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PRESERVATIVES IN ANTIGLAUCOMA EYE DROPS MARKETED: USE PATTERNS AND OCULAR SURFACE SAFETY

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ABSTRACT

Background: Glaucoma is a chronic ophthalmic disease that frequently requires long-term or lifelong topical therapy. Antimicrobial preservatives are commonly incorporated into multidose ophthalmic preparations to prevent microbial contamination during use. However, chronic exposure to certain preservatives, particularly benzalkonium chloride (BAK), has raised concerns regarding ocular surface toxicity.

Objective: This study aimed to identify the antimicrobial preservatives used in antiglaucoma eye drops marketed in Morocco and to assess their potential ocular toxicity, with particular emphasis on BAK and available preservative-reducing or preservative-free alternatives.

Methods: A descriptive cross-sectional study of antiglaucoma eye drops marketed in Morocco was conducted using publicly available pharmaceutical information from the Moroccan Agency for Medicines and Health Products (AMMPS) and Medicament.ma. Information regarding active substances, pharmaceutical presentation, fixed-dose combinations and antimicrobial preservatives was obtained from the Summary of Product Characteristics (SmPC) or package leaflet, when applicable. Published literature was additionally reviewed to characterize the ocular effects of the identified preservatives.

Results: Thirty antiglaucoma eye-drop presentations were identified. Of these, 29 (96.7%) were multidose preparations and only one (3.3%) was a single-dose formulation. Fixed-dose combinations accounted for 46% of products, whereas 54% contained a single active substance. Among the preservatives identified, BAK predominated

(83%), followed by polyquaternium-1 (PQ-1; 11%) and benzododecinium bromide (BDD; 6%). BAK is a quaternary ammonium compound with detergent properties, and experimental and clinical evidence indicates that repeated exposure may adversely affect tear-film stability, corneal and conjunctival epithelial integrity and ocular surface inflammation. PQ-1, a high-molecular-weight polycationic preservative, appears to have a more favorable ocular surface tolerability profile.

Conclusion: Preserved multidose formulations, particularly BAK-containing preparations, predominated among the antiglaucoma eye drops evaluated in the Moroccan market. Considering the chronic nature of glaucoma treatment, cumulative preservative exposure should be considered when selecting topical therapy. Fixed-dose combinations, alternative preservatives, preservative-free formulations and preservative-free multidose delivery systems represent potential strategies for reducing preservative burden while maintaining effective intraocular pressure control.

Keywords: Glaucoma; Eye Drops; Antimicrobial Preservatives; Benzalkonium Chloride; Polyquaternium-1; Ocular Surface Disease; Preservative-Free; Morocco**.**

1 INTRODUCTION

Glaucoma is a chronic progressive optic neuropathy and a major cause of irreversible visual impairment worldwide. Reduction of intraocular pressure (IOP) remains the principal modifiable therapeutic target, and topical IOP-lowering medications continue to play a central role in glaucoma management. Because treatment is generally prolonged and frequently lifelong, long-term tolerability of topical therapy is particularly important [1,2]. Conventional multidose ophthalmic preparations commonly contain antimicrobial preservatives to prevent microbial contamination during repeated use. These agents contribute to the microbiological safety of multidose containers but are repeatedly delivered to the ocular surface together with the active pharmaceutical ingredient [2–4]. Benzalkonium chloride (BAK) has historically been the most widely used antimicrobial preservative in ophthalmic formulations. It belongs to the quaternary ammonium family and combines antimicrobial activity with surfactant properties [3–5]. Although these properties contribute to antimicrobial efficacy, interaction with lipid membranes may also affect mammalian epithelial cells and ocular surface homeostasis [3–6].

Chronic exposure to preserved antiglaucoma medications, particularly those containing BAK, has been associated with tear-film instability, corneal and conjunctival epithelial abnormalities, inflammation and symptoms of ocular surface disease (OSD) [5–8]. These effects are particularly relevant in glaucoma because patients may receive one or several topical medications daily over many years, thereby increasing cumulative exposure to preservatives. Alternative strategies have consequently been developed, including preservatives with potentially improved ocular tolerability such as polyquaternium-1 (PQ-1), oxidative preservative systems, preservative-free single-dose preparations and multidose containers designed to maintain microbiological protection without requiring conventional antimicrobial preservatives [7–10]. The availability and distribution of these different formulations may vary considerably between pharmaceutical markets. Data describing preservatives contained in antiglaucoma preparations available in Morocco remain limited. Therefore, the present study aimed to identify the antimicrobial preservatives used in antiglaucoma eye drops marketed in Morocco, characterize their distribution and discuss their ocular safety on the basis of available experimental and clinical evidence.

