Received: 13 January 2022 | Revised: 31 March 2022 | Accepted: 9 April 2022

DOI: 10.1111/bcp.15359

COMMENTARY

Is it time for a moratorium on the use of benzalkonium chloride in eyedrops?

Luca D'andrea[1] | Marina Montemagni[2] | Giuseppe Celenza[3] | Roberto Iorio[3] | Ciro Costagliola[2]

[1]Department of Public Health, University of Naples Federico II, Naples, Italy

[2]Department of Neurosciences, Reproductive and Dentistry Sciences, University of Naples Federico II, Naples, Italy

[3]Department of Biotechnological and Applied Clinical Sciences, University of Aquila, Aquila, Italy

Correspondence
Marina Montemagni, MD, Department of Neurosciences, Reproductive and Dentistry Sciences, University of Naples Federico II, Naples, Italy. Via Sergio Pansini 15, 80131. Naples, Italy.
Email: marinamontemagni91@gmail.com

KEYWORDS: BAC, benzalkonium chloride, glaucoma, neuroinflammation, OSD, toxicity

Benzalkonium chloride (BAC) is a quaternary ammonium compound introduced in 1935 and widely used as a skin and surface disinfectant and preservative in many household cleaning and personal care products. Due to its antimicrobial activity against many common pathogens, BAC is also employed as a preservative in several multidose eyedrops at concentrations varying from 0.004% to 0.02%. The success and longevity of BAC are attributable to its undeniable antibacterial efficacy and, not least, its low production cost.[1]

As a cationic surfactant, BAC has an amphipathic nature, and it expresses antimicrobial activity by denaturing proteins and disrupting cytoplasmatic membranes. BAC is also used as an excipient to stabilize poor water-soluble drugs and as a penetration enhancer of active compounds through ocular membranes. Indeed, it is believed that BAC can solubilize the intercellular junctions in corneal epithelium, enhancing drug delivery.[2]

Although anecdotal reports have been circulating in recent years about the adjuvant effect of BAC as an enhancer of prostaglandin analogue efficacy, recent studies have demonstrated that BAC does not change the pharmacokinetics of the active ingredients. In fact, many studies on glaucomatous patients show a similar intraocular pressure (IOP) reduction in patients receiving BAC-containing and preservative-free formulations. Pellinen and Lokkilla compared corneal penetration of 0.01% BAC-preserved and preservative-free tafluprost in rabbit aqueous humor after topical administration. No statistically significant difference in the mean concentration over time was recorded (the maximum drug concentration was 4.50 ng/mL for preservative-free tafluprost and 3.99 ng/mL for 0.01% BAC-preserved tafluprost, and the time to maximum drug concentration was 45 min for both).[3] This finding demonstrated that BAC is far from an ideal penetration enhancer.

Eyedrops containing BAC are associated with some adverse events, particularly when used chronically, as in glaucomatous patients. The European Medicine Agency suggests avoiding preservatives in glaucomatous patients, especially in those with pre-existing ocular surface disease (OSD) or in those developing dry eye or ocular irritation over time.

The development of OSD in glaucomatous patients depends primarily on BAC, which affects lipid layer and tears film stability. Moreover, it decreases tear break-up time and induces apoptosis of conjunctival cells with a breakdown of corneal epithelial junctions and loss of superficial epithelial cells. It is not surprising that patients treated with IOP-lowering eyedrops show a higher percentage of OSD compared to the general elderly population (50% *vs* 15%).[4]

A positive correlation between the number of BAC-preserved eyedrops used and OSD was observed.[5] OSD causes significant morbidity and influences treatment compliance, quality of life and surgical outcomes.[6,7] On the other hand, it is not surprising that topical adverse effects represent a source of poor adherence and a common reason for drop-out in clinical situations and clinical trials, representing an important barrier to the effective management of IOP.[8,9] Long-term use of topical eyedrops rich in preservatives can modify eye surfaces, compromising the success rate of trabeculectomy. In most cases, the failure of glaucoma surgery originates from a fibroblastic conjunctival response to inflammation at the bleb level, which

occurs in the early postoperative months. A significant relationship between the number of drugs used, duration of treatment, inflammatory cell and fibroblast infiltration in the conjunctiva, and the risk of failure of filtering surgery has also been found.[6,7]

