessaloniki, 2014
• Glaucoma is a multifactorial optic neuropathy involving progressive optic nerve damage associated with loss of visual function and often with elevated intraocular pressure (IOP).

• In established open-angle glaucoma, lowering IOP is effective and always advised, regardless of whether IOP is abnormal.

• Initial treatment for glaucoma typically involves lowering and subsequent control of IOP with pharmacological therapy.

Quigley HA. Glaucoma. Lancet 2011;377:1367–77
GLAUCOMA TREATMENT

• The most common means to treat glaucoma is by topical delivery of solutions into the conjunctival sac.

• Eye drops usually penetrate via corneal or scleral route with some conjunctival contribution.

• Although well accepted by patients and their physicians, solutions might not be ideal in terms of bioavailability.
GLAUCOMA MEDICATIONS

- In general, solutions have a short contact time.
- Several factors might affect their availability:
  - washing out by tear film
  - limited capacity of conjunctival cul-de-sac,
  - dilution by tears and aqueous humour
  - drainage into the nasolacrimal duct
- Furthermore, the complex structure of the corneal epithelium presents a considerably greater barrier to hydrophilic than to lipophilic drugs.

COMPOSITION OF GLAUCOMA MEDICATIONS

• Currently available bottled antiglaucoma medications have many ingredients:
  — the chemically active component
  — a vehicle for the drug,
  — a preservative
  — buffers
  — other stabilising molecules

• Preservatives have to be included in all multidose (MD) eye drop bottles.
Rationale for Including Preservatives in Ophthalmic Preparations

- Health regulatory agencies mandate that manufacturers of multi-dose topical ophthalmic medications include preservative systems, which:
  - Inhibit growth of microbial contaminants in the bottle
  - Prolongs shelf-life by preventing biodegradation and maintaining drug potency
  - Allow for a convenient and safe multi-dose container for patient use
  - Increase corneal penetration of the drug (not true for many PGs)

Types of Preservatives in Ophthalmic Preparations

- Preservatives can be broadly sub-divided by their chemical class and/or mechanism of action
  - Cationic surfactants (e.g., benzalkonium chloride [BAK])\(^1\)
  - Polycationic (e.g., polyquaternium-1 [POLYQUAD® anti-microbial])\(^1\)
  - Mercurials (e.g., thimerosal)\(^2\)
  - Alcoholic compounds (e.g., chlorobutanol)\(^1,2\)
  - Sorbic acid (e.g., potassium sorbate)\(^3\)
  - Amidines (e.g., chlorhexidine)\(^4\)
  - “vanishing preservatives”:
    - sofZia, Purite, and sodium perborate
      (which converts to water and oxygen on contact with the tear film)

GLAUCOMA MEDICATIONS and PRESERVATIVES

- Only a limited number of preservatives are currently included in topical IOP-lowering medications.
- The most common preservative contained in these medications is benzalkonium chloride (BAK):
  - a cationic surfactant
  - has damaging effects on the ocular surface
- BAK concentration in ophthalmic preparations ranges from 0.004% to 0.02%.

Prevalence of Ocular Surface Disease in Patients with Glaucoma

• Evidence indicates that a large proportion (59%) of patients with POAG or ocular hypertension have symptoms of OSD

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular Surface Disease Index (OSDI) Questionnaire*</td>
<td>• 59% of patients had symptoms in ≥1 eye</td>
</tr>
<tr>
<td></td>
<td>• 27% had severe symptoms</td>
</tr>
<tr>
<td>Schirmer’s Test</td>
<td>• 61% of patients had decreased tear production in ≥1 eye</td>
</tr>
<tr>
<td></td>
<td>• 35% had severe tear deficiency</td>
</tr>
<tr>
<td>Corneal and Conjunctival Lissamine Green Staining</td>
<td>• 22% of patients had positive staining</td>
</tr>
<tr>
<td></td>
<td>- None had severe staining</td>
</tr>
<tr>
<td></td>
<td>- Each additional benzalkonium chloride (BAK)-containing eye-drop associated with a 2x higher odds of abnormal lissamine green staining (odds ratio: 2.0; 95% CI: 1.1–3.9; P=0.034)</td>
</tr>
<tr>
<td>Tear Break-Up Time (TBUT)</td>
<td>• 78% of patients had abnormal tear quality</td>
</tr>
<tr>
<td></td>
<td>• 65% had severe decrease in tear quality</td>
</tr>
</tbody>
</table>

Results from the *German Glaucoma and Dry Eye Register* show that:

