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ORIGINAL RESEARCH

Impact of topical bimatoprost 0.01% and bimatoprost 0.03% on conjunctival irritation in rabbits

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Introduction: The purpose of this study was to examine and compare the conjunctival irritation (congestion, swelling, and discharge) of topical bimatoprost ophthalmic solution 0.01% and bimatoprost ophthalmic solution 0.03% in rabbits.

Methods: Six healthy New Zealand White rabbits were treated with either bimatoprost 0.01% or bimatoprost 0.03% (3 animals/group). One dose (2 drops/dose) of study medication was administered to the right eye of each animal every 30 minutes for 4.5 hours. Approximately 1 hour after the last dose, conjunctival irritation was assessed using a slit-lamp biomicroscope to individually evaluate conjunctival congestion, swelling, and discharge.

Results: The mean conjunctival congestion, swelling and discharge scores for bimatoprost 0.03% were 1.67, 0.33 and 0.33, respectively, and for bimatoprost 0.01% were 2.00, 0.33 and 1.33, respectively.

Conclusions: Despite the lower drug concentration of the 0.01% formulation, bimatoprost 0.01% does not reduce conjunctival irritation, including conjunctival congestion, swelling, and discharge, in rabbits compared to bimatoprost 0.03%. Further studies would be needed to determine whether the increase in the mean conjunctival congestion and discharge scores may be attributed to the increased BAK concentration in the bimatoprost 0.01% formulation.

Keywords: bimatoprost, conjunctiva, ocular toxicity, preclinical, prostaglandin analog, rabbits

Introduction

Reduction of elevated intraocular pressure (IOP) is the only modifiable risk factor for glaucoma, the second leading cause of vision loss worldwide.[1] Prostaglandin analogs are one class of drugs commonly used to reduce IOP. Bimatoprost 0.03% (Lumigan®; Allergan, Inc., Irvine, CA, USA), one such prostaglandin analog,[2,3] reduces IOP by 6.5 to 8.9 mmHg in patients with open-angle glaucoma or ocular hypertension.[4–6] However, this agent is not without side effects; conjunctival congestion is the most frequent adverse event of bimatoprost, affecting 45% of patients and accounting for discontinuation of therapy in 3% of patients.[7]

A new formulation of bimatoprost has been developed that has a lower concentration of drug (0.01%; Lumigan; Allergan, Inc.) in an attempt to improve the safety profile of this agent. The new formulation also has a 4-fold increase in the amount of benzalkonium chloride (BAK) (0.02%) compared to the original formulation (0.005%). BAK is a preservative commonly used in topical ophthalmic agents, but evidence suggests that it may also facilitate drug delivery. Specifically, it has been shown to increase transcorneal drug penetration in rabbits.[8] This characteristic can

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potentially be explained by a loss of tight junctions in the corneal epithelium, which could improve corneal penetration. In fact, McCarey and Edelhauser demonstrated that eyes treated with topical drugs containing BAK display a preferential loss of epithelial tight junctions.[9] However, the presence of BAK in ophthalmic preparations may also cause ocular toxicity, as demonstrated by numerous *in vitro* and *in vivo* studies.[10–15] Thus, the increase in BAK concentration of the new bimatoprost formulation may have implications not only for drug penetration but also for drug safety. The goal of the current study was to examine and compare conjunctival irritation (congestion, swelling, and discharge) of topical ocular bimatoprost 0.01% and bimatoprost 0.03% in rabbits.

Methods

Six healthy New Zealand White rabbits were divided into 2 treatment groups (3 animals per group): commercially available bimatoprost ophthalmic solution 0.01% (Lumigan 0.01%, Allergan Inc., Ontario, Canada) and bimatoprost ophthalmic solution 0.03% (Lumigan 0.03%, Allergan Inc., Irvine, CA). One dose of the bimatoprost ophthalmic solutions (2 drops/dose) was administered to the right eye of each animal every 30 minutes for 4.5 hours, for a total of 10 doses (20 drops). Approximately 1 hour after the last dose, conjunctival irritation of the study eye was assessed using a slit-lamp biomicroscope to individually evaluate conjunctival congestion, swelling, and discharge, according to the Hackett and McDonald Scoring System (Table 1).[16]

Results

The mean conjunctival irritation scores are shown in Table 2. Approximately one hour after the last dose of bimatoprost ophthalmic solutions, mean conjunctival swelling was similar in both groups (0.33 ± 0.6), but both mean conjunctival congestion and discharge scores were higher for bimatoprost 0.01% (2.00 ± 0.0 and 1.33 ± 0.6, respectively) than for bimatoprost 0.03% (1.67 ± 0.6 and 0.33 ± 0.6, respectively).

