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Safety and efficacy of bimatoprost 0.03% versus timolol maleate 0.5%/dorzolamide 2% fixed combination

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PURPOSE. To determine the efficacy and safety of bimatoprost given every evening versus the dorzolamide/timolol fixed combination (DTFC) given twice daily in open-angle glaucoma and ocular hypertensive patients.
METHODS. A double-masked, three-center, prospective, randomized, crossover comparison with two 8-week treatment periods following a 4-week medicine free washout period. Diurnal curve intraocular pressures (IOPs) were taken at 08:00 (trough) and 10:00 and 16:00 hours.
RESULTS. A total of 35 patients were enrolled and 32 completed all evaluations. The diumal untreated baseline intraocular pressures was 24.8 ± 2.4 mmHg. On the last day of treatment the mean diurnal intraocular pressures was 17.4 ± 2.9 for bimatoprost and 18.1 ± 2.8 mmHg for DTFC ($p = 0.35$). The individual time points for intraocular pressures were not statistically different between groups. Both groups statistically reduced the intraocular pressures from baseline for each time point and for the diurnal curve ($p < 0.05$). Regarding ocular safety and tolerability, there was more conjunctival hyperemia with bimatoprost ($n = 15$) than with DTFC ($n = 7$, $p = 0.013$) and more burning and stinging with DTFC ($n = 12$) than with bimatoprost ($n = 0$, $p = 0.0005$). Few systemic adverse events were recorded and there was no statistical difference between groups for any individual event ($p > 0.05$).
CONCLUSIONS. This study indicates that the intraocular pressures are lowered to a statistically similar amount with DTFC compared to bimatoprost in open-angle glaucoma and ocular hypertensive patients. (Eur J Ophthalmol 2005; 15: 336-42)

KEY WORDS. Bimatoprost, Dorzolamide/timolol, Glaucoma, Ocular hypertension

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INTRODUCTION

The dorzolamide 2%/timolol maleate 0.5% fixed combination (Cosopt®, Merck & Company, Inc., Blue Bell, PA, USA) was commercially released several years ago. The pharmacology of this product is believed to be related to its two active ingredients and it is prescribed for twice daily dosing (1). Clineschmidt et al found in 102 patients whose disease was inadequately controlled on timolol maleate alone, that the dorzolamide/timolol fixed combination further reduced the intraocular pressure 1.1 mmHg from baseline at trough and resulted in a 2.8 mmHg further decrease at peak (two hours after dosing) (2). In addition, Boyle et al have found that at morning trough the

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dorzolamide/timolol fixed combination reduced the intraocular pressure by 7.7 mmHg (27.4%) compared with 4.6 mmHg for dorzolamide and 6.4 mmHg for timolol maleate alone (15.5 mmHg and 22.2%, respectively) from untreated baseline (3).

A recent study by Fechtner et al showed equal daytime efficacy between latanoprost and the dorzolamide/timolol fixed combination (4).

In addition, Konstas and coworkers have shown an equal daytime diurnal pressure between latanoprost and the dorzolamide/timolol fixed combination although the dorzolamide-based preparation was statistically more effective in the late evening (5).

However, several recent investigations have suggested that bimatoprost (Lumigan®, Allergan, Irvine, CA, USA), a new medication structurally related to a prostaglandin, could be statistically more effective than latanoprost in reducing the intraocular pressure (6,7).

These findings raise the question whether bimatoprost could provide a greater ocular hypotensive effect than the dorzolamide/timolol fixed combination. Unfortunately, very little data yet exist comparing bimatoprost and the dorzolamide/timolol fixed combination either in efficacy or safety.

The purpose of this study was to evaluate intraocular pressure control obtained from bimatoprost dosed once in the evening versus the dorzolamide/timolol fixed combination given twice daily in patients with open-angle glaucoma or ocular hypertension.

