

Role of fixed-combination brinzolamide 1%/timolol 0.5% in the treatment of elevated intraocular pressure in open-angle glaucoma and ocular hypertension

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Abstract: Brinzolamide 1%/timolol 0.5% is a new fixed-combination for the treatment of open-angle glaucoma or ocular hypertension. Brinzolamide/timolol has a favorable safety profile, with an incidence of ocular burning and stinging <5%. Published data show that brinzolamide 1%/timolol 0.5% and dorzolamide 2%/timolol 0.5% have similar efficacies for lowering intraocular pressure (IOP). There is some evidence that brinzolamide/timolol may be more comfortable. Although patients receiving brinzolamide/timolol may experience more blurred vision on instillation, some data show a preference for brinzolamide/timolol over dorzolamide/timolol. Although available data to assess the role of brinzolamide/timolol in daily clinical practice are still limited, these first results suggest the agent to be a reasonable alternative for patients who do not reach target IOP with monotherapy.

Keywords: brinzolamide, dorzolamide, fixed combination, glaucoma, IOP, timolol

Introduction

Reduction of elevated intraocular pressure (IOP) is the only proven approach to protect against visual field loss in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT), making ocular hypotensive agents critical to the management of these patients. First-line therapy for elevated IOP is typically a single topical agent from one of the following classes of drugs: alpha-2 adrenergic receptor agonists, beta-blockers, topical carbonic anhydrase inhibitors (CAIs), and prostaglandin derivatives/prostamides.¹ If single-agent therapy is effective but not sufficient to reach a patient's target IOP, a second hypotensive drug is added. Evidence shows that this strategy can produce an additional IOP decrease.² The 2-drug combination can be comprised of 2 individual agents or a fixed-combination product. A recent meta-analysis confirmed that these 2 types of glaucoma therapies produce equivalent efficacy.³ In a large study (N = 3333) of patients taking glaucoma medications, the majority (79%) reported that they were satisfied with their eye drops; however, nearly 1 in 10 patients (9%) were likely to have their medication changed at their next visit due to side effects.⁴ Each hypotensive agent has a characteristic side effect profile, but fixed-combination products as a group have a number of advantages over the instillation of 2 individual drugs.⁵ First, a fixed-combination product requires dispensing from only 1 bottle, making it more convenient than dispensing 2 separate doses. The European Glaucoma Society recommended that fixed-combination products be used, whenever available, in place of 2 separate instillations.¹ Fixed-combination products

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also avoid washout, which occurs when inadequate time is allowed between instillation of the first and second drugs.⁶ Moreover, the lifetime exposure to preservatives is reduced with fixed-combination products. Because preservatives have been shown to be associated with both *in vitro* ocular toxicities (eg, cellular apoptosis, conjunctival inflammation),^{7,8} and clinical signs and symptoms of ocular irritation (eg, dry eye, burning/stinging, discomfort),^{9,10} reducing exposure to preservatives should facilitate the maintenance of ocular surface health in these patients requiring chronic topical therapies. Finally, costs and impact on quality of life can lead to non-compliance in patients who have to use multiple medications. Some of these disadvantages can also be reduced by using fixed combinations.¹¹

The fixed-combination dorzolamide 2%/timolol 0.5% (Cosopt®; Merck & Co., Inc., Whitehouse Station, NJ, USA) has been shown to be at least as effective as separate instillations of the component drugs.¹² Side effects that have been described are ocular stinging and burning upon instillation and a bitter taste.¹³ The safety profiles of the individual components show that the incidence of stinging and burning of the fixed-combination product is most similar to dorzolamide (Trusopt®; Merck & Co., Inc., Whitehouse Station, NJ, USA) alone.¹⁴ Recently, the fixed combination dorzolamide/timolol has also become available in several countries in a preservative-free variant. Recently, a new fixed-combination product, brinzolamide 1%/timolol 0.5% (Azarga®; Alcon Laboratories, Inc., Fort Worth, TX, USA), has been introduced. The aim of this review article is to explore the molecular and clinical characteristics of brinzolamide/timolol to determine its potential role in the management of patients with OAG or OHT.