Topically instilled BAC could act not only on superficial structures but also reach deeper tissues, such as trabecular meshwork and optic nerve areas, with a greater impact in case of long exposure (inflammatory cell infiltration and Müller glial cell activation).[10] In rabbit models, BAC is able to penetrate healthy eyes even after a short exposure and was found also in deeper tissues (trabecular meshwork and optic nerve), which triggered an inflammatory reaction. Although these findings have been recorded in animal models, they represent a warning of the detrimental effects also in humans. Detrimental BAC effects could result in progressive loss of efficacy of IOP-lowering compounds. Moreover, the presence of this preservative along the optic nerve could be a sight-threatening issue: BAC side effects could account for the percentage of glaucomatous patients whose disease progresses despite good IOP control.[10]

Stevens et al showed that short-term BAC administration induces inflammation in the anterior segment.[11,12] When a pro-inflammatory stimulus arises during injury or disease, astrocytes, Müller cells and microglia become activated and produce cytokines and chemokines. This recruits blood-derived immune cells to the retina, which causes amplification of the inflammatory response in the retina. Thus, glaucomatous insult or elevation of IOP triggers the responses of microglia, astrocytes and Müller cells to participate in the process of neuroinflammation. Glaucomatous patients present inflammatory dysfunction of the retinal ganglion cell layer (RGC) and the optic nerve head. BAC enhances inflammatory response both at the level of the ocular surface and along all the visual pathways.[10] Mitochondrial oxidative stress has been reported to promote OSD. In addition, RGC is a highly vulnerable neuronal cell type with reference to mitochondrial dysfunction. In this sense, BAC has also been shown to induce mitochondrial oxidative stress and detrimental effects on mitochondrial function. OSD due to topical preservatives in eyedrops is just the tip of the iceberg and the visible consequence of iatrogenic inflammation induced by BAC.[13]

Finally, it is also important to consider the effect of BAC on the efficacy of antibiotic therapy. Many studies have shown that exposure to BAC is linked to promoting antibiotic resistance in environmental bacteria and human pathogenic bacteria1.[14–16] Analysis of the ocular microbiota following prolonged treatment with BAC eyedrops showed an increased incidence of methicillin- and fluoroquinolone-resistant bacteria compared to ocular surfaces treated with BAC-free eyedrops.[15] Specifically, concerning glaucomatous patients, a 2017 study[17] showed that the incidence of methicillin-resistant *Staphylococcus epidermidis* in patients treated with BAC-containing prostaglandin analogues increases by approximately 4-fold. Closer analysis of these isolates revealed other susceptibility profiles extended to other antibiotic families such as beta-lactams, aminoglycosides, quinolones and macrolides.[18] Although these findings are of limited significance since they are not associated with clinical problems, their results still raise concerns about the possibility of potentially selecting causative microbes of bleb-related infection after trabeculectomy.

