Twenty-four hour control of intraocular pressure with dorzolamide and timolol maleate in exfoliation and primary open-angle glaucoma

ANASTASIOS G.P. KONSTAS,
ATHANASIOS MALTEZOS,
THEODOROS BUFIDIS,
ALISON G. HUDGINS,
WILLIAM C. STEWART

Abstract

Purpose To determine the efficacy and safety of adding dorzolamide 2% twice daily to timolol maleate solution 0.5% twice daily when treating exfoliation glaucoma or primary open-angle glaucoma.

Methods This was a single-centre, crossover intra-individually controlled comparison. Sixty-two consecutive patients (31 with exfoliation glaucoma and 31 with primary open angle glaucoma) chronically treated with timolol maleate twice daily were included in this trial. Patients then had added dorzolamide 2% twice daily (08:00 and 20:00), instilled approximately 10 min after timolol maleate. Patients underwent diurnal intraocular pressure (IOP) testing (six measurements over 24 h), first on timolol maleate monotherapy and 2 months later following the addition of dorzolamide 2% as adjunctive therapy.

Results On timolol monotherapy patients with exfoliation glaucoma had a higher mean IOP at 02:00, 06:00, 10:00, 14:00 and 22:00 hour time points as well as a higher maximum, minimum and range of IOP throughout the day compared with the primary open-angle glaucoma group ($p < 0.05$). Following the addition of dorzolamide as adjunctive therapy to timolol maleate there was a significant reduction in IOP ($p < 0.05$) at all time points in both glaucomas, but mean IOP at 10:00, 14:00, 18:00 and 22:00 hour time points, as well as the peak and range of IOP, remained higher in the exfoliation glaucoma group. No serious adverse events were noted with dorzolamide. Bitter taste, the most common symptom, was noted in 30% of patients.

Conclusions These data suggest that dorzolamide 2% used adjunctively with timolol maleate 0.5% solution is effective in reducing diurnal IOP in patients with primary open-angle and exfoliation glaucoma but does

not alter the characteristics of higher IOP levels in the latter disease.

Key words Dorzolamide, Exfoliation glaucoma, Primary open-angle glaucoma, Timolol maleate

Exfoliation glaucoma patients have been shown previously to present with higher mean intraocular pressures (IOPs) in general and to have IOPs that are more difficult to control than primary open-angle glaucoma patients.¹ In addition to the higher mean IOPs in exfoliation glaucoma, it has been shown recently that the peak and range of the IOPs throughout the day are greater than in primary open-angle glaucoma.² Also, recent evidence has indicated that a higher mean, range and peak IOP continue to differentiate exfoliation glaucoma and primary open-angle glaucoma despite treatment with monotherapy using timolol maleate solution.³

Because of the difficulty in controlling the IOP with a single agent in exfoliation glaucoma, it becomes important to assess carefully medicines which could be used as adjunctive therapy. Medicines that would be particularly effective in exfoliation glaucoma potentially could be a great benefit in preventing glaucomatous visual loss in these patients by minimising the IOP differences compared with primary open-angle glaucoma.

In the current study we investigated the adjunctive use of dorzolamide 2% used twice daily in conjunction with timolol maleate 0.5% solution used twice daily in both exfoliation glaucoma and primary open-angle glaucoma patients.

Materials and methods

We entered into this prospective study 62 consecutive Greek patients with either exfoliation glaucoma (31) or primary open-

A.G.P. Konstas
A. Maltezos
T. Bufidis
University Department of
Ophthalmology
AHEPA Hospital
Thessaloniki, Greece

A.C. Hudgins
W.C. Stewart
Pharmaceutical Research
Corporation
Charleston
South Carolina, USA

W.C. Stewart
The Carolina Eye Institute
at the University of South
Carolina School of Medicine
Columbia
and
Pharmaceutical Research
Corporation
Charleston
South Carolina, USA

William C. Stewart, MD ✉
Pharmaceutical Research
Corporation
1639 Tatum Street
Charleston
SC 29412-2464, USA

Supported in part by a grant from KESY (Greek Central Council of Health) and in part by an unrestricted grant from Research to Prevent Blindness

Proprietary interest: None

Received: 11 May 1999
Accepted in revised form
22 September 1999

angle glaucoma (31) in whom monotherapy with timolol maleate 0.5% twice daily was not adequate in controlling their IOP.