2 MATERIALS AND METHODS

2.1 Study design

A descriptive cross-sectional study was conducted to characterize antimicrobial preservatives contained in antiglaucoma ophthalmic preparations marketed in Morocco.

Identification of antiglaucoma eye drops Information on marketed medicinal products was obtained from the Moroccan Agency for Medicines and Health Products (AMMPS) and from Medicament.ma.

Antiglaucoma ophthalmic medicinal products identified as commercially available in Morocco during the study period were included.

2.2 Data collection

For each medicinal product, information was collected from the Summary of Product Characteristics (SmPC) or, when necessary, from the package leaflet.

The following variables were recorded:

- active substance(s);
- pharmaceutical presentation (single-dose or multidose);
- presence of a single active substance or a fixed-dose combination;
- presence of an antimicrobial preservative;
- identity of the antimicrobial preservative;
- preservative concentration, when available.

The analysis focused specifically on antimicrobial preservatives rather than on all excipients contained in the ophthalmic formulations.

2.3 Assessment of preservative safety

Published experimental and clinical literature was reviewed to characterize the ocular effects of the preservatives identified in marketed products, with particular attention to BAK and PQ-1. Evidence concerning preservative-associated ocular surface alterations, alternative preservatives and preservative-free glaucoma therapy was considered when interpreting the descriptive findings [3–10].

2.4 Data analysis

Data were analyzed descriptively. Categorical variables are presented as numbers and percentages. No inferential statistical analysis was performed.

3 RESULTS

3.1 Pharmaceutical presentation

A total of 30 antiglaucoma eye-drop presentations were identified. Multidose formulations predominated markedly, representing 29 of 30 presentations (96.7%), whereas only one formulation (3.3%) was available as a single-dose presentation.

Thus, the Moroccan market evaluated in this study was overwhelmingly dominated by multidose ophthalmic delivery systems.

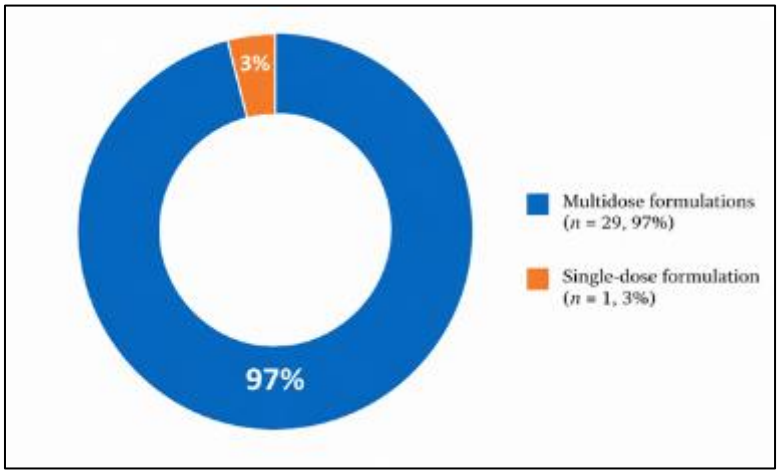


Figure 1: Distribution of antiglaucoma eye drops according to multidose or single-dose presentation.

Among the evaluated products, 54% contained a single active substance, whereas 46% were fixed-dose combinations. Fixed-dose combinations therefore represented almost half of the antiglaucoma formulations included in the survey. (Figure 2)

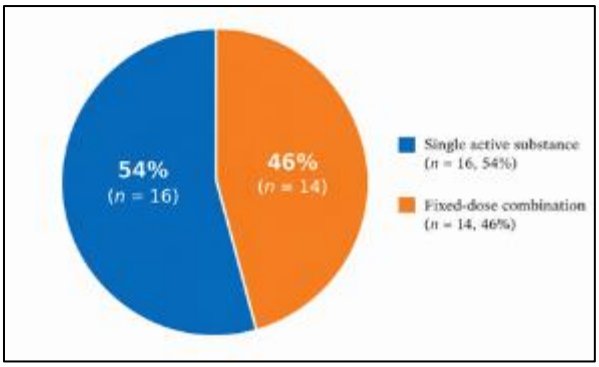


Figure 2: Distribution of antiglaucoma eye drops according to single-agent or fixed-dose combination formulation.

