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GLAUCOMA

Timolol versus brinzolamide added to travoprost in glaucoma or ocular hypertension

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Abstract
Background To compare the efficacy and safety of timolol 0.5% versus brinzolamide 1.0% when added to travoprost monotherapy in patients with primary open-angle glaucoma or ocular hypertension.
Methods Patients meeting selection criteria (IOP one eye 19 mmHg and ≤32 mmHg and IOP both eyes ≤32 mmHg at 8:00 h) were switched to travoprost monotherapy for 4 weeks. Patients then insufficiently controlled on travoprost (IOP at 8:00 h ≥19 mmHg) at baseline were randomized to receive either travoprost and brinzolamide or travoprost and timolol in a double-masked fashion for 12 weeks.
Results Two hundred and fifty-three patients underwent the 4-week run-in period. Switching to travoprost resulted in adequate IOP control (<19 mmHg) for 21.7% of patients. After 3 months of treatment, both drug combinations statistically significantly reduced the mean IOP at each time point (8:00, 12:00 and 16:00 h) and the mean diurnal IOP, which was 17.9±2.6 mmHg for the brinzolamide group and 17.0±3.2 mmHg for the timolol group. Both combinations were well-tolerated. However, a statistically significant difference occurred at 16:00 h, with pressures of 16.4±3.2 mmHg and 17.3± 2.8 mmHg for the timolol and brinzolamide groups, respectively (p=0.038). Fifty percent of patients reported one adverse event, whereas in 13.2% three or more adverse effects were named. Hyperemia was found most often (6.3% of the patients).
Conclusion Both adjunctive combinations moderately reduced IOP in patients inadequately controlled with travoprost monotherapy, with timolol being slightly stronger 8 hours after instillation. Adjunctive treatment with brinzolamide and travoprost may be an alternative for patients not tolerant or not responsive to treatment with timolol and travoprost.

Keywords Intraocular pressure · Travoprost · Timolol · Brinzolamide · Glaucoma

Introduction

Glaucoma is one of the major causes of irreversible blindness worldwide. Several risk factors for the progression of glaucoma have been identified[4]. However, only reduction of intraocular pressure (IOP) has been shown to stop or delay progression of glaucoma in primary open angle glaucoma [1, 10]. Pharmacological treatment with topical hypotensive drugs is generally considered to be the first-line therapy for newly diagnosed patients.

For many years, the mainstay treatment was with a β-adrenergic antagonist such as timolol before adding a second drug [21]. More recently, monotherapy with a prostaglandin has become the first-line therapy for newly diagnosed patients. Prostaglandins such as latanoprost or travoprost, given once daily, result in a greater IOP reduction than timolol eye drops administered in a standard twice-daily regimen [6, 17]. Moreover, unlike timolol, which can cause systemic adverse effects that may

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compromise its use in certain glaucoma patients [15, 23], prostaglandins have a favorable systemic safety profile.

Patients with advanced glaucoma and/or very high IOP may not be sufficiently controlled with prostaglandins, and require the addition of an adjunct medication in order to reach the desired IOP target. Generally, drugs with different mechanisms of action are combined to reach an additive effect. The mainstay combined therapy has been the use of the prostaglandin analog latanoprost with timolol. Timolol given in a fixed combination with latanoprost once daily has been shown to result in an additional IOP reduction of 1.2–2.5 mmHg [18]. Other adjunctive drugs are also used with prostaglandin or prostanoid analogs, among them topical carbonic anhydrase inhibitors (CAIs). CAIs decrease aqueous humour secretion, while prostaglandins and prostamide analogs primarily increase uveoscleral outflow. The first topical CAI that became available was dorzolamide, which in combined therapy has a similar efficacy to that of timolol in combined therapy. A recent study, comparing the efficacy of dorzolamide added to latanoprost over 24 hours, resulted in an additional mean diurnal IOP reduction of 2.2 mmHg [9]. Brinzolamide is a newer CAI with a similar efficacy to dorzolamide, but causes less stinging sensation upon instillation and thus causes less discomfort. [13]

The first prostaglandin analog available was latanoprost. Travoprost is a newer prostaglandin analog which has been reported to be highly effective both in monotherapy [2, 5, 16] and with adjuncts. Addition of timolol to travoprost resulted in an additional IOP reduction similar to that seen when added to latanoprost [3]. The main aim of this study was to compare the efficacy and safety of timolol maleate 0.5% solution versus brinzolamide 1% when added to travoprost 0.004% in patients with ocular hypertension or primary open-angle glaucoma unsuccessfully controlled with a prostaglandin analog monotherapy.

