PRESERVATIVES IN OPHTHALMIC MEDICATIONS

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Role

- Inhibit contamination of multi-dose medications by pathogenic micro-organisms.
- Prolonging shelf life of the active drug by preventing biodegradation.

Preservative Effectiveness Test

- A standard concentration of common bacteria is prepared and is tested against each preservative. The inoculated tubes are incubated at 20 or 25 degrees Celsius for four weeks and are examined weekly.
- The preservative is considered effective if there is reduction of the bacterial concentration to 0.1 percent or less of the initial concentration after two weeks and the concentration of yeasts and moulds is kept at or below their original concentration for the remaining two weeks.

Factors affecting the ocular tolerance of preserved ocular medications

1. Combination of preservatives
2. Chemical purity
3. Concentration
4. Frequency of instillation
5. Duration of treatment
6. Pathophysiological state of cornea
7. CL use
8. Thickening agent

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Types

- Detergent
- Oxidizing
- Ionic-buffered

1. **Benzalkonium Chloride (BAK)** – Detergent, alter membrane permeability

BAK is used in more than 70% of the ophthalmic solutions (most common preservative).

- Quaternary ammonium compound, gold standard of preservatives.
- Broad range of microbes and also adenovirus.
- Solubilization of the lipophilic protective layer, instability or rupture of the tear film – Dry eye
- Facilitates the penetration of the active drug into anterior chamber.
- Chemically stable at variable temperature.
- Enhances the potency of antibiotic ED.
- It is well tolerated up to concentrations of 0.005%.
- S/E
    - dosing more than 6 times/day.
    - Interference with the membrane function and energy production. BAK induces ATP release and myosin light chain dephosphorylation in corneal epithelial cells. The dephosphorylation and impaired contraction of actin affects the normal cytoskeletal functions necessary for the maintenance of epithelial barrier integrity.

- Increase in apoptosis by BAK.
- Alter the precorneal mucin.

2. **Sorbate (sorbic acid)**

- Sorbic acid interferes with the microbial cellular function by causing acidification.
- It also depletes the microbial cell energy stores by activating energy dependent ion pumps.
- Punctate keratitis may result.
- Sensitive eyes and for contact lenses.

3. **Chlorbutanol** – Detergent, alter membrane permeability

- Broad spectrum antimicrobial action.
- Corneal epithelial damage and ocular irritation.
- It can become unstable when kept at room temperature for prolonged duration.

4. **Polyquaternium-1** – Detergent

- Polymeric quaternary ammonium derived from BAK.
- It has mainly antibacterial activity with less efficacy against fungi and amoeba.
- It can significantly decrease conjunctival goblet cells and the aqueous tear film production but the damage is superficial and the effect on corneal epithelial cells is less pronounced than with BAK.

5. **Polyhexamethylene Biguanide (PHMB)**

- Used in contact lens solutions.
- Altering the permeability of microbial cell wall.
- Binds with the microbial DNA and causes DNA disruption by adversely affecting transcription.
- Highly efficacious against acanthamoeba. It is also effective against bacteria and to a lesser extent against fungi.

6. **Edetate disodium (EDTA)**

- Chelating agent and can help preserve a solution by binding to small amount of heavy metals.
- Synergistic with BAK, BAK and thiomersal.

7. **Sodium perborate** – Oxidative

- Causes oxidative damage to microbial cell membranes, alters the protein synthesis, and disrupts enzymatic function.
- On coming in contact with aqueous environment, it releases hydrogen peroxide which is a potent microbicidal.
- It has good antibacterial and antifungal activity.

8. **Stabilized Oxychloro Complex (Purite)** – Oxidative

- Well tolerated, non-irritant preservative.
- It damages the bacterial protein synthesis.
- It has a broad antimicrobial spectrum. It has also viricidal activity.
- When it comes in contact with light, disintegrates into components such as sodium, chloride, water and oxygen which are normally present in tears – safe

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9. **SofZia** – Ionic buffered – Oxidizing

- Composed of 4 - boric acid, propylene glycol, sorbitol and zinc chloride.
- Active in container, inactive in eye (cations that are normally encountered in the tear film of the eye)
- Fewer corneal changes and less conjunctival inflammation.

Side effects – 1. Irritant, 2. Allergic

Quaternary ammoniums (benzalkonium chloride) – irritant

Organomercurials (thimerosal) and the alcohols (Chlorbutanol) – allergic

In a study the order of **decreasing toxicity** of some of the commonly used concentrations was:

stabilized thimerosal (0.0025%) > benzalkonium chloride (0.025%) > Chlorbutanol (0.25%) > methyl paraben (0.01%) > sodium perborate (0.0025%) approximately EDTA (0.01%)

Adverse external ocular effects induced by preservatives

1. Conjunctiva - cicatrization (pseudo pemphigoid), allergic reactions, papillary or follicular irritative/ toxic conjunctivitis (redness, chemosis), deposition or dyschromia and microbial imbalance accompanied by tearing (discharge).

2. Tears - BAK is the most disruptive of the ophthalmic preservatives to the stability of the lipid film. BAK caused almost instantaneous disruption of the tear film by solubilizing the tear lipid layer. Thiomersal, which is not surface-active, as well as chlorobutanol and EDTA seem not to influence the tear film stability.

