A Randomized Trial Comparing the Dorzolamide–Timolol Combination Given Twice Daily to Monotherapy with Timolol and Dorzolamide

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Objective: To compare the efficacy and safety of a fixed combination of 2.0% dorzolamide and 0.5% timolol administered twice daily with each of the individual components administered in their usual monotherapy dose regimens in patients who had washed out all ocular hypotensive medications.

Design: A 3-month, parallel, randomized, double-masked, active-controlled, multicenter clinical trial.

Participants: A total of 335 patients with bilateral ocular hypertension or open-angle glaucoma participated.

Intervention: After completing a washout of ocular hypotensive medications, patients were randomized to receive either the dorzolamide–timolol combination twice daily plus placebo once daily, 0.5% timolol twice daily plus placebo once daily, or 2.0% dorzolamide three times daily.

Main Outcome Measures: Intraocular pressure (IOP) was measured at morning trough (hour 0) and peak (2 hours postdose) on day 1, week 2, and months 1, 2, and 3. Ocular and systemic safety were evaluated at each study visit.

Results: Intraocular pressure reduction was greater on average in the combination group than in the dorzolamide and timolol groups. At morning trough (month 3, hour 0), the mean reduction in IOP from baseline was 27.4% (−7.7 mmHg) for the combination, 15.5% (−4.6 mmHg) for dorzolamide, and 22.2% (−6.4 mmHg) for timolol. At morning peak (month 3, hour 2), the mean IOP reduction from baseline was 32.7% (−9.0 mmHg), 19.8% (−5.4 mmHg), and 22.6% (−6.3 mmHg) for the combination, dorzolamide, and timolol, respectively. Overall, the incidence of clinical adverse experiences was comparable between the combination and each of its components. The proportion of patients who discontinued from the study because of clinical adverse experiences was also comparable between the combination and dorzolamide, although it was significantly greater in the combination group than in the timolol group (7% vs. 1%, $P = 0.036$). Similarly, comparable numbers of patients in the combination and dorzolamide groups reported ocular symptoms; however, when compared to the timolol group, more patients receiving the combination reported blurred vision, burning eye, stinging eye, and tearing eye.

Conclusions: After a washout of ocular hypotensive therapy, the IOP-lowering effect of the dorzolamide–timolol combination was greater than that of either of its components administered as monotherapy. The combination is generally well-tolerated and provides a convenient alternative to concomitant therapy with its individual components. *Ophthalmology 1998;105:1945–1951*

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Ms. Boyle, Dr. Ghosh, and Dr. Adamsons were employees of Merck & Co., Inc, the manufacturer of timolol and dorzolamide, at the time this study was conducted. COSOPT and TRUSOPT are trademark products of Merck & Co., Inc, Whitehouse Station, New Jersey. The other authors have no proprietary interest in timolol, dorzolamide, or Merck.

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Open-angle glaucoma is a chronic disease characterized by the painless elevation of intraocular pressure (IOP), progressive optic nerve damage, and visual field loss leading to blindness. Currently, lowering IOP is the only established medical treatment for open-angle glaucoma. There is increasing evidence that reducing IOP as much as possible improves the likelihood of delaying or halting progression of optic nerve damage and visual field loss.[1] The most common first-line therapy for the treatment of glaucoma is topical beta-blockers, specifically timolol maleate. Because glaucoma is a chronic progressive disease, however, the majority of patients eventually require more than one medication to control their IOP. Dorzolamide hydrochloride (TRUSOPT, Merck & Co., Inc, Whitehouse Station, NJ) is a topical carbonic anhydrase inhibitor that is frequently prescribed as adjunctive therapy to timolol to achieve ad-

ditional IOP reduction. In controlled clinical trials; dorzolamide provided additional IOP reduction when used as adjunctive therapy to timolol regardless of which of the two drugs was used as the initial therapy.[2–4] In addition to the demonstrated efficacy of dorzolamide and timolol, the safety profiles of these agents are well-established.