- The occurrence of dry eye is linked to several factors.
  - Type of glaucoma (PEXG>POAG>PDG)
  - The quantity of eye drops (> three medications)
    (while POAG is usually treated with one drug, PEXG and PDG tend to be treated with multiple drugs)
- The gender difference in the occurrence of dry eye becomes apparent from the age 50 years.
- Because of the vicious circle of dry eye, antiglaucoma eye drops containing benzalkonium chloride compromises patient compliance.
IOP-Lowering Medications, Preservatives and the Ocular Surface

• Long-term administration of topical IOP-lowering agents has been linked with ocular surface changes\textsuperscript{1,2}
  – It has been suggested that the cytotoxic effects of preservatives associated with long-term IOP-lowering therapy are often under-recognized\textsuperscript{3}

• Ocular surface changes induced by preservatives lead to poor tolerance to IOP-lowering eye-drops\textsuperscript{1}

BENZALKONIUM CHLORIDE

- (+) charge interacts with microbial cell membrane
- Detergent properties linked to hydrophobic pole
  - Emulsification (soap effect)
  - Cell membrane destruction (break lipids)
BAK effect on tear film and conjunctiva

Effect of BAK on tear film
Soap effect
Tear film lipid layer damage
Higher evaporation

Cytotoxicity
Loss of goblet cells
Reduced tear mucus
Tear stability loss
Overview of Mechanistic Effect of BAK on the Ocular Surface

Topical Application of BAK onto Ocular Surface

Tear Film Instability

Corneal and Conjunctival Epithelial Cell Damage

Loss of Epithelial Cell Integrity

Epithelial Apoptosis and Loss of Corneal Permeability Barrier

Loss of Goblet Cells and Decreased MUC5AC Production

Increased Inflammatory Response

IMMUNOPATHOLOGY of the CONJUNCTIVA

IL-1α: small number of subepithelial cells
CD3: weak staining of some SE cells
CD20, IL-10, TNF-α, TGF-α: no staining

Irkec M, Orhan D 2010
HLA-DR overexpression is a nonspecific indicator of inflammation.

HLA-DR expression is parallel to the concentrations of BAK contained in the eyedrops; that is, the higher the concentration, the higher the HLA-DR expression.
The apoptosis observed in the conjunctival epithelial cells might be due to the preservative benzalkonium chloride in the antiglaucoma medications because the apoptosis rates did not differ in patients using different types of medications.
BLEB APPEARANCE

PO 1\textsuperscript{st} mo

IOP 23 mm Hg

PO 2\textsuperscript{nd} mo

IOP 24 mm Hg

IV CONFOCAL MICROSCOPY

Epithelium

S.propria
Toxicity of preservatives

Toxic pseudopemphigoid after 20 years of antiglaucoma treatments

Baudoin C Cornea 2009;28(Suppl. 1):S14–S19
DO WE REALLY NEED PRESERVATIVES in OPHTHALMIC SOLUTIONS?

• Cationic preservatives, particularly BAK, have been shown to enhance the ocular absorption of a number of drugs varying in molecular size and lipophilicity:
  — pilocarpine,
  — prednisolone
  — β-blockers

• It could be claimed that this effect is desirable since more permeation of a drug might result in a more intense pharmacological effect.

• BAK was thought to be required as a penetration enhancer in the past due to the more hydrophilic nature of ophthalmic solutions.
• Many modern topical medications do not necessitate damaging effects on the corneal epithelium in order to achieve efficacy at the target tissues.
• The use of preservative-free single-dose units (SDUs) is a solution to avoid the preservatives and adverse effects associated with their usage.
A study assessed the non-inferiority of the nonpreserved T-Gel 0.1% (carbomer +timolol) SDU versus its BAK-preserved MD reference.

The mean percentage reduction from baseline IOP was 24% for both treatment groups, which was consistent with previous studies.

The safety results were comparable in both treatment groups.

The overall study results demonstrated that T-Gel 0.1% SDU is not inferior to T-Gel 0.1% MD.

Efficacy and tolerability of preservative-free eye drops containing a fixed combination of dorzolamide and timolol in glaucoma patients

Renieri, G; Führer, K; Scheithe, K; Lorenz, K; Pfeiffer, N; Thieme, H

*J Ocul Pharmacol Ther*, 2010 vol. 26(6) pp. 597-603

PURPOSE: To evaluate the efficacy and tolerability of preservative-free eye drops (dorzolamide/timolol) in routine management of preservative-sensitive glaucoma patients.

