Preservatives and Dry Eye Disease:
an evidence based review[1]

Definitions

Dry eye

Dry eye disease (DED) is defined as: *"a multifactorial disease of the ocular surface characterized by a* ***loss of homeostasis*** *of the tear film, and accompanied by ocular symptoms, in which* ***tear film instability*** *and* ***hyperosmolarity****,* ***ocular surface inflammation and damage****, and neurosensory abnormalities play etiological roles."*[2]

Preservatives

Any multidose drop must have some way of maintaining its sterility throughout its intended length of use. Preservatives are antimicrobial agents and are added to multidose drops for this purpose. They must balance an ability to be efficacious against a wide variety of pathogens, whilst minimizing their toxic effects on the cells of the ocular surface.[3]

DED may require dosing of drops several times a day, over a period of many years. Any agents included in dry eye therapies must minimise their impact on an ocular surface that is already compromised

Benzalkonium chloride (BAK)

Mode of action

BAK is an ammonium quaternary compound. Its detergent properties dissolve the cells walls of bacteria. It is most effective against Gram +ve species, with good fungicidal and some Gram –ve activity as well.[3] BAK's mode of action is not limited to pathogenic cells however, mammalian cells can also absorb it.

Effect on the ocular surface

Evidence gathered over many years from clinical, *in vivo* and *in vitro* studies consistently demonstrate BAK induces adverse changes to the ocular surface, in a time-dependent and dose-dependent manner.[3-6]

Use of BAK-preserved drops has been associated with symptoms including burning, stinging, dry eyes and foreign body sensations.[7] Clinically, superficial punctate keratitis, conjunctival hyperemia, increased tear film osmolarity and reduced tear break up time occur.[7,8]
At the cellular level, BAK reduces the number of goblet cells and increases inflammatory responses.[9,10]

Use of ocular lubricants preserved with BAK should be avoided in DED, particularly in those patients with severe disease[11]

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Alternative preservatives

Polyquaternium-1 (POLYQUAD®)

POLYQUAD® is a hydrophilic, cationic quaternary compound that is around 27x larger than BAK and has a different mode of action.[12] In studies, although some cell changes have been seen *in vitro*,[13] it consistently results in significantly less disruption to the ocular surface compared to BAK-preserved formulations.[3,14-16]

Oxidising preservatives

Oxidising preservatives maintain antimicrobial properties in solution, decomposing to harmless by-products once applied to the eye. Examples include: stabilized oxychloro complex (Purite® and OcuPure®), and sodium perborate (GenAqua™) Previous review papers highlight the lack of studies for some preservatives in this group, but in general conclude that they have significantly less effect on the ocular surface compared to BAK.[3,5]

Alternative preservatives result in significantly less disruption to the ocular surface than BAK

Preservative-free

Preservative-free (PF) formulations often come in single-use vials. Multidose drops are available which use specialized bottles designed to prevent contamination.

PF drops result in low levels of ocular surface disruption, with significant improvements in signs and symptoms, and fewer cellular changes compared to BAK-preserved drops.[7,17-21] Depending on study design, PF drops either show no significant difference in performance compared to non-BAK preservatives,[22-24] or cause less disruption than preserved formulations.[16,17,25]

Usability of single-use drops must also be considered, with review papers citing concerns with greater difficulty in handling, and significantly higher cost compared to multidose drops, which may lead to reuse of single-dose vials.[3,4,15]

In practice: Evidence suggests use of BAK-preserved drops should be avoided in all patients with DED

The first step in the DEWS II staged management approach suggests the most appropriate ocular lubricant from all other BAK-free options be recommended.[11]

If those measures are inadequate, step two recommends the use of PF drops for patients with significant ocular surface disruption or severe DED.[11]

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