Dorzolamide and timolol have been formulated as a combination product (COSOPT, Merck & Co., Inc, Whitehouse Station, NJ) that would provide a more convenient dosing regimen for patients requiring multiple medications. Kass and associates[5] have shown that although patient noncompliance is a factor regardless of the medication prescribed, the rate of compliance (mean ± standard deviation) with timolol administered twice daily (84.3% ± 14.0%) is greater than the rate of compliance with pilocarpine (77.7% ± 18.7%), which was administered four times daily. An even greater decrease in compliance with increasing dosing frequency was reported by Cramer et al.[6] These investigators found that compliance with epilepsy medications decreased from 87% for medications taken once daily to 39% for medications taken four times daily. Furthermore, patients' compliance to take their medication during the dosing interval window (i.e., 9–15, 6–10, and 4–8 hours for twice-daily, three-times-daily, and four-times-daily regimens, respectively) also decreased with increased dosing frequency.[7] Although reducing the number of products and the number of required daily instillations is unlikely to eliminate the problem of noncompliance entirely, the combination formulation may improve the rate of compliance and consequently improve IOP control.

The combination has previously been evaluated in patients inadequately controlled with timolol monotherapy (Strohmaier K, et al. Invest Ophthalmol Vis Sci 1996;37:S1102). The current trial was designed to evaluate the combination in comparison to its components in a broader patient population than has been studied previously, namely those withdrawn from ocular hypotensive therapy.

Materials and Methods

This was a 3-month, parallel, randomized, double-masked, active-controlled study conducted at 27 centers in the United States, all of which received ethical review committee approval of the protocol; informed consent was obtained from all patients before beginning the study. Males and postmenopausal or sterilized females 21 to 85 years of age with bilateral open-angle glaucoma or ocular hypertension were eligible for enrollment. Among the ocular conditions for which patients were excluded were visual acuity worse than 20/80 in both eyes, history or evidence of acute or chronic angle closure glaucoma, or history or evidence of intraocular surgery or significant ocular trauma within 6 months of study start. However, patients may have had intraocular laser therapy up to 3 months before study start. Other reasons for exclusion included any contraindication to timolol or carbonic anhydrase inhibitors, known severe or serious hypersensitivity to sulfonamides, concomitant therapy with medications known to affect IOP, and previous exposure to the dorzolamide–timolol combination.

Before entering the study, patients discontinued all ocular hypotensive medications according to the following schedule: 21 days for beta-blockers and oral carbonic anhydrase inhibitors, 7 days for epinephrine or dipivefrin, and 72 hours for pilocarpine, carbachol, or aceclidine. After this washout period, patients returned to the clinic on day 1 for baseline examinations. Baseline IOP measurements were recorded at 8:30 AM (hour 0) and 10:30 AM (hour 2) to correspond to morning trough and peak measurements. Patients with an IOP of greater than or equal to 24 mmHg in at least one eye (the same eye) at hours 0 and 2 were then randomly assigned, according to a computer-generated allocation schedule, to receive one of the following three masked treatments: 0.5% timolol–2.0% dorzolamide twice daily plus placebo once daily; 0.5% timolol twice daily plus placebo once daily; or 2.0% dorzolamide three times daily.

The formulation of timolol used was TIMOPTIC (Merck & Co., Inc, Whitehouse Station, NJ), a phosphate-buffered solution (pH 6.8) of timolol maleate. The formulation of dorzolamide used was TRUSOPT, a buffered (pH 5.6), slightly viscous, aqueous solution of dorzolamide hydrochloride. The fixed combination of dorzolamide–timolol was formulated by adding timolol maleate to the TRUSOPT formulation and therefore was a slightly viscous solution with a pH of 5.6. All formulations were isotonic; benzalkonium chloride was the preservative. In a study in pigmented rabbits, the bioavailability of timolol and dorzolamide in the iris–ciliary body was very comparable whether the drugs were administered as separate components or as the fixed combination (Sugrue MF, et al. Invest Ophthalmol Vis Sci 1998;39:S926).

The first dose of test drug was administered in the afternoon on day 1. All patients were dispensed medication labeled with instillation instructions and packaged by allocation number in identical bottles. A disclosure panel, which identified the contents of each bottle beneath a mask, was separated from each bottle at the time of dispensing and was kept with the patients' records. In the event of an emergency requiring the identification of test drug, the disclosure panel could have been swabbed with alcohol to remove the mask and show the contents of the bottle. No labels were unmasked during the study. Measurements were obtained immediately predose at morning trough (hour 0) and 2 hours after the morning dose at morning peak (hour 2). Ocular symptoms, signs, and adverse experiences were also recorded at each visit. An adverse experience was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with any use of study medication whether or not considered related to the use of the study drug. Additional safety measurements included a physical examination, a complete ophthalmic examination, computerized visual fields, and laboratory evaluations (blood chemistry and hematology) during the washout period and at poststudy.