Three antimicrobial preservatives were identified:

- benzalkonium chloride (BAK): 83%;
- polyquaternium-1 (PQ-1): 11%;
- benzododecinium bromide (BDD): 6%.

BAK was therefore by far the predominant preservative among the evaluated formulations.

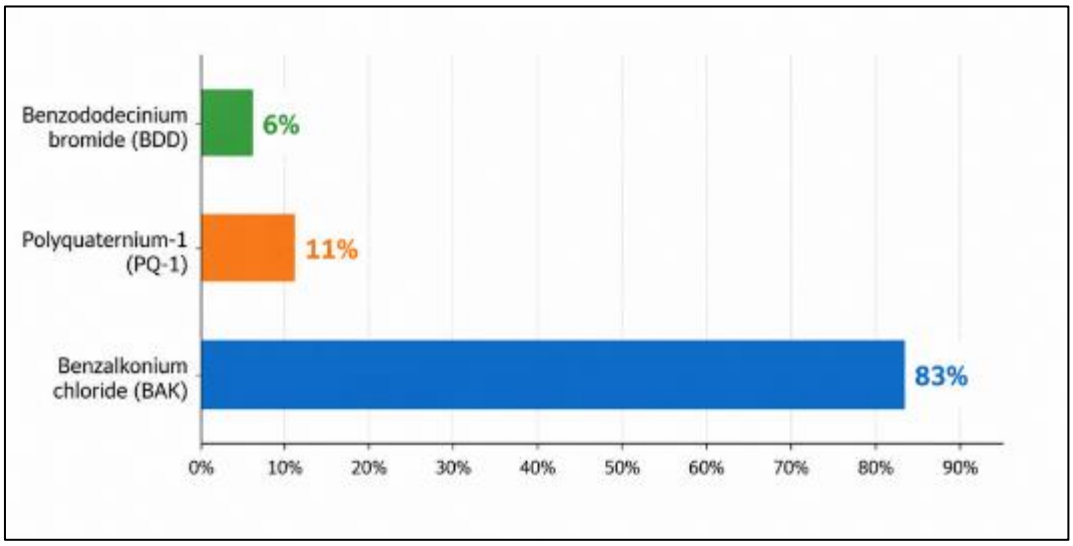


Figure 3: Distribution of antimicrobial preservatives identified in antiglaucoma eye drops marketed in Morocco.

BAK is a mixture of alkylbenzyldimethylammonium chlorides and has been extensively used as an antimicrobial preservative in ophthalmic preparations [3–5].

BAK is generally used in ophthalmic preparations at relatively low concentrations. In the original analysis, concentrations ranging from approximately **0.004% to 0.02%** were considered. Its molecular structure combines a positively charged hydrophilic region with a hydrophobic alkyl chain, allowing interaction with lipid membranes. This physicochemical property contributes to antimicrobial activity but also explains its detergent effect on biological membranes [3–6]. Experimental evidence indicates that BAK-related cytotoxicity is dependent on both concentration and exposure duration. Reported effects include alterations in tear-film stability, epithelial cell damage, inflammatory responses and delayed corneal epithelial healing [3–8].

3.2 Polyquaternium-1

PQ-1 (Polyquad®) is a polycationic quaternary ammonium preservative with a substantially larger molecular size than BAK [9].Although it possesses antimicrobial activity through interactions with microbial membranes, its high molecular weight is thought to limit penetration into mammalian cells. Experimental and clinical evidence generally suggests a

more favorable ocular surface tolerability profile than that associated with conventional BAK-containing formulations [7,9]. In the evaluated Moroccan formulations, PQ-1 represented **11%** of the identified preservatives.