TABLE I - MEAN INTRAOCULAR PRESSURES AND REDUCTION FROM BASELINE (mmHg ± standard deviation)

		Number of patients = 32			
	Time	**Baseline**	**Bimatoprost**	**DTFC**	**p value**
Mean intraocular pressures	08:00	25.9 ± 2.4	17.3 ± 3.1	18.8 ± 3.1	0.07
	10:00	24.8 ± 2.7	17.3 ± 3.3	17.5 ± 3.6	0.49
	16:00	24.0 ± 3.4	17.3 ± 3.2	17.9 ± 3.1	0.24
	Diurnal	24.9 ± 2.4	17.4 ± 2.9	18.1 ± 2.8	0.35
Reduction from baseline	08:00		8.5 ± 2.9	7.1 ± 2.5	0.04
	10:00		8.0 ± 4.0	7.3 ± 3.6	0.47
	16:00		7.2 ± 4.8	6.1 ± 3.2	0.28
	Diurnal		7.5 ± 2.9	6.8 ± 2.6	0.34

DTFC = Dorzolamide/timolol fixed combination

TABLE II - OCULAR ADVERSE EVENTS (number of events, two or more incidences)

	Bimatoprost	**DTFC**	**p value**
Conjunctival hyperemia	15	7	0.013
Burning/stinging	0	12	0.0005
Itching	5	4	> 0.999
Decreased vision	5	4	> 0.999
Ocular pain	4	1	0.38
Superficial punctate keratitis	3	1	0.63
Exudates	3	1	0.63
Foreign body sensation	3	0	0.25
Tearing	2	1	> 0.999
Lids itching	2	0	0.5
Eye discharge/film over eye	1	1	> 0.999
Follicles (lid)	1	1	> 0.999
Swelling	1	1	> 0.999
Punctate epithelial erosion	1	1	> 0.999
Periorbital pigmentation	1	1	> 0.999

DTFC = Dorzolamide/timolol fixed combination

TABLE III - SYSTEMIC ADVERSE EVENTS (one or more events)

	Bimatoprost	**DTFC**	**p value**
Sinusitis	1	1	> 0.999
Influenza	0	1	> 0.999
Taste perversion	0	1	> 0.999
Gastric upset	0	1	> 0.999
Hiatal hernia	0	1	> 0.999
Shortness of breath	0	1	> 0.999
Hypercholesterolemia	0	1	> 0.999

DTFC = Dorzolamide/timolol fixed combination

MATERIALS AND METHODS

Patients

We included patients who had: a clinical diagnosis of primary open-angle, pigment dispersion, or exfoliation glaucoma, or ocular hypertension in at least one eye (study eye); a safe intraocular pressure at screening according to the investigator's judgment, in both eyes, in such a way that should assure clinical stability of vision and the optic nerve throughout the trial; a 24-35 mmHg inclusive intraocular pressure at baseline at the 08:00 measurement (Visit 2); and a visual acuity of 20/200 or better in the study eye(s).

Patients were excluded from this study if they demonstrated a history of: any abnormality preventing reliable applanation tonometry in study eye(s); any opacity or patient uncooperativeness that restricted adequate examination of the study eye; any concurrent infectious/noninfectious conjunctivitis, keratitis or uveitis in either eye; or any history of allergic hypersensitivity or poor tolerance to any components of the preparations used in this trial. Also not allowed were: women of childbearing potential not using reliable means of birth control; pregnant or lactating women; any clinically significant, serious, or severe medical or psychiatric condition; participation in any investigational drug or device trial within the previous 30 days prior to Visit 1; intraocular conventional surgery or laser surgery within the past 2 months in the study eye(s); according to the investigator's best judgment risk of visual field or visual acuity worsening as a consequence of participation in the trial; inability to understand the trial procedures; any anticipated change in systemic hypotensive therapy during the active treatment portion of the trial (Visits 2-6); progressive retinal or optic nerve disease apart from glaucoma; history of bronchial asthma, chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock, or hypersensitivity to any component of products included in this study; history of allergy to sulfa, ocular herpes simplex or cystoid macular edema.