Patients and methods

This prospective, double-masked and randomized study was conducted in 20 ophthalmology study sites across Germany, France, Italy and Spain. Patients were included in the study between February 2004 and May 2005. All patients gave informed written consent before being included in the study. The main inclusion criteria included patients of 18 years or over with a clinical diagnosis of ocular hypertension, primary open-angle glaucoma or pigment dispersion glaucoma in at least one eye (study eye) who had been treated with any prostaglandin analog monotherapy (excluding unoprostone) and had an IOP in at least one eye of ≥19 mmHg and ≤32 mmHg and an IOP in both eyes ≤32 mmHg at 8:00 h at the screening visit. Best-corrected visual acuity had to be 20/200 or better. Exclusion criteria were the presence of exfoliation syndrome or exfoliation glaucoma, abnormalities preventing reliable applanation tonometry in study eye(s), concurrent conjunctivitis, keratitis or uveitis, history of allergic hypersensitivity, pregnancy, severe psychiatric condition, previous laser or intraocular surgery, change in systemic hypotensive therapy which might include adjustments to oral ß-adrenergic blockers, α-agonists and blockers, angiotensin converting enzyme inhibitors and calcium channel blockers, progressive retinal or optic nerve disease, history of (or at risk for) uveitis or cystoid macular edema, history of ocular herpes simplex, and contraindications to ß-blocker therapy including reactive airway disease, secondary or third degree heart block, bradyarrhythmias, and uncontrolled heart failure. Patients fulfilling the selection criteria were switched from their previous treatment with topical prostaglandins to travoprost monotherapy for 4 weeks.

At baseline visit, i.e., after the travoprost run-in period, those patients with an IOP of ≥19 mmHg and ≤2 mmHg and IOPs in both eyes ≤32 mmHg at 8:00 h were randomized to receive either an unfixed combination of travoprost 0.004% and 1% brinzolamide (referred to as brinzolamide group), or travoprost 0.004% and 0.5% timolol maleate therapy (timolol group). Travoprost was given “open label”, while brinzolamide and timolol where given in a double-masked fashion. The drugs were retained in the exact same sterile bottles. Patients were instructed to instill one drop of travoprost at 20:00 hours daily, and one drop of brinzolamide or timolol maleate at 8:00 hours and at 20:00 hours daily for 12 weeks. The 20:00 hour medication was given with a 5-minute interval between both drugs.

Those patients that after the run-in period on travoprost had an IOP lower than 19 mmHg in both eyes were defined as “responders” and were withdrawn from the study. Even if both eyes required treatment, only the worst eye was considered in the efficacy analysis. The worst eye was defined as the eye with the highest IOP at 8:00 hours at baseline visit. If both eyes were equal, then the right eye was included in the analysis.

A total of four visits were scheduled during the study. The IOP was measured with Goldmann applanation tonometry at each visit. At screening, the IOP was measured at 8:00 h only, while at the baseline visit and the final visit after 12 weeks of treatment, a diurnal IOP curve was performed with measurements at 8:00, 12:00 and 16:00 h. The third visit was scheduled at 4 weeks after initiation of either study drug combinations. This was a safety visit in which IOP was read at 16:00 h. At screening, patients underwent a complete ophthalmologic examination. Visual acuity and slit-lamp biomicroscopy were assessed at all visits. This was a multicenter study which

was conducted at 20 sites; for participating centers, see below. The study was approved by the ethical review committees of all participating centers.