Brinzolamide 1%/timolol 0.5%

The brinzolamide/timolol fixed combination is comprised of the CAI brinzolamide and the beta-blocker timolol and is recommended to be dosed twice daily (bid).¹⁵ It is delivered as a suspension with a pH of 7.2 and is preserved with benzalkonium chloride 0.01%.¹⁵ The concentration of brinzolamide is 1% (10 mg/mL), equal to that of brinzolamide ophthalmic suspension (Azopt®; Alcon Laboratories, Inc., Fort Worth, TX, USA)¹⁶ and the timolol concentration is 0.5% (5 mg/mL), equal to that of single-agent timolol.¹⁷⁻¹⁹

Mechanisms of action and pharmacokinetics

Brinzolamide is a highly specific, reversible inhibitor of carbonic anhydrase, an enzyme which is present in the lens,

cornea, ciliary body and retina.^{20,21} Blocking this enzyme is believed to reduce aqueous humor formation by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.¹⁶ Brinzolamide-induced inhibition of CA II, a key carbonic anhydrase isoenzyme, occurs both during the day and at night, apparently not subjected to the circadian rhythm.^{22,23} A single drop of brinzolamide can lower IOP for approximately 12 hours, and its washout time after chronic instillation is 7 days.²²

Contraindications of topical carbonic anhydrase inhibitors are renal failure and sulfonamide allergy. Caution should be taken in patients with a compromised corneal endothelium.

Beta-adrenergic antagonists (beta blockers) reduce IOP through blocking of the B₁-adrenoreceptor (non-selective and selective beta blockers) and B₂-adrenoreceptors (non-selective beta blockers) of the ciliary body epithelium which leads to a reduced inflow of aqueous humor in the anterior chamber of the eye. Most beta blockers are dosed bid, although the gel-forming solutions are often equally efficacious in a once daily regime.²⁴⁻²⁶ The activity of timolol is subject to circadian changes, showing less efficacy at night.²⁷ Contraindications for the use of timolol are asthma, obstructive pulmonary disease, sinus bradycardia and heart block.

Effect on ocular blood flow

Some aspects of ocular blood flow may be reduced in certain patients with glaucoma.²⁸ Reduced ocular perfusion pressure probably is an independent risk factor for the development of OAG.²⁹⁻³⁴

Numerous studies have shown that timolol does not affect ocular blood flow,³⁵⁻³⁷ however, several studies have reported a possible increased resistance to blood flow.^{38,39} Although there is no conclusive evidence, many studies have suggested that the topical carbonic anhydrase inhibitor dorzolamide probably has a positive effect on ocular blood flow. In addition, a positive effect on ocular blood flow for the fixed combination of dorzolamide/timolol has been shown.⁴⁰⁻⁴⁶ The effect of brinzolamide on ocular blood flow is less well established, mainly due to a limited number of publications on the subject. Several studies have shown that brinzolamide positively affects ocular blood flow,⁴⁷⁻⁴⁹ but others have shown no effect.^{50,51} Until now, the effects of brinzolamide/timolol on ocular blood flow have been unclear. Studies on the effects of the combination brinzolamide/timolol (concomitant or fixed combination) on ocular blood flow are scarce.

IOP-lowering efficacy

We performed a systematic review of the IOP-lowering efficacy of the combination of brinzolamide and timolol. Articles were identified through a computerized search in Medline, Embase, and the Cochrane Controlled Trials Register. For details on search strategy, selection process and data extraction we refer to the papers of van der Valk et al⁵² and Webers et al^{2,53}. Potentially eligible for inclusion in this systematic review were randomized clinical trials on the combination of timolol and brinzolamide written in English, French, German or Dutch and published between January 1995 and July 2009.

The initial search revealed 1169 papers. Based on the title, abstract and medical subject heading (MeSH) words, 1128 papers were excluded. The most important reasons for excluding articles were that the primary endpoint in the studies was not IOP but, for instance, side-effects, visual field outcome or impact on ocular blood flow, that articles reported on glaucoma topics other than IOP lowering of drugs, or that studies reported on IOP lowering of monotherapies. From the remaining 41 papers that were printed or photocopied 36 papers had to be excluded. The major reasons were a non-randomize design (n = 9), a combination of other drugs (n = 7) or a different outcome parameter (n = 9).

The results of the included studies⁵⁴⁻⁵⁸ are shown in Table 1.