METHODS

Patients signed an Institutional Review Board approved informed consent agreement before any procedures were performed. At the screening visit (Visit 1, Week –4) patients underwent an examination, as well as at the other visits, consisting of Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity, slit lamp biomicroscopy and Goldmann applanation tonometry. Additionally, at the screening visit only, a visual field assessment (Humphrey Field Analyzer, Program 24-2, Dublin, CA), dilated funduscopy and gonioscopy were performed. Qualified patients were discontinued from their current ocular medications. If required, up to a 4-week washout period of glaucoma medications was completed before

TABLE IV - OCULAR SYMPTOMS SURVEY (continued)

	Answer	Baseline	Bimatoprost	DTFC	p value
Dry eye	Yes	9	6	5	0.68
	No	23	26	27	
Pain	Yes	3	4	4	> 0.999
	No	29	28	29	
Vision blurred	Yes	10	8	12	0.39
	No	22	24	20	
Teared more	Yes	7	7	4	0.51
	No	25	25	28	
Sting and/or burn	Yes	N/A	7	21	0.0007
	No		25	11	
Crusting	Yes	3	4	7	0.45
	No	29	28	25	
Itching	Yes	14	10	8	0.75
	No	18	22	24	
Sandy/gritty feeling in eye	Yes	3	7	3	0.29
	No	29	25	29	

DTFC = Dorzolamide/timolol fixed combination

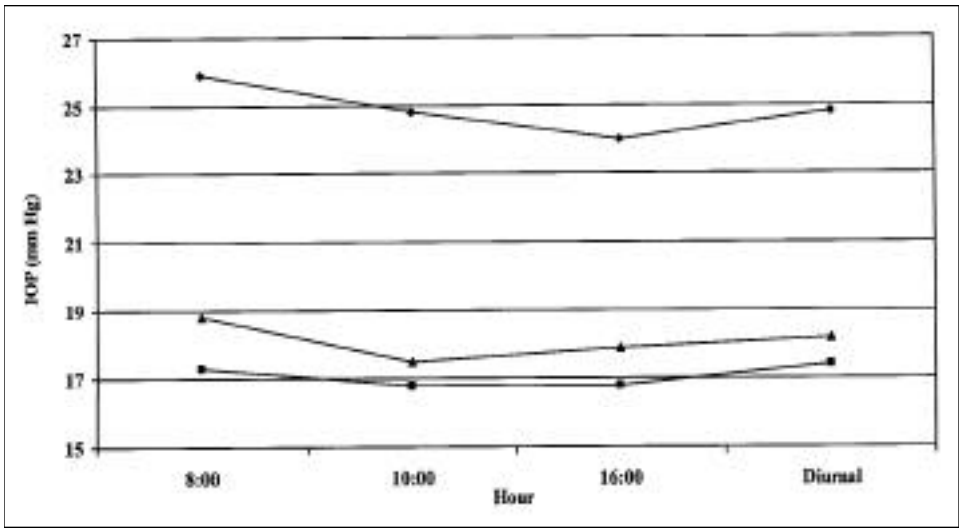

Fig. 1 - Diurnal intraocular pressures at baseline (diamonds), on bimatoprost treatment (squares) and on the dorzolamide/timolol fixed combination (triangles) treatment.

treatment with study medication. Patients returned to clinic at Visit 2 (Day 0) in which their morning intraocular pressure was measured at 08:00.

Patients with a pressure of 24-35 mmHg inclusive were enrolled into the study. Patients then had their intraocular pressure measured at 10:00 and 16:00 hours. The baseline ocular symptom survey was performed. Patients were randomly assigned to receive either placebo once every morning (08:00) and bimatoprost 0.03% (Lumigan®, Allergan, Irvine, CA) once every evening (20:00) or the dorzolamide 2%/timolol maleate 0.5% fixed combination twice daily (08:00 and 20:00) (Cosopt®, Merck & Company, Inc., Bluebell, PA) for the first 8-week treatment period and then were crossed over to the second treatment period. Patients had safety pressure measurements performed 2 weeks after each treatment period began (Visit 3, Week 2). During the last day of the 8-week treatment period (Visit 4, Week 8), patients underwent assessment of their trough 08:00 intraocular pressure following which they were dosed with the masked study medicine. The 8-week treatment period was chosen to avoid a carryover effect of the medications under investigation. No washout period was scheduled between treatment periods. At each end of the treatment period visit patients completed an ocular symptom survey. Both the patient and medical staff were masked to the medication at this visit. One re-