3.3 Benzododecinium bromide

BDD accounted for **6%** of the preservatives identified. Like BAK, BDD belongs to the quaternary ammonium family and possesses antimicrobial properties. Its use was substantially less frequent than that of BAK in the formulations evaluated in this study.

4 DISCUSSION

The principal finding of this study is the marked predominance of preserved multidose formulations among antiglaucoma eye drops marketed in Morocco. Of the 30 presentations identified, 29 were multidose formulations, while BAK accounted for 83% of the preservatives identified. These findings are particularly relevant because glaucoma treatment differs from short-term ophthalmic therapy. Patients may receive one or several topical medications daily for many years. Consequently, even low preservative concentrations can result in repeated and cumulative ocular surface exposure [5–8].

4.1 Predominance of BAK

The predominance of BAK observed in the present study is consistent with its longstanding use as a major antimicrobial preservative in ophthalmic preparations [3–7].

BAK provides effective antimicrobial preservation and is compatible with numerous ophthalmic formulations. Its surfactant activity may also modify corneal epithelial permeability. However, this detergent property constitutes an important limitation because BAK can interact with mammalian cell membranes [3–6]. Experimental studies have demonstrated concentration- and exposure-time-dependent effects on ocular epithelial cells. Goldstein et al. further highlighted that repeated exposure to BAK may affect multiple ocular tissues and that the cumulative preservative burden should be considered in chronically treated patients [6].

4.2 BAK and ocular surface disease

OSD is frequently reported among patients receiving chronic topical glaucoma therapy. Manifestations can include ocular discomfort, burning, foreign-body sensation, dry-eye symptoms, conjunctival hyperemia, reduced tear-film stability and corneal epithelial abnormalities [7,8,11]. Several mechanisms may contribute to these effects. BAK may alter the tear-film lipid layer, disrupt epithelial cell membranes, induce cellular stress and promote inflammatory responses within the conjunctiva and cornea [5–8]. Recent systematic evidence supports an association between prolonged BAK exposure and ocular surface alterations, including increased corneal staining, reduced tear-film stability and higher OSDI scores [7]. Nevertheless, the relationship between BAK and clinically significant ocular toxicity should be interpreted cautiously. OSD in patients with glaucoma is multifactorial. The active pharmaceutical ingredient, number of medications, instillation frequency, treatment duration, baseline ocular surface status, age and concomitant ocular conditions may all influence tolerability [7,8,11]. Importantly, Hedengran et al. evaluated 16 randomized controlled trials comparing BAK-preserved eye drops with alternatively preserved or preservative-free formulations [12]. Their meta-analysis of IOP outcomes included 4,201 patients and did not demonstrate a clinically significant difference in IOP-lowering efficacy. Clear differences for several safety outcomes could not be established, partly because of heterogeneous safety reporting and methodological limitations [12].

Thus, available evidence supports reducing unnecessary preservative exposure, particularly in susceptible patients, without implying that every BAK-containing formulation is necessarily clinically harmful.

4.3 Polyquaternium-1 and alternative preservatives

PQ-1 represented 11% of preservatives identified in the present study. Although PQ-1 belongs to the broader quaternary ammonium group, its polymeric structure and considerably greater molecular size differentiate it from BAK [9]. PQ-1 maintains antimicrobial activity while exhibiting a generally more favorable ocular surface tolerability profile. Rolando et al. described PQ-1 as a viable alternative to BAK in ophthalmic formulations [9]. More recent systematic evidence also identifies Polyquad® and other alternative preservative systems among approaches that may reduce preservative-associated ocular surface damage [7]. Other preservative systems, including stabilized oxychloro complexes such as Purite® and ionic-buffer systems such as SofZia®, have also been developed with the aim of maintaining antimicrobial efficacy while improving ocular surface tolerability [7]. However, improved tolerability should not be interpreted as complete biological inertness. The ocular effects of a preserved formulation depend on the preservative, its concentration, the vehicle, the active pharmaceutical ingredient and cumulative exposure.