Statistical analysis

All efficacy data analyses were two-sided, with an α-level of 0.05. The data were analyzed for intention-to-treat and per protocol, but only the per-protocol results are shown here. The per-protocol population included all intention-to-treat patients without any protocol violation and thus with all IOP readings available, while the intention-to-treat analysis included all patients even if they did not finish the study per protocol, as long as they contributed at least one measurement. However, there were no major differences between the intention-to-treat and the per-protocol analysis. The primary efficacy variable, the mean diurnal IOP (average of the IOP at the three individual time points), as well as all individual IOPs were analyzed by an unpaired *t*-test for intra-group analysis and repeated measures of analysis. The power of the test was calculated to provide an 80% power that a 1.5 mmHg difference could be excluded between treatments if at least 80 patients were included in each treatment arm, assuming a standard deviation of 3.5 mmHg.

Results

IOP reduction

A total of 253 patients fulfilled the selection criteria at the screening visit, and underwent a 4-week run-in period with travoprost. These 253 patients were considered the safety population. Among these patients, 55 were ineligible for randomization as they were successfully controlled (responders) at the end of the travoprost run-in period. A further eight patients withdrew from the study, and one was excluded from the intention-to-treat analysis as the patient failed to fulfill selection criteria at visit 1 despite being randomized. The remaining 189 patients (96 in the brinzolamide group and 93 in the timolol group) were considered evaluable for intention-to-treat analysis and 180 (90 in the brinzolamide group and 90 in the timolol group) for the per-protocol analysis.

The efficacy results were similar for the intention-to-treat and the per-protocol analysis, but only the results for the per-protocol analysis are shown here. The baseline characteristics of randomized patients are given in Table 1. Both therapeutic groups had similar baseline demographic and pachymetry characteristics.

At screening, the majority of patients (60.6%) reported being on monotherapy with latanoprost, while 11.8% of them were on travoprost and 9.8% on bimatoprost. Due to inability to report previous treatment this was not clear for 17.8% of the patients.

The mean IOP at screening (8:00 hours) was similar between both treatment groups (22.1±2.1 mmHg in the brinzolamide group and 22.2±2.2 mmHg in the timolol group). After the run-in phase with travoprost, 55 patients showed an IOP of the worst eye lower than 19 mmHg and were therefore defined as responders. Responders corresponded to 29.2% of patients previously treated with latanoprost, 20.0% of patients on bimatoprost and 17.8% of patients for whom the precise previous treatment was not clear. One of the patients who had not previously responded to travoprost monotherapy was classified as a responder after the 4-week run-in phase. The mean IOP decrease between 8:00 h at screening visit and 8:00 h at baseline visit was similar for the responders within the group of patients previously treated with latanoprost (4.3±3.2 mmHg) and bimatoprost (4.7±3.4 mmHg), but was lower for responders for whom the previous medication was travoprost (1±0 mmHg) or not clear (2.1±2.3 mmHg).

At baseline visit, the mean individual IOPs as well as the mean diurnal IOP were similar for both groups (Table 2). After 3 months treatment, a decrease in all individual IOPs was observed for both randomized groups (Table 2). This decrease was already observed at the week 4 visit (safety visit). At the 16:00 hour reading, the IOP for the brinzolamide group was

Table 1 Demographic and disease baseline characteristics of patients

		Brinzolamide	Timolol	*P*-value
N		96	93	
Age (years)		62.7±10.6	65.5±13.5	0.111
Gender	Male	36.5%	48.4%	0.097
	Female	63.5%	51.6%	
Race	Caucasian	96	93	NA
Previous PG*	Bimatoprost	12	7	NA
	Latanoprost	56	52	
	Travoprost	13	16	
Pachymetry (μ)		563.0±31.7	561.3±35.7	NA

The demographic and disease baseline characteristics of patients randomized to either travoprost and brinzolamide (brinzolamide) or to travoprost and timolol (timolol) are shown. *The previous prostaglandin (PG) analog was unknown for some of the patients.

