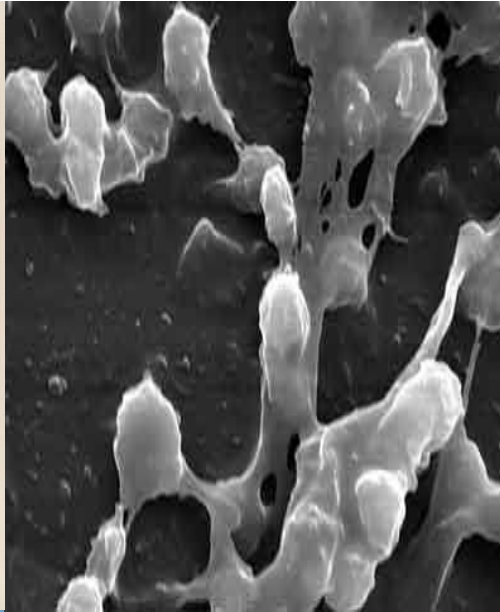


Opening Pandora's box- topical medications, toxicity and compliance



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Introduction – Role of preservatives



- If you could get away without a preservative that would be better as long as you could assure:
 - that the drug was going to be stable
 - not going to be any contamination in the drug's container
 - Less is thought to be better - chronic medications
 - Dry eyes - artificial tears or
 - Glaucoma medications that are going to be used everyday indefinitely
- Ophthalmic antibiotic arena - preservative would be a benefit

German register for glaucoma patients with dry eye. I. Basic outcome with respect to dry eye

Carl Erb • Ulrike Gast • Dieter Schremmer

- 20,506 glaucoma patients
- 52.6% concomitant diagnosis of dry eye
- Impact of glaucoma type on dry eye was significant:
 - 60.9% in PEX; 52.0% in POAG; 45.2% in PDG
 - Most POAG patients on monotherapy
- Impact of glaucoma duration significant
- Presence of preservatives

Types of preservatives

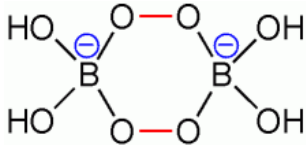




Chemical Class	Compounds	Commercial name
Quaternary ammoniums	Benzalkonium Chloride (BAK)	
	Cetrimide	
	Polyquaternium-1	Polyquad[®] - Alcon
Mercury derivatives	Thiomersal or thimerosal	
Oxidative complexes (Soft preservatives)	Sodium Perborate NaBO ₃	Gen Aqua[®] - Novartis
	S.O.C (Stabilized Oxychloro Complex)	Purite[®] - Allergan Ocupure[®] - AMO
	S.C.P (Stabilized Chlorite Peroxide)	Oxyd[®] - Tubilux
Amidines	Chlorhexidine	
Alcohols	Chlorobutanol	
	Phenylethanol	
Parabens	Methylparaben	

Quaternary Ammonium Compounds & BAK

- Quaternary ammonium molecules have detergent properties and are easily incorporated into epithelial cell membranes
- They break up intercellular junctions, letting through aqueous or ionic substances
- They can trigger changes in the tear film causing eye dryness and patient discomfort
- Instillation of a single drop of 0.01% BAK halved Tear Film Break-Up Time in healthy volunteers¹

¹ = Wilson WS, Duncan AJ, Jay JL. Br J Ophthalmol 1975; 59: 667-9.

The Oxidative Complexes

Compounds	Commercialization	Mode of action(1)/claims
<p>Sodium Perborate</p> 	<p>GenAqua® in GenTeal® range (Novartis)</p> 	<p>In presence of water, the perborate is transformed in ion borate and hydrogen peroxide (H₂O₂), which is an oxidative compound.</p> <p>Claim: <i>“it turns into pure water and oxygen upon contact with your eye”</i></p>
<p>S.O.C (Stabilized Oxychloro Complex)</p> <p>Chlore derivative composed mainly by Chlorite (NaClO₂) and Chlorate-Chlorine</p>	<p>- Purite® in Refresh Tears® (Allergan)</p>  <p>- Ocupure® in Blink Tears® (A.M.O)</p> 	<p>Chlorite acts by producing a high degree of oxidation of glutathione, thus reducing the cell's defenses against oxidative stress.</p> <p>Claim: <i>“dissipates into water and sodium chloride-components of natural tears when exposed to ambient light”</i></p>
<p>S.C.P (Stabilized Chlorite Complex)</p> <p>Chlorite (NaClO₂) + H₂O₂</p>	<p>Oxyd® in Oxyal® (Tubilux)</p> 	<p>Chlorite acts by producing a high degree of oxidation of glutathione, thus reducing the cell's defenses against oxidative stress.</p> <p>The H₂O₂ is eliminated in water and oxygen by enzymes of the tissues.</p>

Cytotoxicity of Preservatives

- Cytotoxic effects occur at concentrations lower than those in some commercial preparations^{10,11}
- At high conc. preservatives produce cytotoxic effects within minutes of application¹²
- Some cellular modifications are irreversible, and eliminating the preservative may not enable cells to recover^{12,13}