All patients treated with timolol maleate 0.5% b.i.d. whose IOP was greater than 21 mmHg at 08:00 hours met the criteria for inclusion in the present study. Patients with a history of ocular surgery/trauma, contact lens use, corneal abnormality, or any condition that prevented reliable applanation tonometry, were excluded. Similarly all patients with evidence of ocular infection, inflammation, or a history of renal or hepatic impairment were excluded from this study. In patients with bilateral glaucoma one eye was randomly selected to be included in this study. Patients were diagnosed and followed at the Glaucoma Unit of the University Department of Ophthalmology, AHEPA Hospital, Thessaloniki, Greece. Eligible glaucoma patients were recruited and the study was conducted between July 1996 and September 1997.

Eighteen patients were excluded from the study altogether. Fifteen were excluded because they demonstrated a well-controlled IOP on timolol alone or were too young or old and were disallowed for the purpose of matching. Patients were matched by age (± 2 years) to eliminate any effect of a potentially older age population on IOP in the exfoliation glaucoma group.^{2,3} Two additional patients declined due to the inconvenience of hospitalisation and one other patient could not be admitted for the last phasing due to another unrelated medical condition.

The methods for this study were similar to those described previously.^{2,3} All 62 patients in the present study were treated with timolol maleate 0.5% solution (Merck Sharp & Dohme/Vianex, Athens) twice daily with the dosing regimen set at 08:00 and 20:00 hours. The signing of an institutional review board informed consent was not required. Patients were admitted to the hospital for the baseline 24 h IOP diurnal curve on timolol maleate after at least 3 months of chronic dosing. Pressure measurements were performed by the same investigators (A.M., T.B.), using the same instrument (Goldmann applanation tonometer). Patients were admitted in the morning and measurements were recorded at 10:00, 14:00, 18:00, 22:00, 02:00 and 06:00 hours. At the 22:00 hour measurement patients were awake at bed rest. The 06:00 hour IOP measurement was performed immediately after waking. Patients were encouraged to lead as normal a life as possible within the hospital boundaries.

Following discharge from the hospital patients who met the inclusion criteria for this study and whose IOP was not controlled sufficiently (i.e. IOP > 21 mmHg at 08:00 hours on timolol maleate alone) were started on dorzolamide 2% drops (Merck Sharp & Dohme/Vianex, Athens) twice daily. The dosing regimen of dorzolamide was set at 08:00 and 20:00 hours. Patients were instructed regarding study medication instillation and compliance. Dorzolamide drops were instilled approximately 10 min after timolol maleate drops. Patients who could not comply were excluded. All 62 patients who completed

Table 1. Patient baseline data

	EXG	POAG	<i>p</i> value
Age (years)	68.5 $\pm$ 6.9	68.1 $\pm$ 7.7	0.863
Gender			
Male	16	18	
Female	15	13	
Visual acuity	0.64 $\pm$ 0.4	0.70 $\pm$ 0.3	0.495
Cup-to-disc ratio	0.69 $\pm$ 0.1	0.65 $\pm$ 0.2	0.400
Visual field mean defect ^a	10.7 $\pm$ 5.5	8.9 $\pm$ 5.4	0.162

EXG, exfoliation glaucoma; POAG, primary open-angle glaucoma.

^aOctopus 500 EZ, GI program; analysis by Peridata 6.2c, Interzeag AG, Zurich, Switzerland.

the dosing regimen were readmitted 2 months after their first diurnal curve with timolol for a second 24 h phasing while using dorzolamide and timolol maleate drops. Follow-up visits and appropriate treatment steps were scheduled according to the result of the diurnal curve.