Table IV - OCULAR SYMPTOMS SURVEY

	Answer	Baseline	Bimatoprost	DTFC	p value
Deep pain	Yes	3	5	1	0.22
	No	29	27	31	
Red eye	Yes	7	14	8	0.18
	No	25	8	24	
Other people noticing red eye	Yes	3	6	4	0.75
	No	29	26	28	

DTFC = Dorzolamide/timolol fixed combination

search coordinator was unmasked in order to perform ocular dosing.

Following Period 1 patients were switched to the opposite treatment and returned in 2 weeks (Visit 5, Week 10) for the Period 2 safety check. Patients returned in 6 weeks for the end of Period 2 (Visit 6, Week 16) and the same assessments were performed as in Period 1.

Statistics

All data analyses were two-sided and a 0.05 alpha level was used. The primary efficacy variable was the diurnal intraocular pressure difference between Visit 4 and 6, which was analyzed by a paired t-test for intra-group analysis (8). An average eye analysis was used. The secondary efficacy variables, trough intraocular pressure and intraocular pressure at each time point at Visits 4 and 6, were analyzed by a paired t-test (8). This study provided an 80% power that a 1.5 mmHg difference can be excluded between groups if 27 patients completed the study. An intergroup standard deviation of 2.8 mmHg was assumed (9-12).

Safety parameters for intra-group analysis were evaluated with a Wilcoxon Sign Rank test including the ocular symptom query (8). Visual acuity was analyzed by a paired t-test (8). Adverse events were evaluated with a McNemar test (13).

RESULTS

Patients

Thirty-five patients were enrolled in this study, of which 32 had trough assessments. Of these patients 17 were Caucasian and 15 were African American. Nine were male and 23 were female with an average age of 61.5 ± 9.4 years. Thirteen patients had ocular hypertension and 19 had primary open-angle glaucoma.

Intraocular pressure

This study found that the mean untreated baseline diurnal intraocular pressure was 24.8 ± 2.4 mmHg.

The treated diurnal intraocular pressures were 17.4 ± 2.9 for bimatoprost and 18.1 ± 2.8 mmHg for the dorzolamide/timolol fixed combination ($p = 0.35$).

The mean intraocular pressures at each time point are provided in Table I and diagramed in the Figure 1. For each individual time point (08:00, 10:00 and 16:00 hours), the mean intraocular pressure was not statistically different between treatments.

The reductions at each time point and for the diurnal curve were not statistically different between groups except at the 08:00 time point in which the decrease was greater with bimatoprost therapy ($p < 0.04$)

Safety

The ocular adverse events for this study are shown in Table II. More burning and stinging was found with the dorzolamide/timolol fixed combination ($p = 0.0005$), and more hyperemia was noted with bimatoprost ($p = 0.013$).

Three patients exited the study early and their intraocular pressure data were incomplete and not used. One patient on the dorzolamide/timolol fixed combination was discontinued per protocol when systemic anti-hypertensive therapy was initiated.

The second patient, on bimatoprost, suffered a serious adverse event from a gastrointestinal problem, not believed to be related to the study medicine, which required surgery. Another patient on bimatoprost exited early due to photophobia. An additional patient completed only the trough portion of the trial because they were advanced to the next period early due to ocular pain and photophobia while on bimatoprost. The systemic adverse events are shown in Table III. There were no significant differences between groups. The results of the ocular symptom survey are shown in Table IV. Similar to the unsolicited side effects, when asked, patients admitted to more stinging/burning with the dorzolamide/timolol fixed combination. There was a trend of more conjunctival hyperemia with bimatoprost, but this was not statistically significant.