Table 2 Mean IOP in mmHg at the baseline, week 4 and week 12 visits (Visits) and IOP reduction between visits (IOP reduction)

	IOP readings	Brinzolamide (n=90)	Timolol (n=90)	P-value
Visits				
Baseline	8:00 h	21.9±2.1	22.3±2.5	0.252
	12:00 h	21.1±2.6	21.1±2.5	0.80
	16:00 h	20.0±3.0	20.2±2.7	0.641
	Diurnal	21.0±2.2	21.2±2.2	0.623
Week 4	16:00 h	17.9±2.9	16.9±3.0	0.032
Week 12	8:00 h	18.3±2.8	17.5±3.4	0.093
	12:00 h	18.0±2.7	17.1±3.6	0.071
	16:00 h	17.3±2.8	16.4±3.2	0.038
	Diurnal	17.9±2.6	17.0±3.2	0.052
IOP reduction (mmHg)				
Baseline–week 4	16:00 h	2.2±2.7	3.3±2.7	0.004
Baseline–week 12	8:00 h	3.6±2.8	4.7±3.1	0.008
	12:00 h	3.2±2.8	4.0±3.5	0.11
	16:00 h	2.7±2.7	3.9±2.6	0.005
	Diurnal	3.2±2.4	4.2±2.8	0.009

The mean (±SD) of the individual and diurnal IOP values for baseline, week 4 and week 12 visits are givenin the 'Visits' section of the table. The mean (±SD) for the IOP decrease between baseline and week 4 and baseline and week 12 visits are shown for each of the therapeutic groups in the 'IOP reduction' section.

17.9±2.9 mmHg, and 16.9±3.0 mmHg for the timolol group. Thus, the IOP at 16:00 hours was statistically significantly lower (p=0.033) for the timolol group. The IOP decrease between the baseline and week 4 visits was also statistically significantly different (p=0.004), being greater for the timolol group. At week 12, a further IOP decrease was observed for all IOP readings in both groups. The mean IOPs in the brinzolamide group were 18.3±2.8 at 8:00 h, 18.0±2.7 at 12:00 h and 17.3±2.8 at 16:00 h, while for the timolol group, the IOPs were 17.5±3.4 at 8:00 h, 17.1±3.6 at 12:00 h and 16.4±3.2 at 16:00 h. The mean diurnal IOPs were 17.9±2.6 mmHg for the brinzolamide group and 17.0±3.2 mmHg for the timolol group. Only the 16:00 hours reading was statistically significantly different between groups (p=0.038).

The IOP decrease between baseline and week 12 was similar for both groups for the 12:00 h values (p=0.111), but was statistically significantly greater for the timolol group at the 8:00 and 16:00 hour readings as well as for the diurnal values. The IOP reduction observed after 3 months treatment corresponded to 14.8±10.5% for the brinzolamide group and 19.6±12.7% for the timolol group (p=0.006, Table 2).

Safety

Safety and tolerability were assessed on the 253 patients that received at least one dose of any of the study drugs. Within the non-randomized group, 15.6% (10/64) of patients reported adverse events, while 16.7% (16/96) of patients in the brinzolamide group and 12.9% (12/93) of the patients in the timolol group had one or more adverse events. All adverse events were mild. Half of the patients reporting adverse events only reported one adverse event throughout the study, while 13.2% of these patients had three or more adverse events. Out of the 15 adverse events registered before randomization, three (20.0%) were defined as related to travoprost. In the brinzolamide group, two of the adverse events (n=26) were classified as related to the study drug, and in the timolol group, one (4.6%) was classified as drug related.

The adverse event with the highest incidence was hyperemia (6.3% of the patients). The other two most frequently reported adverse events were conjunctival follicles and ocular itching, with an incidence of 2.4% and 2% of the patients included in the study respectively (Table 3).

Visual acuity remained similar throughout the study, and no statistically significant or clinically relevant differences were observed between groups. Although no serious adverse events took place during the study, three patients decided to withdraw from the study due to adverse events, which were: eye itching related to brinzolamide, intense ocular pain and conjunctival hyperemia that started after being randomized to travoprost and brinzolamide, and palpitations and decrease in blood pulse that started after instillation of travoprost and timolol.