*Data from a prospective, open, noncomparative, multicenter, noninterventional study including 2,298 glaucoma patients.*

CONCLUSIONS: This observational study confirms the IOP lowering effect of preservative-free eye drops containing the fixed combination of dorzolamide/timolol in a large patient's population. The drug was well tolerated and improved the local tolerability in the vast majority of patients.
Globally, prostaglandin analogues have become the major first line therapeutic agents for medical treatment of glaucoma — superb efficacy — good safety profile.

Prostaglandin analogues with BAK may exert cytotoxic effect on the ocular surface.

Latanoprost, the most widely used prostaglandin analogue, contains 0.02% of the preservative BAK:
— twice that of most other glaucoma drops.
• Recent studies contradicted the results of other earlier studies, which supported the hypothesis that BAK preservation plays an important role in the drug penetration into the eye.
• Prostaglandin analogues (mostly prodrugs in an ester form) have ideal tissue penetration.
• Bimatoprost may be an exception, however, it reaches the target tissues favoring the conjunctival/scleral absorption route.
• Findings of intact bimatoprost in the target ciliary body indicated its direct involvement in reducing IOP.
• Bimatoprost acid may have only a limited contribution and does not necessitate BAK preservation for permeation through cornea.

Cucherat, M; Stalmans, I; Rouland, JF J. Glaucoma, 2014;23:e69-75
Relative efficacy and safety of preservative-free latanoprost (T2345) for the treatment of open-angle glaucoma and ocular hypertension: an adjusted Indirect comparison meta-analysis of randomized clinical trials
Cucherat, M; Stalmans, I; Rouland, JF

*J. Glaucoma*, 2014 vol. 23(1) pp. e69-75

AIM: To assess the relative efficacy and tolerability of preservative-free latanoprost (T2345) compared with other prostaglandin analogues (PGA) for the treatment of open-angle glaucoma and ocular hypertension by adjusted indirect comparison meta-analysis.

*Twenty-one studies were included in the meta-analysis.*

CONCLUSIONS: Indirect comparisons never found preservative-free latanoprost (T2345) to be statistically significantly inferior to the other PGA in terms of efficacy on IOP. The risk of hyperemia was statistically significantly lower with T2345 than with all the other PGA.
Bimatoprost 0.03% preservative-free ophthalmic solution versus bimatoprost 0.03% ophthalmic solution (Lumigan) for glaucoma or ocular hypertension: a 12-week, randomised, double-masked trial.

Day, DG; Walters, TR; Schwartz, GF; Mundorf, TK; Liu, C; Schiffman, RM; Bejanian, M


BACKGROUND/AIM: To evaluate efficacy and safety of bimatoprost 0.03% preservative-free (PF) ophthalmic solution versus bimatoprost 0.03% (Lumigan) ophthalmic solution for glaucoma or ocular hypertension.

RESULTS: 597 patients were randomised (bimatoprost PF, n=302 and bimatoprost, n=295). Both treatments showed decreases in mean average eye IOP at all follow-up time points (p<0.001), were safe and well tolerated.

CONCLUSIONS: Bimatoprost PF is non-inferior and equivalent to bimatoprost in its ability to reduce IOP-lowering with a safety profile similar to bimatoprost.
Tafluprost, a relatively new prostaglandin analogue, is a prodrug in an ester form, which has ideal tissue penetration.

Tafluprost is a preservative-free, once-daily topical prostaglandin analogue approved to decrease IOP in open-angle glaucoma and ocular hypertension.

Tafluprost has been shown to be non-inferior to glaucoma drops, including β-blockers and prostaglandin analogues.

Its improved adverse effect profile makes it a viable alternative in patients with preservative associated ocular surface disease.

TAFLUPROST PRESERVATIVE FREE

• A recent study compared the 24-h IOP control obtained with preservative-free tafluprost 0.0015% with branded BAK-preserved latanoprost 0.005% administered as first-choice monotherapy in patients with primary open-angle glaucoma or ocular hypertension.

• In this prospective, crossover study, the authors demonstrated clearly that preservative-free tafluprost achieved similar 24-h IOP reduction to branded latanoprost.

CONCLUSIONS

• Preservatives are not necessary to improve the efficacy of unidose glaucoma drops, including β-blockers, carbonic anhydrase inhibitors and various prostaglandin analogues.

• Several studies have put into question the notion that preservatives in glaucoma medications enhance drug penetration since preserved and unpreserved glaucoma drops have similar efficacy.

• In current practice, glaucoma patients, particularly those with ocular surface disease, are fortunate to have efficacious but safer alternatives with the introduction of preservative-free topical medications.

• However, preservative-free preparations are yet expensive and, for certain patients, somewhat inconvenient to use.
THANK YOU FOR YOUR ATTENTION