DISCUSSION

Woodward et al have described bimatoprost as a prostamide (14). This compound is thought to be a derivative of a class of medicines called anandamides, which are cannabinoid receptor agonists (15). Accordingly, Woodward et al have demonstrated that bimatoprost does not demonstrate receptor agonism at any known receptor including the cannabinoid and FP receptors (14, 16). However, Sharif et al have noted in several studies

that bimatoprost, as well as its free acid, are agonists at the FP receptor (16-17). Further, a specific prostamide receptor, and any associated clinical effect, remains as yet described.

Bimatoprost was shown in Phase II and III regulatory trials to demonstrate greater efficacy than timolol, providing a reduction of 9.2 mmHg (35%) versus 6.7 mmHg (26%) reduction respectively at 08:00 in the latter study (19). In a separate Phase II trial, bimatoprost demonstrated statistical equivalence to latanoprost although there was a trend to greater efficacy with bimatoprost (20). In a subsequent trial, Noecker and coworkers demonstrated at least a trend that bimatoprost was more effective than latanoprost (1.0-1.5 mmHg difference in absolute pressure levels) at three time points (08:00, 12:00 and 16:00 hours) (7).

The purpose of this trial was to evaluate the efficacy and safety of bimatoprost given once every evening versus the dorzolamide/timolol fixed combination given twice daily.

This study found that both bimatoprost and the dorzolamide/timolol fixed combination statistically reduced the intraocular pressure from baseline at each time point (08:00, 10:00 and 16:00 hours) and for the diurnal curve. When both treatments were compared there was no statistical difference at each time point and for the diurnal curve. However, there was a significantly greater reduction with bimatoprost at the 08:00 time point despite the lack of statistically significant difference in absolute pressure levels.

These results are similar to Fechtner et al, and Konstas et al, who showed that evening dosed latanoprost and the dorzolamide/timolol fixed combination provided statistically equal daytime pressure levels (4, 5). However, in the study with Konstas and associates the dorzolamide/timolol fixed combination demonstrated a statistically greater reduction at the 22:00 time point than latanoprost (5). However, it is not known whether the dorzolamide/timolol fixed combination also would provide a better pressure reduction than bimatoprost since evening pressures were not evaluated in this current study.

Regarding safety, with both solicited and unsolicited side effects, there was statistically more stinging/burning with the dorzolamide/timolol fixed combination. This was probably due to dorzolamide for which stinging/burning is a known side effect (1-3, 21). In contrast, patients made greater unsolicited complaints of conjunctival hyperemia with bimatoprost, which has also been previously described (19).

This study indicates that the intraocular pressure is lowered to a statistically similar amount with the dorzolamide/timolol fixed combination compared to bimatoprost in open-angle glaucoma and ocular hypertensive patients.

This study did not compare bimatoprost given every morning compared to the dorzolamide/timolol fixed combination. It could be that morning dosing could have changed the diurnal curve comparison characteristics of this trial. Also, only three daytime time points were measured in this study. Nighttime or potentially other daytime time points could have provided a different result.

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REFERENCES

1. Stewart WC. New perspectives in the medical treatment of glaucoma. Current Opinion Ophthalmol 1999; 127: 142-7.
2. Clineshmidt CM, Williams RD, Snyder E, Adamsons IA. A randomized trial in patients inadequately controlled on timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. Ophthalmology 1999; 106: 17-24.
3 Boyle JE, Ghosh K, Gieser DK, Adamsons IA. A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol or dorzolamide. Ophthalmology 1999; 106: 10-6.
4. Fechtner R, Clineschmidt C, Getson A, Adamsons IA, for the Cosopt Study Group. A Three Month, Parallel, Randomized, Observer-Masked, Multicenter study Comparing Cosopt to Xalatan in Patients with Elevated IOP. Invest Ophthalmol Vis Sci 1999; 40 (Suppl): S665.
5. Konstas AGP, Papapanos P, Tersis I, Houliara D, Stewart WC. 24-hour diurnal curve comparison of commercially