Discussion

In this study, both formulations of bimatoprost caused mild to moderate conjunctival irritation in rabbits. After an exaggerated dosing of 20 drops over 4.5 hours, it was noted that congestion was the primary conjunctival toxicity caused by bimatoprost in this study, which is consistent with the safety profile of this agent in clinical studies.[7,17–19]

The conjunctival congestion and discharge scores observed after the last dose were higher for bimatoprost 0.01% than for bimatoprost 0.03% (congestion: 2.00 vs 1.67; and discharge: 1.33 vs 0.33). Thus, despite the reduced concentration of bimatoprost in the 0.01% formulation, no improvement in ocular toxicity scores was observed. While the number of animals per group was small, the individual animal responses within each group were similar, supporting this conclusion.

A potential explanation for these results may be related to the BAK concentrations present in the two bimatoprost formulations. Bimatoprost 0.03% contains one of the lowest levels of BAK typically used in ophthalmic preparations, 0.005%, whereas bimatoprost 0.01% contains one of the highest levels, 0.02%. It is well established that BAK alone causes both corneal and conjunctival toxicity in preclinical testing;[10–12,15,20,21] this same association between BAK and ocular toxicity is also observed when comparing BAK-preserved to BAK-free topical ocular medications, either under *in vitro* conditions[22–24] or using a rabbit model similar to the current study.[25–31] Not surprisingly, clinical studies of patients with glaucoma have reported increased ocular toxicity with medications containing BAK.[14,32–34] Moreover, ocular surface effects caused by BAK are dose-dependent,[11,12,21]

Table 1 Conjunctival irritation scales

Conjunctival assessment	Scale				
	0	1	2	3	4
Congestion	None	Flushed reddish; slight perilimbal injection	Bright red; ≥75% perilimbal injection	Dark, beefy red; bulbar, palpebral, perilimbal injection; presence of petechia	N/A[a]
Swelling	None	Swelling above normal with no lid eversion	Swelling with misalignment of lids; upper > lower	Swelling with partial eversion; upper = lower	Marked eversion; upper > lower
Discharge	None	Present on inner portion of eye	Abundant on lids and hair	Marked discharge on periocular skin	N/A[a]

[a]NA, not applicable.

Table 2 Mean conjunctival irritation scores (n = 3)[a]

Conjunctival assessment	Bimatoprost 0.03%	Bimatoprost 0.01%
Congestion	1.67 ± 0.6	2.00 ± 0.0
Swelling	0.33 ± 0.6	0.33 ± 0.6
Discharge	0.33 ± 0.6	1.33 ± 0.6

[a]Data presented as mean ± SD.

which suggests that the higher concentration of BAK in bimatoprost 0.01% may increase any BAK-associated toxicity. The European Medicines Agency (EMEA) has recognized the ocular surface effects of ophthalmic preservatives and recommends using preservative-free formulations or the lowest concentration of preservative with satisfactory antimicrobial effectiveness. Therefore, increasing the concentration of BAK by 4-fold in the bimatoprost 0.01% formulation, relative to the bimatoprost 0.03% formulation, is not in accordance with the EMEA's position and has a negative impact on the benefit-to-risk ratio for the product.[35]

Due to the potential differences between rabbits and humans in response to BAK-induced ocular toxicity, the differences in the dosing methodology of this animal study as compared to dosing in a clinical setting, and the varying concentrations of bimatoprost, the two bimatoprost formulations investigated in this study should be evaluated for both safety and efficacy in a randomized clinical trial. Nonetheless, the current study suggests that, despite its lower drug concentration, bimatoprost 0.01% does not reduce conjunctival irritation in rabbits compared to bimatoprost 0.03%.

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Disclosures

The authors are employees of Alcon Research, Ltd.

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