Statistical analysis was performed after patients with these two glaucomas were matched for age and sex (Table 1). Statistical analyses on the IOP at each time point were evaluated by an unpaired *t*-test between diagnostic groups.⁴ A paired *t*-test was used to evaluate the reduction in IOP from baseline within groups after the addition of dorzolamide. This study had an 80% power to detect a 1.7 mmHg difference in the IOP following the addition of dorzolamide as adjunctive therapy. A standard deviation of 3.2 mmHg was used.^{5,6} An *F*-test was used to evaluate differences in the standard deviations between groups at each time point.⁴ The significance level was set at 5% and all tests were a two-way analysis. Differences in visual acuity and cup-to-disc ratio between groups were analysed by a Mann-Whitney *U*-test.⁷ Differences in mean defect between groups were evaluated with an unpaired *t*-test.

Results

Patients

Sixty-two patients (31 with exfoliation glaucoma and 31 with primary open-angle glaucoma) were included in this trial. Baseline patient data are shown in Table 1: age, gender, visual acuity, cup-to-disc ratio and visual field mean defect. No statistical difference between groups was noted for any parameter. All patients were ethnic Greek and Caucasian.

Intraocular pressure

Data in exfoliation glaucoma and primary open-angle glaucoma patients when treated with timolol maleate only are shown in Table 2. A significant difference existed at each time point except at 18:00 hours between exfoliation glaucoma and primary open-angle glaucoma patients for the IOP ($p < 0.05$). Likewise, a significant difference in the maximum and minimum IOP as well as the standard deviation of the pressure at each time point existed between groups ($p < 0.05$).

Table 2. Baseline mean intraocular pressure (mmHg ± SD) on timolol maleate

Time (hours)	EXG (n = 31)	POAG (n = 31)	p value ^a
06:00	26.8 ± 7.5	22.8 ± 3.2	0.001
10:00	28.1 ± 7.9	22.8 ± 3.6	0.001
14:00	25.9 ± 7.0	21.9 ± 3.7	0.006
18:00	24.6 ± 7.1	21.9 ± 4.2	0.075
22:00	24.3 ± 6.6	20.5 ± 4.1	0.008
02:00	24.5 ± 6.2	20.9 ± 3.4	0.005
Maximum	30.4 ± 8.0	24.8 ± 3.3	0.001
Minimum	21.9 ± 5.8	18.8 ± 3.2	0.012
Range	8.5 ± 3.6	6.0 ± 2.3	0.002

EXG, exfoliation glaucoma; POAG, primary open angle glaucoma.

^aIndicates the difference in mean intraocular pressure between groups.

Table 3 shows the IOP results of both groups after dorzolamide was added to timolol maleate. A significant difference in IOP between groups remained at each time point except at 02:00 and 06:00 hours. A significant difference in the average maximum pressure still existed between groups but not for the minimum pressure. In addition, following the addition of dorzolamide only the daytime hours of 06:00, 10:00 and 14:00 hours showed a significant difference in the standard deviation of the IOP between groups.

Table 4 shows the percentage and absolute reductions in IOP in patients on timolol maleate only compared with treatment with timolol maleate and dorzolamide together. A statistically significant reduction from baseline was shown at each time point for both exfoliation glaucoma and primary open-angle glaucoma patients ($p < 0.05$). The percentage reduction was not different between groups, however, at each time point ($p > 0.05$). However, the absolute reduction was significantly greater in exfoliation glaucoma patients ($p < 0.05$) in the early morning hours (02:00 and 06:00).