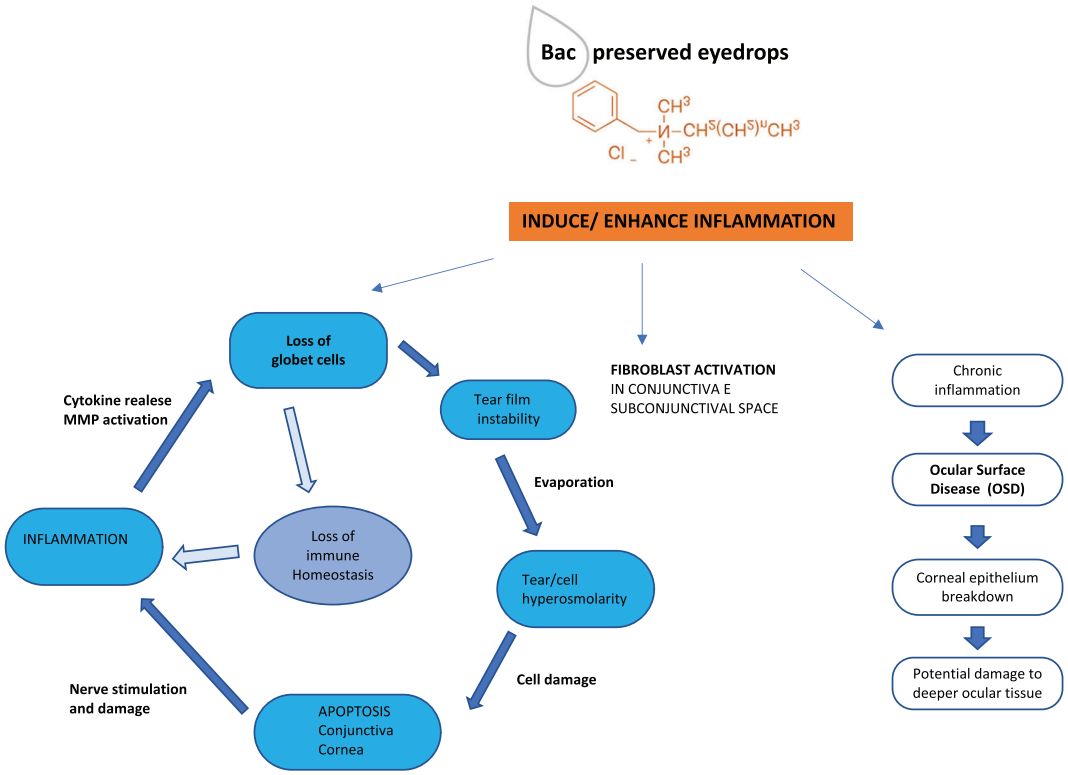

FIGURE 1 Detrimental effects of benzalkonium chloride on the ocular surface

In conclusion, clinical and experimental evidence demonstrates that BAC causes instability of the tear layer, loss of goblet cells, apoptosis, subclinical neuroinflammation and antibiotic resistance (Figure 1). These findings strongly suggest avoiding the use of this preservative in eyedrops. At present, topical formulations containing alternative preservatives (ie, Polyquad, Purite, SofZia, GenAqua) and preservative-free formulations which exhibit a similar efficacy to eyedrops containing BAC, but with a considerably lower grade of ocular toxicity, are available.[19]

Considering the validity of the alternative formulations, it is unreasonable to persist in using such toxic compounds and perhaps it is time for a moratorium on the use of BAC in eyedrops.

COMPETING INTERESTS

The authors declare no conflict of interest.

CONTRIBUTORS

L.D.: writing – original draft preparation, writing – review & editing. M.M.: writing – original draft preparation, writing – review & editing. C.G.: writing – original draft preparation, writing – review & editing. I.R.: writing – original draft preparation, writing – review & editing. C.C.: conceptualization, writing – original draft preparation, writing – review & editing, validation.