Statistical Analysis

Ocular hypotensive effect was assessed using the percent change in IOP from the time-matched baseline values (hours 0 and 2). The percent change from baseline was calculated using the patient's worse eye. If only one eye met the entry criterion, then that eye was defined as the worse eye. However, if both eyes met the criterion, then the worse eye was defined as the eye with the higher IOP at hour 0 on day 1. If both eyes were equal at that time, the eye with the higher IOP at hour 2 on day 1 was selected. If both eyes were equal at hour 2, then the right eye was selected.

The statistical software package SAS, Version 6.10 (SAS Institute Inc, Cary, NC), was used to evaluate the data. The differences in mean percent change in IOP from baseline between the

Table 1. Baseline Demographic Characteristics by Treatment Group: No. (%)

	Combination (N = 114)	Dorzolamide (N = 109)	Timolol (N = 112)	Total (N = 335)
Sex				
Male	54 (47)	55 (50)	62 (55)	171 (51)
Female	60 (53)	54 (50)	50 (45)	164 (49)
Race				
White	94 (82)	94 (86)	88 (79)	276 (82)
Black	18 (16)	12 (11)	19 (17)	49 (15)
Hispanic	1 (1)	2 (2)	3 (3)	6 (2)
Other	1 (1)	1 (1)	2 (2)	4 (1)
Iris color				
Dark brown	18 (16)	15 (14)	18 (16)	51 (15)
Brown	31 (27)	31 (28)	27 (24)	89 (27)
Hazel	24 (21)	21 (19)	31 (28)	76 (23)
Green	5 (4)	8 (7)	5 (4)	18 (5)
Blue	36 (32)	34 (31)	31 (28)	101 (30)
Age (yrs)				
Mean [SD]	62.4 [11.7]	61.3 [11.8]	62.4 [11.1]	62.0 [11.5]
Range	28–83	27–84	36–83	27–84
Baseline IOP – worse eye (mmHg)				
Hr 0				
Mean [SD]	27.8 [5.0]	28.1 [4.7]	27.9 [4.6]	27.9 [4.8]
Hr 2				
Mean [SD]	27.0 [4.4]	27.2 [3.7]	27.2 [4.3]	27.1 [4.1]

SD = standard deviation; IOP = intraocular pressure.

combination and the monotherapy groups were estimated from the weighted average of observed treatment differences in clinics where the weights were proportional to the number of patients enrolled at each clinic. A two-way analysis of variance model was used to evaluate the effect of treatment, investigative site, and their interaction. Ninety-five percent confidence intervals (CIs) for the mean difference in percent change in IOP from baseline were used to determine the superiority of the combination over its components. If the limits of the CIs were negative, the superiority of the combination was concluded. Note that this study was designed to provide 94% power for detecting a difference of 6.0 percentage points in the mean percent change from baseline between any 2 groups, based on a sample size of 100 patients per group and an assumed standard deviation of 12.0 percentage points within each group; these percentage points were based on the results of a previous study of the combination.[6]

The primary efficacy analysis was based on the All-Patients-Treated, Last Observation Carried Forward (APT–LOCF) approach. In this approach, all patients randomized to study medication with efficacy data for at least one visit after randomization were included. Missing data were estimated from previous time-matched observations occurring within the study period. Patients with missing data at the first visit of the study were not included until a visit with data was reached.

To validate the primary analysis, a secondary analysis was performed using the Per-Protocol-Observed Cases (PP–OC) approach in which examinations associated with a serious violation of the protocol were excluded and missing data points were not estimated. The results from this approach were similar to those of the APT–LOCF approach, and therefore only results from the APT–LOCF approach will be presented. Treatment group comparisons with regard to the incidence of adverse experiences and ocular signs and symptoms were made using Fisher's exact test (two-tailed).

Results

Demographics and Patient Accounting

A total of 335 patients (171 males and 164 females) entered this study and were randomized to 1 of the 3 treatment groups. Table 1 presents the baseline demographic characteristics of the study population. The mean age was 62 years and 82% of patients were white. There were no statistically significant differences between the treatment groups with regard to the proportion of males and females, race distribution, iris color, age, or baseline IOP (worse eye).