3. Cornea
    1) Cytotoxicity – Alcoholic compounds disorganize the bacterial membrane, increasing its permeability, thus causing the leakage of the cytoplasmic contents. Phenolic chemicals disrupt the cell wall and the cytoplasmic membrane, also causing a cellular lysis. Quaternary ammoniums, due to their surface-active properties, break the cellular membrane and precipitate the cytoplasmic enzymes. Sorbic acid inhibits the oxidation of fumarate, a bacterial enzyme. Chlorhexidine inhibits potassium transmembrane transport. Finally, mercurial preservatives poison microbial enzymes fixing their thiol groups and kill microorganisms by affecting internal cell respiration.
    2) Cornea - BAK dissolve the membrane of corneal epithelial cells. At low concentration, they induce a loss of microvilli from the cell surface and at a higher concentration they cause lifting of cell borders and cellular desquamation. Allergic reactions caused by thiomersal and non-specific irritation reactions (edema, eye redness) generated by chlorhexidine and alcoholic preservatives. BAK induces toxic endothelial degeneration.

4. Wound healing - Negatively affect the wound healing rate and interfere with corneal re-epithelialization.

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5. Crystalline lens - deposits of mercury, mercuria lentis is characterized by a yellowish-brown coloration of the anterior lens capsule, thiomersal.
6. Allergy – less common than toxic reaction. The main preservatives involved in allergic contact reactions are thiomersal, chlorhexidine, EDTA, benzethonium chloride, BAK, sorbic acid, phenylmercuric nitrate and polyquat.
7. CL - Sorbic acid, degrade, mixed aldehydes that could discolor protein deposits on the lenses

Future directions

1. **Sustained release formulations**
    a. Once-daily form of timolol maleate (Timoptic-XE) with 0.012% BDD, a preservative similar to BAK.
    b. BDD - Dimethyldodecylbenzylammonium bromide

2. **Safe, mild, and less-toxic preservatives**
    a. As compared to BAK, Purite and SofZia appear to be benign to the ocular surface.

3. **Non-preserved solutions**
    a. Preservative free preparations, unit-dose eye drops.
    b. Disadvantages
        i. More difficult for a patient to use correctly.
        ii. More expensive.

4. **Novel multidose devices for eye drops**
    a. Use of a special filter device.
        i. Either the device contains a sterile preservative-free solution protected against microbial contamination by a 0.2-micron porosity filter or
        ii. a preservative (BAK for instance) is contained in the solution and retained by a filter (adsorbing resin) upon instillation.
    b. In both cases, a preservative-free eye drop is delivered to the eye.
    c. The cost of this new packaging system, though higher than the traditional multidose bottle, is lower than the unit dose packages.
    d. These devices are prone to bacterial colonization of the space between the bottle tip and the cap or along the threads of the container cap

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Preservative	Class	Advantages	Disadvantages	Medication examples
SofZia®	Oxidative	Modified into harmless elements upon instillation; smaller amounts of conjunctivo–corneal inflammation compared with BAK	Newer agent requiring more studies to understand ocular safety profile of the preservative independent of active ingredients	Travatan Z®
Sodium perborate (GenAqua®)	Oxidative	Catalyzed into hydrogen peroxide, water and oxygen upon instillation; activity against *Aspergillus*; less toxicity than BAK	Few studies documenting ocular tolerability and side-effect profile	Genteal®
Stabilized oxychloro complex (SOC/Purite®)	Oxidative	Dissociates into water, oxygen, sodium and chlorine free radicals	As with sofZia, more studies are needed to assess ocular side effects independent of active ingredients	Alphagan-P®, Refresh Tears®
Polyquaternium-1 (Polyquad®)	Detergent	Less toxicity to corneo–conjunctival surface than BAK	Superficial corneal epithelial damage reduces density of conjunctival goblet cells	Tears Naturale II®, Opti-Free® Express Disinfecting Solution
Chlorobutanol	Detergent	Toxic effects take longer to manifest than BAK; doesn't affect stability of lipid component of tear film; extensive antimicrobial activity	Causes keratitis and irritation to ocular surface; decreased amount of mitoses to corneal epithelial cells; unstable when stored at room temperature	TobraDex® Ointment
Cetrimonium chloride	Detergent	Excellent antiseptic qualities	Causes keratinization and inflammatory infiltrates at the limbus and within the conjunctival stroma and epithelium	Civigel®
Benzalkonium chloride	Detergent	Excellent antimicrobial efficacy; disruption of corneal cell–cell junctions allow medicinal entry to anterior chamber; well-established familiarity in industry	Breakdown of corneal epithelium; apoptosis of ocular surface cells; accumulation in surface tissues; tear-film instability	Timoptic®, Azopt, Lumigan®, Xalatan
Edetate disodium	Chelating agent	Inactivates trace amounts of heavy metals	Few studies documenting chronic side effects	Acular®, Betagan®

BAK: Benzalkonium chloride.

Medscape

Source: Expert Rev Ophthalmol © 2009 Expert Revies Ltd

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