An earlier systematic review showed no significant differences between concomitant and fixed use of the combination of 0.5% timolol bid and 2% dorzolamide bid.² The mean additional IOP decrease of 2% dorzolamide bid or tid when added to 0.5% timolol bid was 15.7% at trough and 20.1% at peak.⁵³ The present study gives similar results for the IOP decrease of the concomitant use of 0.5% timolol bid and 1% brinzolamide bid or tid, varying between 13.2% at trough and 20.3% at peak. The 2 papers reporting on the fixed combination brinzolamide/timolol^{57,58} revealed similar IOP-lowering results. These studies both used a washout design. Moreover, the Manni study⁵⁸ also reported similar IOP-lowering results for the brinzolamide/timolol combination when directly compared with the fixed combination dorzolamide/timolol.

Safety and tolerability

In the study by Kaback⁵⁷ et al a higher incidence of blurred vision was found in the group of patients treated with brinzolamide/timolol versus patients treated with timolol 0.5% alone; however, reported dysgeusia was markedly lower with the fixed combination. The Manni study showed similar

safety profiles for brinzolamide/timolol and dorzolamide/timolol, with the exceptions of a lower incidence of any adverse events and fewer patients with ocular burning and stinging. In the brinzolamide/timolol group, a higher incidence of blurred vision was reported.⁵⁸

A study by Vold and colleagues⁵⁹ directly examined the ocular discomfort associated with the use of brinzolamide/timolol or dorzolamide/timolol after 1 week of dosing. Mean ocular discomfort scores (judged from a scale of 0 [none] to 4 [very severe]) were significantly lower in patients receiving brinzolamide/timolol than in those receiving dorzolamide/timolol. Although this study had a very short follow-up period, the results confirm the results from the Manni study.

Because the beta-blocker component of the 2 CAI-containing fixed-combination products is identical, any dissimilarities in tolerability are likely due to differences in pH between brinzolamide and dorzolamide. Dorzolamide/timolol is formulated at an acidic pH of 5.65,¹³ whereas brinzolamide/timolol has a near physiologic pH of 7.2.¹⁵ This hypothesis is supported by results from 2 multicenter studies published in 2000 which used study designs similar to the Vold comfort study, comparing the ocular comfort of the single agents brinzolamide and dorzolamide.⁶⁰ Significantly more patients in both studies reported no ocular discomfort with brinzolamide than with dorzolamide. In an ocular discomfort study in which patients taking latanoprost, dorzolamide, and timolol combination therapy were randomized to switch the CAI component to brinzolamide or to continue dorzolamide, patients in the brinzolamide group, but not the control group, experienced a significant decrease in ocular irritation, although these patients had a numerical increase in blurred vision.⁶¹ Another study from Michaud and colleagues, which compared brinzolamide and dorzolamide each given twice daily in addition to timolol 0.5%, also found significantly less ocular burning and stinging in the brinzolamide group.⁵⁵

The results from the studies mentioned above suggest that brinzolamide/timolol may be more tolerable than (preserved) dorzolamide/timolol, at the cost of an increase in blurred vision. The authors are not aware of any studies comparing the ocular comfort of unpreserved dorzolamide/timolol to preserved dorzolamide/timolol or other topical medication.

Patient preference

All of the clinical characteristics described above – efficacy, safety, and tolerability – probably affect patient preference. Patient preference, in turn, may improve adherence. Barnebey et al suggested that better patient adherence after

Table I Run-in medication, treatment combination after adding brinzolamide, baseline characteristics, time point(s) of intraocular pressure measurements and absolute (mmHg) and relative (%) decrease from baseline intraocular pressure for peak and trough time points