The most common concomitant medical conditions present in patients participating in the study were hypertension, arthritis, hypercholesterolemia, and headache. The most common prior therapies were timolol maleate, aspirin, pilocarpine, and levobunolol hydrochloride. The most common concomitant therapies were ibuprofen, aspirin, and acetaminophen.

Of the 335 patients in this study, 334 contributed IOP data for the primary analysis of efficacy (APT–LOCF). One patient who did not have any IOP measurements after baseline was excluded. All 335 patients were included in the evaluation of clinical and laboratory adverse experiences.

Efficacy Results

The IOP summary statistics for each study visit are presented in Table 2. At the end of the study, at morning trough (month 3, hour 0), the percent mean IOP reduction from baseline was 27.4% (−7.7 mmHg) in the combination group, 15.5% (−4.6 mmHg) in the dorzolamide group, and 22.2% (−6.4 mmHg) in the timolol group. At morning peak (month 3, hour 2), the mean IOP reduction from baseline was 32.7% (−9.0 mmHg) in the combination group, 19.8% (−5.4 mmHg) in the dorzolamide group, and 22.6% (−6.3 mmHg) in the timolol group.

Table 2. Intraocular Pressure (mmHg) Summary Statistics: Mean (Standard Deviation)*

Examination	Treatment	N	Baseline	Treatment	Change	% Change
Hr 0						
Wk 2	Combination	113	27.9 (5.0)	19.7 (4.1)	−8.1 (4.6)	−28.5 (13.3)
	Dorzolamide	109	28.1 (4.7)	23.4 (4.4)	−4.6 (3.7)	−16.1 (11.6)
	Timolol	111	27.9 (4.6)	21.5 (3.8)	−6.4 (4.0)	−22.4 (11.8)
Mo 1	Combination	114	27.8 (5.0)	19.8 (4.3)	−8.0 (4.5)	−28.2 (13.0)
	Dorzolamide	109	28.1 (4.7)	23.1 (4.2)	−5.0 (3.8)	−17.4 (11.4)
	Timolol	111	27.9 (4.6)	20.9 (4.0)	−7.0 (3.9)	−24.6 (11.7)
Mo 2	Combination	114	27.8 (5.0)	20.1 (4.5)	−7.7 (4.2)	−27.3 (12.7)
	Dorzolamide	109	28.1 (4.7)	23.4 (4.3)	−4.7 (3.9)	−16.3 (12.0)
	Timolol	111	27.9 (4.6)	21.4 (4.6)	−6.5 (3.8)	−23.2 (12.0)
Mo 3	Combination	114	27.8 (5.0)	20.1 (4.5)	−7.7 (4.2)	−27.4 (13.1)
	Dorzolamide	109	28.1 (4.7)	23.5 (4.2)	−4.6 (4.3)	−15.5 (13.5)
	Timolol	111	27.9 (4.6)	21.5 (4.0)	−6.4 (4.1)	−22.2 (12.5)
Hr 2						
Wk 2	Combination	111	27.1 (4.4)	18.0 (3.5)	−9.1 (3.9)	−33.1 (11.2)
	Dorzolamide	109	27.3 (3.8)	21.3 (3.9)	−6.0 (3.1)	−21.9 (10.6)
	Timolol	110	27.3 (4.4)	20.3 (3.5)	−7.0 (4.9)	−24.6 (14.5)
Mo 1	Combination	112	27.1 (4.3)	17.8 (3.7)	−9.3 (4.4)	−33.7 (13.1)
	Dorzolamide	109	27.3 (3.8)	21.2 (3.9)	−6.1 (3.3)	−22.1 (11.0)
	Timolol	110	27.3 (4.4)	20.2 (3.9)	−7.0 (4.9)	−24.8 (15.0)
Mo 2	Combination	112	27.1 (4.3)	17.7 (3.7)	−9.4 (4.4)	−34.1 (12.6)
	Dorzolamide	109	27.3 (3.8)	21.3 (3.8)	−5.9 (3.3)	−21.5 (10.9)
	Timolol	110	27.3 (4.4)	20.7 (4.4)	−6.6 (5.2)	−23.3 (16.8)
Mo 3	Combination	112	27.1 (4.3)	18.1 (3.8)	−9.0 (4.3)	−32.7 (12.9)
	Dorzolamide	109	27.3 (3.8)	21.8 (4.3)	−5.4 (3.6)	−19.8 (12.6)
	Timolol	110	27.3 (4.4)	21.0 (4.7)	−6.3 (4.7)	−22.6 (15.6)

SD = standard deviation.