Safety

Two of 62 patients (3%) developed a moderate ocular intolerance to dorzolamide over the 2 months of therapy but tolerated the medication sufficiently to complete the second diurnal curve. Another patient who developed marked ocular intolerance 2 weeks after initiation of dorzolamide was discontinued from the study and is not

Table 3. Baseline mean intraocular pressure (mmHg ± SD) on dorzolamide and timolol maleate

Time (hours)	EXG (n = 31)	POAG (n = 31)	p value ^a
06:00	20.4 ± 5.0	18.6 ± 3.4	0.103
10:00	21.8 ± 6.4	18.3 ± 3.3	0.000
14:00	20.5 ± 5.1	17.8 ± 3.1	0.014
18:00	20.5 ± 4.4	17.9 ± 3.3	0.013
22:00	19.8 ± 3.9	17.6 ± 3.3	0.019
02:00	19.8 ± 4.1	18.1 ± 3.7	0.082
Maximum	24.0 ± 6.4	20.1 ± 3.6	0.005
Minimum	17.9 ± 3.7	16.3 ± 2.5	0.054
Range	6.1 ± 4.1	3.8 ± 2.2	0.009

EXG, exfoliation glaucoma; POAG, primary open angle glaucoma.

^aIndicates the difference in mean intraocular pressure between groups.

included in the data reported here. Accordingly, the overall ocular incidence of intolerance was 3 of 63 patients (5%).

Nineteen of 62 (30%) patients reported a bitter taste after instillation. Three patients (5%) experienced ocular side-effects (temporary blurring of vision in 1 patient and burning/stinging or dryness after administration in 2 patients). These unsolicited symptoms did not affect the investigation but resulted in discontinuation of the medication in one of these patients after completion of the study. Non-ocular side-effects were not reported during the course of this investigation.

Discussion

Dorzolamide 2% is a topical carbonic anhydrase inhibitor which reduces the IOP by suppressing aqueous formation reduction.⁸ Wang and associates⁸ showed that aqueous production is reduced by between 13% and 18% by dorzolamide as monotherapy and by 24% when dorzolamide is added to timolol maleate; there is no apparent influence on outflow facility.⁸⁻¹³ Dorzolamide is most effective as a single agent given in the 2% concentration t.i.d.¹⁴ As monotherapy, dorzolamide has been reported to reduce the IOP from baseline by 10-26%.¹⁴⁻¹⁸ The peak IOP reduction from baseline appears to be between 17% and 24% and the trough effect between 13% and 18%.¹⁷ Strahlman and co-workers¹⁸ found that the efficacy of dorzolamide was slightly, but statistically less, than that of timolol maleate. In their

Table 4. Percentage and absolute intraocular pressure (mmHg ± SD) reduction from baseline

Time (hours)	Percentage reduction			Absolute reduction		
	EXG	POAG	p value	EXG	POAG	p value
06:00	22.6% ± 11.6%	18.2% ± 12.3%	0.138	6.4 ± 4.7	4.23 ± 2.8	0.018
10:00	21.3% ± 12.8%	19.1% ± 13.8%	0.251	6.3 ± 5.0	4.55 ± 3.5	0.059
14:00	19.1% ± 16.5%	18.4% ± 10.2%	0.424	5.4 ± 4.7	4.16 ± 2.6	0.106
18:00	14.5% ± 15.3%	17.1% ± 12.9%	0.212	4.2 ± 4.4	4.00 ± 3.3	0.426
22:00	15.6% ± 17.8%	12.4% ± 15.5%	0.235	4.5 ± 4.9	2.87 ± 3.3	0.078
02:00	17.5% ± 13.0%	12.8% ± 13.3%	0.103	4.7 ± 4.0	2.77 ± 3.1	0.025
Maximum	20.0% ± 12.2%	18.9% ± 9.5%	0.359	6.4 ± 4.8	4.71 ± 2.6	0.047
Minimum	16.7% ± 13.0%	12.2% ± 12.1%	0.080	4.0 ± 3.4	2.52 ± 2.5	0.022

EXG, exfoliation glaucoma; POAG, primary open angle glaucoma.

study, dorzolamide tended to be more effective than betaxolol both at peak and trough levels.¹⁸ However, these differences were not statistically significant.