ORCID

Marina Montemagni https://orcid.org/0000-0002-7981-3383

REFERENCES

1. Steven DW, Alaghband P, Lim KS. Preservatives in glaucoma medication. *Br J Ophthalmol*. 2018;102(11):1497-1503. doi:10.1136/bjophthalmol-2017-311544
2. Nakamura T, Yamada M, Teshima M, et al. Electrophysiological characterization of tight junctional pathway of rabbit cornea treated with ophthalmic ingredients. *Biol Pharm Bull*. 2007;30(12):2360-2364. doi:10.1248/bpb.30.2360
3. Pellinen P, Lokkila J. Corneal penetration into rabbit aqueous humor is comparable between preserved and preservative-free tafluprost. *Ophthalmic Res*. 2009;41(2):118-122. doi:10.1159/000192082
4. Fechtner RD, Godfrey DG, Budenz D, Stewart JA, Stewart WC, Jasek MC. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. *Cornea*. 2010;29(6):618-621. doi:10.1097/ico.0b013e3181c325b2
5. Rossi GC, Pasinetti GM, Scudeller L, Raimondi M, Lanteri S, Bianchi PE. Risk factors to develop ocular surface disease in treated glaucoma or ocular hypertension patients. *Eur J Ophthalmol*. 2013;23(3):296-302. doi:10.5301/ejo.5000220
6. Baudouin C. Ocular surface and external filtration surgery: mutual relationships. *Dev Ophthalmol*. 2017;59:67-79. doi:10.1159/000458487
7. Lavin MJ, Wormald RP, Migdal CS, Hitchings RA. The influence of prior therapy on the success of trabeculectomy. *Arch Ophthalmol (Chicago, Ill: 1960)*. 1990;108(11):1543-1548.
8. Thygesen J. Glaucoma therapy: preservative-free for all? *Clin Ophthalmol*. 2018;12:707-701. doi:10.2147/OPTH.S150816
9. Konstas AG, Labbé A, Katsanos A, et al. The treatment of glaucoma using topical preservative-free agents: an evaluation of safety and tolerability. *Expert Opin Drug Saf*. 2021;20(4):453-466. doi:10.1080/14740338.2021.1873947
10. Brignole-Baudouin F, Desbenoit N, Hamm G, et al. A new safety concern for glaucoma treatment demonstrated by mass spectrometry imaging of benzalkonium chloride distribution in the eye, an experimental study in rabbits. *PloS One*. 2012;7(11):e50180. doi:10.1371/journal.pone.0050180
11. Stevens AM, Kestelyn PA, De Bacquer D, Kestelyn PG. Benzalkonium chloride induces anterior chamber inflammation in previously untreated patients with ocular hypertension as measured by flare meter: a randomized clinical trial. *Acta Ophthalmol*. 2012;90(3):e221-e224. doi:10.1111/j.1755-3768.2011.02338.x
12. Kestelyn PA, Kestelyn PG, De Bacquer D, Stevens AM. Switch from BAK-preserved to preservative-free latanoprost decreases anterior chamber flare in POAG patients. *Int Ophthalmol*. 2019;39(1):105-109. doi:10.1007/s10792-017-0792-z
13. Rogov AG, Goleva TN, Sukhanova EI, et al. Mitochondrial dysfunctions may be one of the major causative factors underlying detrimental effects of benzalkonium chloride. *Oxid Med Cell Longev*. 2020;2020(14):8956504. doi:10.1155/2020/8956504
14. Kim M, Weigand MR, Oh S, et al. Widely used benzalkonium chloride disinfectants can promote antibiotic resistance. *Appl Environ Microbiol*. 2018;84(17):e01201-18. doi:10.1128/AEM.01201-18
15. Iwasaki T, Nejima R, Miyata K. Ocular surface flora and prophylactic antibiotics for cataract surgery in the age of antimicrobial resistance. *Jpn J Ophthalmol*. 2022;66(2):111-118. doi:10.1007/s10384-021-00899-5 Epub 2022 Jan 10. PMID: 35006494
16. Nordholt N, Kanaris O, Schmidt SBI, Schreiber F. Persistence against benzalkonium chloride promotes rapid evolution of tolerance during periodic disinfection. *Nat Commun*. 2021;12(1):6792. doi:10.1038/s41467-021-27019-8 PMID: 34815390; PMCID: PMC8611074
17. Ohtani S, Shimizu K, Nejima R, et al. Conjunctival bacteria flora of glaucoma patients during long-term administration of prostaglandin analog drops. *Invest Ophthalmol Vis Sci*. 2017;58(10):3991-3996. doi:10.1167/iovs.16-20853 PMID: 28796877
18. Lee J, Iwasaki T, Ohtani S, et al. Benzalkonium chloride resistance in *Staphylococcus epidermidis* on the ocular surface of glaucoma patients under long-term administration of eye drops. *Transl Vis Sci Technol*. 2020;9(8):9. doi:10.1167/tvst.9.8.9 PMID: 32855856; PMCID: PMC7422782
19. Hedengran A, Begun X, Müllertz O, et al. Benzalkonium chloride-preserved anti-glaucomatous eye drops and their effect on human conjunctival goblet cells in vitro. *Biomed Hub*. 2021;6(2):69-75. Published 2021 Aug 13. doi:10.1159/000517845

How to cite this article: D'andrea L, Montemagni M, Celenza G, Iorio R, Costagliola C. Is it time for a moratorium on the use of benzalkonium chloride in eyedrops? *Br J Clin Pharmacol*. 2022;1-3. doi:10.1111/bcp.15359