4.4 Preservative-free formulations

The very low proportion of single-dose presentations observed in the studied sample highlights an important potential area for diversification of antiglaucoma therapy in Morocco. Preservative-free formulations eliminate direct exposure to antimicrobial preservatives and may be particularly useful in patients with pre-existing OSD, intolerance to preserved medications, long anticipated treatment duration or exposure to multiple topical therapies [7,10,13]. Clinical evidence supports the feasibility of switching to preservative-free treatment without compromising IOP control. Denis et al. reported clinical benefits following the use of preservative-free latanoprost in patients with open-angle glaucoma or ocular hypertension [13].

More recently, Bacharach et al. compared preservative-free latanoprost 0.005% with BAK-preserved latanoprost 0.005% in a randomized phase III trial involving 335 patients with primary open-angle glaucoma or ocular hypertension [14]. Preservative-free latanoprost provided effective IOP control comparable to the BAK-preserved formulation, while supporting the use of a preservative-free alternative in chronically treated patients. Additional randomized studies have similarly investigated ocular surface outcomes following treatment with preserved versus preservative-free prostaglandin analogues [15,16]. Importantly, preservative-free therapy is no longer necessarily restricted to conventional single-dose containers. Modern multidose delivery systems can use mechanical valves, filtration systems or other technological approaches to limit microbial contamination without requiring an antimicrobial preservative in the formulation. Such systems may combine the convenience of multidose administration with avoidance of chronic preservative exposure.

4.5 Role of fixed-dose combinations

Fixed-dose combinations represented 46% of the formulations identified in the present study. This finding has potential implications for cumulative preservative exposure. Patients requiring several IOP-lowering agents may otherwise administer multiple separate eye drops each day, potentially increasing the number of preservative-containing instillations. Combining active substances in a single formulation can reduce the number of daily instillations and may consequently reduce preservative exposure compared with administration of the same active substances from separate preserved bottles. Recent clinical evidence reinforces the potential role of preservative-free fixed-dose combinations. In a randomized trial comparing preserved and preservative-free brimonidine/timolol fixed combinations, IOP-lowering efficacy was maintained, while the preservative-free group showed advantages for several ocular surface and tolerability parameters [17]. More recent evidence has also evaluated preservative-free fixed combinations containing timolol, dorzolamide and brimonidine, illustrating the continuing development of preservative-free multidrug strategies for glaucoma management [18]. Fixed-dose combinations may additionally simplify therapeutic regimens and potentially improve treatment convenience. Nevertheless, the preservative composition of the combination itself remains relevant, and a preserved fixed-dose combination should not be considered equivalent to preservative-free therapy.

4.6 Clinical implications

Preservative selection should be integrated into the overall therapeutic strategy rather than considered independently of the active glaucoma treatment. For patients who tolerate preserved therapy and have a healthy ocular surface, continued treatment may remain appropriate. Conversely, OSD, dry-eye symptoms, allergy, chronic ocular inflammation, multiple topical therapies or high cumulative exposure should prompt consideration of strategies to reduce preservative burden [7,8,11]. Potential strategies include reducing the number of daily preserved instillations, using fixed-dose combinations when clinically appropriate, selecting alternative preservatives with more favorable ocular tolerability, and using preservative-free single-dose or multidose formulations. Current research continues to compare BAK-preserved, alternatively preserved and preservative-free glaucoma therapies, reflecting persistent uncertainty regarding the optimal balance between antimicrobial protection, ocular surface safety and treatment practicality [19].

5 CONCLUSION

This descriptive study demonstrates that the antiglaucoma eye drops evaluated in the Moroccan market were predominantly multidose formulations and that BAK was by far the most frequently identified antimicrobial preservative. While antimicrobial preservation remains important for maintaining the microbiological quality of conventional multidose ophthalmic preparations, chronic exposure to BAK may contribute to ocular surface alterations, particularly in susceptible patients and those receiving long-term multidrug therapy. The choice of glaucoma therapy should therefore consider not only IOP-lowering efficacy but also long-term ocular surface tolerability and cumulative preservative exposure. Greater use of fixed-dose combinations, alternative preservatives with improved tolerability, preservative-free formulations and preservative-free multidose delivery technologies may help reduce preservative burden while maintaining effective glaucoma treatment. Given the chronic nature of glaucoma, optimization of the

entire ophthalmic formulation—not solely the active pharmaceutical ingredient—should be considered an integral component of long-term patient care.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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