As adjunctive therapy Nardin *et al.*¹⁹ and Strahlman and associates²⁰ found that dorzolamide given twice daily may provide a peak response of an additional 13–20% reduction in the IOP when added to timolol maleate. Heijl and co-workers²¹ showed in exfoliation glaucoma patients that as monotherapy timolol maleate was more effective in lowering the IOP than dorzolamide (29% vs 24%). Additionally, dorzolamide had about 15% additivity to timolol maleate both at daytime peak and trough levels.²¹ However, previous work with exfoliation glaucoma patients frequently demonstrates a peak IOP outside normal office hours.^{2,3} Additionally, few data compare the effect of dorzolamide in exfoliation glaucoma patients and primary open-angle glaucoma patients.

The purpose of this study was to investigate the efficacy of dorzolamide added to timolol maleate solution 0.5% given twice a day in patients with primary open-angle glaucoma or exfoliation glaucoma.

This study found that while using timolol maleate only, exfoliation glaucoma patients had higher baseline IOPs than primary open-angle glaucoma patients. Differences were observed between groups in mean IOPs at each time point throughout the day as well as between the average maximum and minimum IOPs across all patients. Also, on timolol maleate treatment only, the standard deviations of the IOPs at each time point were statistically higher in exfoliation glaucoma compared with primary open-angle glaucoma. These findings were consistent with past diurnal curve data comparing timolol maleate in exfoliation and primary open-angle glaucoma patients according to Topper and Brubaker.²²

Following treatment with dorzolamide, differences in IOP between groups for most of the parameters discussed above remained. A statistical difference between groups in mean IOP still was observed at the 10:00, 14:00, 18:00 and 22:00 hour time points, as well as in the average maximum IOP. Likewise, standard deviations between groups remained statistically different at 06:00, 10:00 and 14:00 hours. The percentage decrease in IOP was similar between groups from baseline following adjunctive treatment with dorzolamide at each time point. However, the absolute reduction in IOP was greater in the exfoliation glaucoma group during the early morning hours (02:00 and 06:00). The reason for this is not entirely clear from our results.

Safety following the addition of dorzolamide to timolol maleate was similar between exfoliation glaucoma and primary open-angle glaucoma groups and the incidence and types of side-effects were consistent with past studies.²³ Three patients experienced ocular intolerance, one of whom was discontinued from the study prior to the diurnal curve with dorzolamide. Two of these patients continued in the study despite the intolerance. Bitter taste, blurred vision, stinging and burning also were noted. One patient discontinued

dorzolamide following the completion of the second diurnal curve because of ocular intolerance. No systemic side-effects were noted during the study.

This study suggests that dorzolamide as adjunctive therapy is equally effective in lowering the IOP in patients with exfoliation glaucoma as in those with primary open-angle glaucoma. However, it does little to change the basic IOP characteristics which distinguish exfoliation glaucoma from primary open-angle glaucoma.

Further study is needed to determine the best treatment regimen for exfoliation syndrome as well as to find IOP levels which are safe for these patients over a long period of time. Likewise, determining other factors besides the IOP which are associated with visual loss in exfoliation glaucoma may be important in preserving these patients' vision.