Discussion

The main aim of this study was to compare the efficacy and safety of timolol versus brinzolamide eye drops when added to travoprost in patients not responding to prostaglandin analog monotherapy. The results of this study show that the addition of any of these two drugs results in a significant IOP reduction after 12 weeks of treatment. The reduction was observed for mean IOP at all timepoints at all

Table 3 Most frequently reported adverse events

	Non-randomized			Brinzolamide			Timolol		
	N	*n*	%	*N*	*n*	%	*N*	*n*	%
Conjunctival hyperemia	4	4	6.3	10	8	8.3	5	5	5.4
Ocular itching	4	3	4.7	-	-	0	2	2	2.2
Conjunctival follicles	3	3	4.7	3	3	3.1	-	-	-
Eye lid hyperemia	1	1	1.6	2	1	1.0	-	-	-
Other	3	3	4.7	11	8	8.3	15	10	10.8
Total adverse events	15			26			22		
Total patients*		10	15.6		16	16.7		12	12.9

The table shows the number of adverse events (*N*) registered in each of the study groups, as well as the number (*n*) and percentage (%) of patients reporting them within these groups. When patients reported multiple episodes of the same adverse event, each episode was considered as an adverse event. In these cases, *N* is higher than *n*.

*The total number of patients reporting adverse events does not add up to the sum of the number of patients reporting each adverse event, as several patients reported more than one different adverse event throughout the study.

days, and the mean diurnal IOP at 12 weeks. However, timolol was more effective than brinzolamide in decreasing mean diurnal IOP (4.2±2.8 versus 3.2±2.4 mmHg). The mean IOP values for the 8:00 h (18.3±2.8 for the brinzolamide group and 17.5±3.4 for timolol) and 12:00 h (18.0±2.7 for brinzolamide and 17.1±3.6 for timolol) readings were similar between both groups, but the 16:00 hour values were statistically significantly lower for the timolol group (17.3±2.8 for the brinzolamide group and 16.4±3.2 for the timolol group). Despite the greater reduction of IOP using timolol, mean diurnal IOPs for both groups showed no statistically significant difference (17.9±2.6 mmHg for brinzolamide and 17.0±3.2 mmHg for timolol).

The level of IOP decrease observed in our study for the combination of travoprost and brinzolamide was lower than that seen in other studies. In the open-label Brinzolamide study [3], after 12 weeks of treatment with this combination, the IOP values were reduced by 4.2 mmHg. Shoji and colleagues also observed a greater IOP reduction (5.3 mmHg) and percentage reduction (23.5%) than those seen in our study [20]. Despite the variability of these results, the IOP decrease induced by brinzolamide added to travoprost seemed to be higher than that obtained when dorzolamide was added to latanoprost (2.2 mmHg) [9].

Our results differ from those of Reis et al. and Hollo et al. Reis and colleagues [19] found in an open-label study that addition of brinzolamide to travoprost had, after 28 days of treatment, the same IOP reduction effect as timolol maleate 0.5% twice daily added to travoprost. The results of their study showed no statistically significant differences for IOP reduction or percent reduction between the two groups. The IOP reduction observed after 28 days of treatment was greater in the brinzolamide group (4.0±2.1 vs 3.9±1.8 mmHg). In another study similar to ours, Hollo and colleagues [7] found mean IOP reductions of 3.4±2.1 vs 3.2±2.4 mmHg for brinzolamide and timolol twice daily respectively, as concomitant treatment with travoprost. Differences in the study populations and designs may account for part of the differing results.