Trial	Run-in medication	Treatment combination after run-in	No. of patients baseline (% with-drawals)	Sex (M/F)	Mean age (y)	POAG (%)
Trough						
Shin 2000 ⁵⁴	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide tid	53 (11.3)	28/25	61	59
Michaud et al 2001 ⁵⁵	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide bid	104 (6.7)	54/50	nr	57
Martinez et al 2009 ⁵⁶	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide bid	76 (54)	41/35	64	100
Kaback et al 2008 ⁵⁷	washout	0.5% timolol/1% brinzolamide bid (fixed)	171 (7.5)	80/91	nr	63
Manni et al 2009 ⁵⁸	washout	0.5% timolol/1% brinzolamide bid (fixed)	220 (7.3)	96/124	65	78
Peak						
Shin 2000 ⁵⁴	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide tid	53 (11.3)	28/25	61	59
Michaud et al 2001 ⁵⁵	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide bid	104 (6.7)	54/50	nr	57
Martinez et al 2009 ⁵⁶	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide bid	76 (54)	41/35	64	100
Kaback et al 2008 ⁵⁷	washout	0.5% timolol/1% brinzolamide bid (fixed)	171 (7.5)	80/91	nr	63
Manni et al 2009 ⁵⁸	washout	0.5% timolol/1% brinzolamide bid (fixed)	220 (7.3)	96/124	65	78

a transition from dorzolamide to brinzolamide correlated with a patient preference for brinzolamide.⁶² In a crossover study, Mundorf and colleagues found better comfort scores for brinzolamide/timolol than for dorzolamide/timolol.⁶³ Although the follow up in this study was very limited, a majority of patients preferred brinzolamide/timolol. Ocular burning and stinging are very frequent side effects of topical glaucoma medications.⁴ In a willingness-to-pay analysis of topical ocular medications, it was found that nearly 75% of patients would be willing to pay a premium for a medication that would eliminate stinging and burning upon instillation.⁶⁴

Summary

Published data show that brinzolamide 1%/timolol 0.5% and dorzolamide 2%/timolol 0.5% have similar efficacies for lowering IOP. The main difference between these agents appears to be in the safety profiles, with dorzolamide/timolol producing more ocular burning and stinging, probably due to differences in pH. In several studies,

brinzolamide/timolol was rated as the more comfortable medication for new users. Although patients receiving brinzolamide/timolol may experience more blurred vision upon instillation, some data suggest a preference for brinzolamide/timolol over dorzolamide/timolol in new users. However, the follow up of these studies was short or very short. Patients who have used their medication for a longer period may probably be more satisfied with their medication. The effect of excluding preservatives in dorzolamide/timolol on comfort and/or patient preference has not been studied.

Thus, although available data to assess the role of brinzolamide/timolol are still limited, its apparently similar efficacy and probably improved tolerability relative to dorzolamide/timolol make it a reasonable alternative for patients who do not reach target IOP with monotherapy.

Further evaluation of the fixed combination brinzolamide/timolol in daily clinical practice will elucidate how this novel combination agent will be accepted by physicians and ultimately incorporated into the management of patients with elevated IOP.

OHT (%)	Endpoint of measurement (months)	Baseline IOP (mmHg) mean \pm SD	Time point(s) of IOP measurements	IOP decrease (mmHg) mean \pm SD	IOP decrease (%) mean \pm SD
41	1	25.5 \pm nr	+0 timolol +0 brinzolamide	-3.3 \pm nr	-13.2 \pm nr
37	1	25.5 \pm 1.9	+0 timolol +0 brinzolamide	-3.6 \pm 3.0	-14.1 \pm 11.4
0	60	22.7 \pm 1.2	nr	-4.3 \pm nr	-18.9 \pm nr
37	3	27.1 \pm 2.7	+0 timolol +0 brinzolamide	-8.3 \pm 3.8	-30.6 \pm 13.6
22	3	27.3 \pm nr	+0 timolol +0 brinzolamide	-9.1 \pm nr	-33.3 \pm nr
41	1	25.5 \pm nr	+2 timolol +2 brinzolamide	-3.3 \pm nr	-14.3 \pm nr
37	1	25.5 \pm 1.9	+2 timolol +2 brinzolamide	-4.9 \pm 2.6	-20.3 \pm 10.5
0	60	22.7 \pm 1.2	nr	-4.3 \pm nr	-18.9 \pm nr
37	3	25.8 \pm 3.0	+2 timolol +2 brinzolamide	-8.7 \pm 3.9	-33.7 \pm 14.7
22	3	25.9 \pm nr	+2 timolol +2 brinzolamide	-9.1 \pm nr	-34.9 \pm nr

Abbreviations: M, male; F, female; Y, year; POAG, primary open-angle glaucoma; OHT, ocular hypertension; IOP, intraocular pressure; SD, standard deviation; bid, twice daily; tid, thrice daily; nr, not reported.

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