References

1. Konstas AGP, Stewart WC, Stroman GA, *et al.* Clinical presentation and initial treatment patterns in patients with exfoliation versus primary open-angle glaucoma. *Ophthalmic Surg Lasers* 1997;28:111–7.
2. Konstas AGP, Mantziris DA, Stewart WC. Diurnal intraocular pressure in untreated exfoliation and primary open-angle glaucoma. *Arch Ophthalmol* 1997;115:182–5.
3. Konstas AGP, Mantziris DA, Cate EA, *et al.* Effect of timolol on the diurnal IOP in exfoliation and primary open-angle glaucoma. *Arch Ophthalmol* 1997;115:975–9.
4. Book SA. *Essentials of statistics*. New York: McGraw Hill, 1978:117–22, 205–15.
5. Stewart WC, Cate EA, Pruitt CA. Additivity of latanoprost 0.0005% to timolol hemihydrate 0.5% in ocular hypertensive or chronic open-angle glaucoma patients. Ciba Vision Ophthalmics internal report, 1997.
6. Feghali J, Kaufman P. Decreased intraocular pressure in the hypertensive human eye with betaxolol, a β_1 -adrenergic antagonist. *Am J Ophthalmol* 1985;100:777–82.
7. Moses L, Emerson J, Hosseini H. Statistics in practice: analysing data from ordered categories. *N Engl J Med* 1984;311:442–8.
8. Wang RF, Serle JB, Podos SM, Sugrue MF. MK-507 (L-671, 152), a topically active carbonic anhydrase inhibitor, reduces aqueous humor production in monkeys. *Arch Ophthalmol* 1991;109:1297–9.
9. Wayman LL, Larsson L-I, Maus TL, Brubaker RF. Additive effect of dorzolamide on aqueous humor flow in patients receiving long-term treatment with timolol. *Arch Ophthalmol* 1998;116:1438–40.
10. Larsson L-I, Alm A. Aqueous humor flow in human eyes treated with dorzolamide and different doses of acetazolamide. *Arch Ophthalmol* 1998;116:19–24.
11. Wayman L, Larsson L-I, Maus T, Alm A, Brubaker R. Comparison of dorzolamide and timolol as suppressors of aqueous humor flow in humans. *Arch Ophthalmol* 1997;115:1368–71.
12. Maus TL, Larsson L-I, McLaren JW, Brubaker RF. Comparison of dorzolamide and acetazolamide as suppressors of aqueous humor flow in humans. *Arch Ophthalmol* 1997;115:45–9.
13. Vanlandingham BD, Maus TL, Brubaker RF. The effect of dorzolamide on aqueous humor dynamics in normal human subjects during sleep. *Ophthalmology* 1998;105:1537–40.
14. Lippa EA, Carlson LE, Ehinger B, *et al.* Dose response and duration of action of dorzolamide, a topical carbonic anhydrase inhibitor. *Arch Ophthalmol* 1992;110:495–9.

15. Lippa EA, Schuman JS, Higginbotham EJ, *et al.* MK-507 versus sezolamide: comparative efficacy of two topically active carbonic anhydrase inhibitors. *Ophthalmology* 1991;98:308–13.
16. Wilkerson M, Cyrilin M, Lippa EA, *et al.* Four-week safety and efficacy study of dorzolamide, a novel, active topical carbonic anhydrase inhibitor. *Arch Ophthalmol* 1993;111:1343–50.
17. Kitazawa Y, Azuma I, Iwata K, *et al.* Dorzolamide, a topical carbonic anhydrase inhibitor: a two-week dose response study in patients with glaucoma or ocular hypertension. *J Glaucoma* 1994;3:275–9.
18. Strahlman E, Tipping R, Vogel R, *et al.* A double masked, randomized one-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. *Arch Ophthalmol* 1995;113:1009–16.
19. Nardin G, Lewis R, Lippa EA, Keates E, Coleman A, Clineschmidt Panebianco D, *et al.* Activity of the topical CAI MK-507 bid when added to timolol bid. *Invest Ophthalmol Vis Sci* 1991;32(Suppl):989.
20. Strahlman ER, Vogel R, Tipping R, *et al.* The use of dorzolamide and pilocarpine as adjunctive therapy to timolol in patients with elevated intraocular pressure. *Ophthalmology* 1996;103:1283–93.
21. Heijl A, Strahlman E, Sverrisson T, *et al.* A comparison of dorzolamide and timolol in patients with pseudoexfoliation glaucoma or ocular hypertension. *Ophthalmology* 1997;104:137–42.
22. Topper JE, Brubaker RF. Effects of timolol, epinephrine, and acetazolamide on aqueous flow during sleep. *Invest Ophthalmol Vis Sci* 1985;26(Suppl):1315–9.
23. Stewart WC. Current and future glaucoma therapy. *Ciba Vision Ophthalmics Clinical Symposium*, 1997:1–43.