* All patients treated analysis (last observation carried forward) − worse eye.

Figure 1A displays IOP treatment means and standard errors for all treatments at the trough timepoint (hour 0) for each study visit. Treatment means for the peak timepoint (hour 2) are shown in Figure 1B. At baseline, mean IOP was comparable among the three treatment groups, and at both trough and peak at all visits the combination group showed a greater reduction in IOP from baseline than either the dorzolamide group or the timolol group. The difference in IOP reduction from baseline was greater at hour 2 than at hour 0.

The differences between treatment groups in mean percent change in IOP from baseline are presented in Table 3 along with CIs and probability values. At month 3, hour 0, the mean difference between the combination and dorzolamide was −12.0 percentage points, and the 95% CI was −15.3, −8.7. At the same timepoint, the mean difference between the combination and timolol in effect on IOP was −4.9 percentage points with a 95% CI of −8.2, −1.6. The negative limits of the CIs indicate that at all timepoints, the combination has a greater IOP-lowering effect than dorzolamide or timolol administered as monotherapy. No interaction between the treatments and the sites was found, indicating that the differences in treatment effects were consistent across sites.

Safety Results

Table 4 presents a summary of the adverse experiences reported during this study. Of the 335 patients in the study, 173 (52%) had a clinical adverse experience: 57 while receiving the combination,

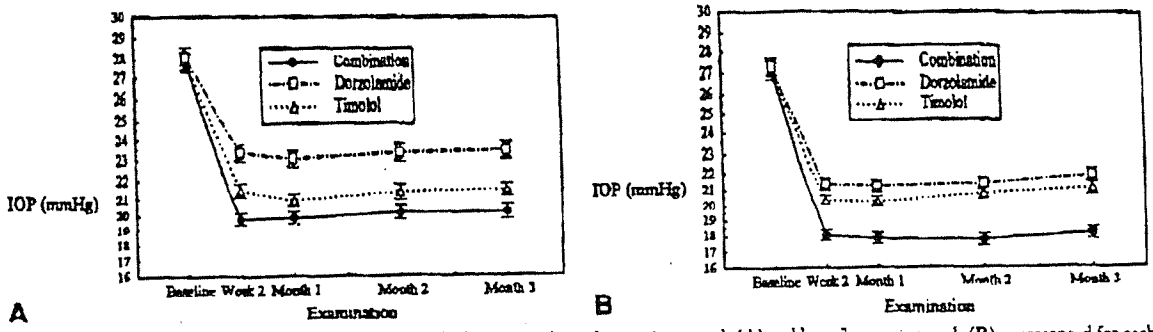

Figure 1. The mean intraocular pressure (IOP) (and standard errors) at hour 0, morning trough (A) and hour 2, morning peak (B) is presented for each treatment group at all study visits. At both timepoints and at all study visits, the patients receiving the combination experienced a greater drop in IOP than did the patients receiving either timolol or dorzolamide monotherapy.

Table 3. Estimated Differences, Confidence Intervals, and P Values for Difference between Treatments in Mean Percent Change in Intraocular Pressure (IOP) from Baseline*

Examination	Combination − Dorzolamide†			Combination − Timolol†		
	Percentage Point Difference‡	95% CI	P	Percentage Point Difference‡	95% CI	P
Hr 0						
Wk 2	−12.4	−15.6,−9.1	<0.001	−5.9	−9.2,−2.7	<0.001
Mo 1	−11.0	−14.0,−8.1	<0.001	−3.4	−6.3,−0.5	0.024
Mo 2	−11.5	−14.6,−8.3	<0.001	−4.0	−7.1,−0.9	0.011
Mo 3	−12.0	−15.3,−8.7	<0.001	−4.9	−8.2,−1.6	0.003
Hr 7						
Wk 2	−11.3	−14.4,−8.1	<0.001	−8.1	−11.2,−5.0	<0.001
Mo 1	−11.7	−15.0,−8.5	<0.001	−8.5	−11.8,−5.3	<0.001
Mo 2	−12.7	−16.2,−9.2	<0.001	−10.5	−14.0,−7.1	<0.001
Mo 3	−12.9	−16.4,−9.4	<0.001	−9.9	−13.4,−6.4	<0.001

CI = confidence interval.

* All patients treated analysis (last observation carried forward) − worse eye.

† (Percent change in IOP with combination) − (percent change in IOP with component).