10 = Lapalus P, *et al.* Lens Eye Tox Res 1990; 7: 231-42

11 = Salonen EM, *et al.* J Toxicol Cutan and Ocul Toxicol 1991; 10: 157-66

12 = De Saint Jean M, *et al.* Curr Eye Res 2000; 20: 85-94

13= Tripathi BJ, Tripathi RC, Kolli SP. Lens Eye Toxic Res 1992; 9: 361-75

Preservatives in Eye Drops

- Quaternary Ammonium Compounds such as benzalkonium chloride (aka BAK) are the most frequently used preservatives in eye treatments
- They are also the most toxic for the ocular surface
- Studies have shown that preservatives have a role in topical toxicity of eye drops - especially in long term treatment

Switching Studies

- Changing from poorly-tolerated preserved eye drops to preservative-free eye drops leads to a rapid improvement in:
 - ocular symptoms^{23,24,25,26,27}
 - tear film^{25,28}
- Changing to preservative-free can reduce symptoms by a factor of 3 to 4^{23,27}

23 = Pisella PJ, Pouliquen P, Baudouin C. Br J Ophthalmol 2002; 86: 418-23.

24 = Bron A, *et al.* J Fr Ophtalmol 2003; 26: 668-74

25 = Campagna P, *et al.* Acta Ophthalmol Scand Suppl 1997; 224: 53

26 = De Jong C, *et al.* Graefe's Arch Clin Exp Ophthalmol 1994; 232: 221-4

27 = Levrat F, Pisella PJ, Baudouin C. J Fr Ophtalmol 1999; 22: 186-91

28 = Laflamme MY, Swieca R.. Can J Ophthalmol 1988; 23: 174-6

Are all preservatives toxic?

Evaluation of the cellular viability in a Human cornea cell line after preserved and preservative-free treatments⁽¹⁾.

	24h	24h + 24h	72h
Control	Normal (100%)	Normal (100%)	Normal (100%)
BAK 0.01%	No toxic	Viability decline (43%)	Toxic (0 %)
BAK 0.1%	Toxic (0 %)	Toxic (0 %)	Toxic (0 %)
Perborate	No toxic	No toxic	Viability decline (75%)
Polyquad	No toxic	No toxic	Viability decline (70%)
Thiomersal	No toxic	No toxic	Toxic (1 %)
Oxyd	No toxic	Viability decline (71%)	Toxic (4.5 %)
COMOD	No toxic	No toxic	No toxic
ABAK	No toxic	No toxic	No toxic

(1) Meloni M et al. Occludin gene expression as an early in vitro sign for mild eye irritation assessment. Toxicology in vitro (2009).

Preservative Adverse Effects

Toxic reactions

Responsible for the most of the adverse clinical effects

Widely described in literature specially for detergent preservatives such as BAK

Allergic reactions

Less common than toxic reactions

Usually contact allergies



All ocular structures can be affected

Superficial ocular tissues

conjunctiva, cornea and tear film

Internal structures

trabeculum, lens, retina... leading to complications:

- Cataract cystoid macular edema
- Chronic conjunctival fibrosis and failure of glaucoma filtering surgery.

BAK Impairs the Tear Film

- Impairment of the tear film (altered Schirmer test and Break Up Time) and decreased goblet cell density have been shown after treatment with preserved anti-glaucoma eye drops¹⁸
- BAK induces mucus-layer and lipid-layer alterations, resulting in a globally impaired tear film with tear instability, excessive evaporation and increased osmolarity^{19,20,21,22}

18 =Herreras JM, *et al.* Ophthalmology 1992;99:1082-88

19 = Chung SH, *et al.* Mol Vis. 2006;12:415-21

20 = Gobbels M, Spitznas M. Graefes Arch. Clin Exp Ophth. 1989;227:139-41

21 = Gobbels M, Spitznas M.. Ophthalmology 1992;99:873-78

22 = Labbe A, *et al.* J.Ocul. Pharmacol. Ther. 2006;22:267-78

Compliance – adherence , capacitance

- Medicine compliance
 - degree to which a patient correctly follows medical advice (medication or drug compliance)
 - **Significant role of preservatives**
- Compliance - World Health Organization (2003) indicate that only about 50% of patients with chronic diseases living in developed countries follow treatment recommendations.^[1]

So.....what really makes an ideal eye drop formulation?

- Free from preservatives & phosphates
- Mimic the behaviour of the tear film
 - efficient drug delivery or symptomatic relief
- The pH is near neutral or slightly alkaline
- Protects the ocular surface against the osmolar challenge
- Addresses the hyperosmolarity of a dry eye
- Protects the ocular surface from stress (cold, dryness, high osmolarity)

Summary – Primum non nocere

- Preservatives in eye drops induce adverse effects of variable intensity and severity
- Prolonged use of preserved eye drops leads to alterations of the superficial and deeper ocular structures
- The major deleterious role of preservatives is confirmed by studies comparing preserved eye drops and preservative-free equivalents
- It is advisable to restrict use of preserved eye drops and replace them with preservative-free alternatives wherever possible

Future – Role of preservatives

- If you could get away without a preservative that would be better as long as you could assure:
- Recent developments in Oxidizing and ionizing preservatives portend a future movement away from detergent preservatives
- Newer agents and newer technology multidose bottles
 - while causing fewer side effects on corneal and conjunctival tissues
- Use of unit-dose bottles
 - do not require preservatives
 - ? cost effective
- Medications with longer durations of efficacy
- Use of medication depots injected into the eye or in the subconjunctival/sub-Tenon's space will allow for single medication application of without the need for repeated dosing

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