In a different study setting, Hollo and Kothy [8] investigated if combined intraocular pressure-lowering medication with travoprost/timolol fixed combination and brinzolamide was superior to both travoprost monotherapy and travoprost/timolol fixed-combination therapy, in 20 patients with primary open-angle glaucoma or ocular hypertension over a follow-up of 4 weeks. They concluded that adjunctive brinzolamide medication provided further IOP decrease (mean, 1.9 mmHg) in patients receiving evening-dosed travoprost/timolol fixed combination. Furthermore, the travoprost/timolol fixed combination was significantly more effective in IOP reduction than travoprost alone. In our study, mean IOP reduction by brinzolamide was 2.2 mmHg after 4 weeks.

Martínez de la Casa and colleagues [11] observed that patients insufficiently responsive to monotherapy reached a significantly lower mean IOP with an unfixed combination of travoprost and brinzolamide than with a fixed-combination of latanoprost and timolol 0.5%, after 3 months of treatment. The inferiority of the fixed combination of latanoprost and timolol in this study might have been due to the fact that timolol was instilled only once daily. In the European latanoprost fixed-combination study, the addition of timolol 0.5% resulted in 1.2 mmHg IOP reduction after 24 weeks of treatment [18].

Miura et al. [12] investigated the ocular hypotensive effect of brinzolamide and timolol when added to latanoprost in 32 patients with primary open-angle glaucoma, normal-tension glaucoma, or ocular hypertension, over a 12-week period. The results of their study showed a

significant IOP reduction of both brinzolamide (mean, 2.0 mmHg) and timolol (mean, 2.7 mmHg), and were more effective than latanoprost alone. In contrast to our study, no significant differences were found between the drugs, but the number of patients was relatively low and the glaucoma diagnoses were more heterogenous. A limitation for the clinical transferability might be that both timolol or brinzolamide were applied twice daily. This may not be practical in all patients. However, in some patients a once-daily application of timolol may be sufficient. This is less likely to be the case for brinzolamide.

It is of interest to note that in our study switching to travoprost monotherapy resulted in adequate IOP control (IOP<19 mmHg) for 21.7% of patients. The travoprost responders corresponded to 29.2% of the patients previously treated with latanoprost, 20.0% of the patients previously on bimatoprost, and 3.3% of the patients previously on travoprost. This suggests that failing to respond to a prostaglandin monotherapy does not necessarily imply switching to combined therapy. Although improved compliance within a clinical study may well have played an important role, travoprost monotherapy might be an effective alternative to combined therapy for patients inadequately controlled with other prostaglandin or prostanoid analogs. However, our study was not designed to address this issue.

Both adjunctive therapies had good safety and tolerability profiles. None of the adverse events registered throughout the study were considered serious, although three patients withdrew from the study due to adverse events. The adverse events in the brinzolamide group were eye itching for one patient, and ocular pain and conjunctival hyperemia for the other patient. The timolol maleate-assigned patient had palpitations and decreased blood pressure and pulse. Unlike brinzolamide and CAI in general, timolol has been associated with serious systemic side-effects that prohibit its use in patients with respiratory or cardiac pathology. In these patients, brinzolamide might be a good alternative to timolol for adjunctive therapy.

Travoprost instillation was associated with a higher incidence of adverse reactions than brinzolamide and timolol, although the percentage of patients referring travoprost-related adverse events was lower than that seen in other studies. A total of 58.7% of the adverse events registered throughout the study were either possibly or probably related to travoprost, whereas brinzolamide was only probably or possibly related to 4.8% of the adverse events and timolol to 1.6% as rated by the investigator. The adverse event with the highest incidence was conjunctival hyperemia, which was reported by only 7% of the patients. This percentage is lower than that described in the literature [13, 24].

Limitations of this study could be seen in a missing negative control group applying prostaglandins solely during the additivity period. Furthermore, the failure to define the previous medication for 17.8% of patients at the beginning of the study was high, due to referral from external ophthalmologists and insufficient documentation.

Overall, the results of this study indicate that both drugs brinzolamide and timolol brinzolamide are safe and effective as adjunctive therapy to travoprost. Timolol reduced IOP more effectively than brinzolamide. Especially for patients with contraindication to ß-blockers, brinzolamide might be a convincing alternative as adjunctive agent to prostaglandins.

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