available latanoprost 0.005% versus timolol/dorzolamide fixed combination. Ophthalmology 2003; 110: 1357-60.
6. DuBiner H, Cooke D, Dirks M, Stewart WC, VanDenburgh AM, Felix C. Efficacy and safety of bimatoprost in patients with elevated intraocular pressure: A 30-day comparison with latanoprost. Surv Ophthalmol 2001; 45 (Suppl): S353-60.
7. Noecker RS, Dirks MS, Choplin NT, Bernstein P, Batoosingh AL, Whitcup SM. A six-month randomized clinical trial comparing the IOP-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. Am J Ophthalmol 2003; 135: 55-63.
8. Book SA. Essentials of statistics. In: Arthur AA, Rogers JL, Bradley JW (eds). Testing Statistical Hypotheses. New York: McGraw-Hill Book Company, 1978; 117-22.
9. Mundorf TK, Cate EA, Sine CS, Otero DW, Stewart JA, Stewart WC. The safety and efficacy of switching timolol maleate 0.5% solution to timolol hemihydrate 0.5% solution given twice daily. J Ocular Pharm Therap 1998; 14: 129-35.
10. Duff GR. A double-masked crossover study comparing the effects of carteolol 1% and 2% on intraocular pressure. Acta Ophthalmol (Copenh)1987; 65: 618-21.
11. Stewart WC, Leland TM, Cate EA, Stewart JA. Efficacy and safety of timolol solution once daily vs. timolol gel in treating elevated IOP. J Glaucoma 1998; 7: 402-7.
12. Stewart WC, Sharpe ED, Harbin TS Jr, Pastor SA, Day DG, Holmes KT, et al. Brimonidine 0.2% versus dorzolamide 2% each given three times daily to reduce the intraocular pressure. Am J Ophthalmol 2000; 129: 723-7.
13. Siegel S. Non-Parametric Statistics for the Behavioral Sciences, 1st ed. Series in Psychology. New York: McGraw-Hill Book Company, 1956; 63-7.
14. Woodward DF, Krauss AHP, Chen J, Lai RK, Spada CS, Burk RM, et al. The pharmacology of bimatoprost (Lumigan). Surv Ophthalmol 2001; 45 (Suppl): S337-45.
15. Woodward DF, Phelps RL, Krauss AH, Weber A, Short B, Chen J, Liang Y, Wheeler LA. Bimatoprost: a novel antiglaucoma agent. Cardiovasc Drug Rev 2004;22:103-20.
16. Sharif NA, Williams GW, Kelly CR. Bimatoprost and its free acid are prostaglandin FP receptor agonists. Eur J Pharmacol 2001; 432: 211-3.
17. Sharif NA, Kelly CR, Crider JY, Williams GW, Xu SX. Ocular hypotensive FP prostaglandin (PG) analogs: PG receptor subtype binding affinities and selectivities, and agonist potencies at FP and other PG receptors in cultured cells. J Ocul Pharmacol Ther 2003; 19: 501-15.
18. Palkovits M. The brain and the pain: neurotransmitters and neuronal pathways of pain perception and response. Orv Hetil 2000; 141: 2231-9.
19. Sherwood M, Brandt J, for the Bimatoprost Study Groups 1 and 2. Six-month comparison of bimatoprost once-daily and twice-daily with timolol twice-daily in patients with elevated intraocular pressure. Surv Ophthalmol 2001; 45 (Suppl): S361-8.
20. Moroi SE, Gottfredsdottir MS, Schteingart MT, Elner SG, Lee CM, Schertzer RM, et al. Cystoid macular edema associated with latanoprost therapy in a case series of patients with glaucoma and ocular hypertension. Ophthalmology 1999; 106: 1024-9.
21. Strahlman E, Tipping R, Vogel R. A double masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. Arch Ophthalmol 1995; 113: 1009-16.