‡ Negative values for the percentage point differences favor the combination.

63 while receiving dorzolamide, and 53 while receiving timolol. There were no statistically significant differences between the combination group and its components in the proportion of patients with any adverse experience, with drug-related adverse experiences, or with serious adverse experiences. A significantly greater proportion of patients discontinued from the study due to adverse experiences in the combination group than in the timolol group (7% vs. 1%, $P = 0.035$). Of the eight patients who discontinued while receiving the combination, five discontinued because of drug-related adverse experiences. Three of these five patients discontinued because of ocular adverse experiences including ocular swelling, follicular conjunctivitis, foreign body sensation, cloudy vision, burning and/or stinging, photosensitivity, and eye pain. The other two patients receiving the combination who discontinued because of drug-related adverse experiences reported nausea, dyspepsia, anorexia, tinnitus, and nasal congestion. The one patient receiving timolol who discontinued did so because of a nonocular, nondrug-related adverse experience.

The most frequent adverse experience was ocular or local in nature. Table 5 presents the number of patients with ocular and local adverse experiences that occurred in more than 2% of patients in any treatment group. Although the most common ocular adverse experience in all three treatment groups was burning and/or stinging eye, only one patient, who was receiving the combination, discontinued from the study because of burning and stinging. The next most frequent adverse experience was taste perversion, which was reported by significantly more patients receiving the combination than timolol (8% vs. 1%, $P = 0.019$).

The most common nonocular clinical adverse experiences other than taste perversion reported during the study were upper respiratory infection and headache, which occurred in generally the same frequency in all treatment groups.

Table 6 displays the ocular symptoms reported by at least 1% of the patients in any treatment group. The most commonly reported ocular symptoms in all three groups were blurred vision, stinging eye, and burning eye. There were no significant differ-

Table 4. Adverse Experience Summary: No. (%) of Patients

	Combination	Dorzolamide	Timolol
Patients evaluated	114	109	112
With any adverse experience	57 (50)	63 (58)	53 (47)
Without any adverse experience	57 (50)	46 (42)	59 (53)
Serious adverse experience	3 (3)	2 (2)	1 (1)
Withdrawn due to adverse experience*	8 (7)	4 (4)	1 (1)
Patients who died	1 (1)	0	0
Drug-related adverse experience†	29 (25)	30 (28)	21 (19)

* Combination versus timolol, $P = 0.035$.

† Drug-related implies possibly, probably, or definitely drug-related as determined by the investigator.

Table 5. Ocular and Local Adverse Experiences (Incidence >2% in Any Treatment Group)*

Adverse Experience	Combination (N = 114)	Dorzolamide (N = 109)	Timolol (N = 112)
Patients with any special senses AE	38 (33)	39 (36)	24 (21)
Blurred vision	5 (4)	4 (4)	5 (4)
Burning/stinging, eye†	21 (18)	15 (14)	7 (6)
Discharge, eye	1 (1)	1 (1)	4 (4)
Foreign body sensation	2 (2)	3 (3)	1 (1)
Injection, ocular	3 (3)	4 (4)	1 (1)
Itching, eye	4 (4)	3 (3)	0
Perversion, taste‡	9 (8)	11 (10)	1 (1)
Tearing	3 (3)	3 (3)	1 (1)

AE = adverse experience.

* If a patient reported a particular adverse experience more than once, the patient was counted only once with that adverse experience. Patients with more than one clinical adverse experience in a body system are counted only once in the body system total.

† Combination versus timolol, $P = 0.006$.

‡ Combination versus timolol, $P = 0.019$.

Table 6. Emergent or Worsening Ocular Symptoms Occurring in ≥1% of Patients in Any Treatment Group: No. (%)

	Combination (N = 114)	Dorzolamide (N = 109)	Timolol (N = 112)
Patients evaluated	114 (100)	109 (100)	111 (99)
Patients with any ocular symptoms*	70 (61)	63 (58)	34 (31)
Blurred vision*	23 (20)	19 (17)	10 (9)
Burning eye*	30 (26)	31 (28)	10 (9)
Dryness of eye	2 (2)	7 (6)	8 (7)
Eye pain	4 (4)	0 (0)	2 (2)
Eyelid pain or discomfort	1 (1)	2 (2)	1 (1)
Foreign body sensation	4 (4)	2 (2)	4 (4)
Itching, eye	8 (7)	9 (8)	4 (4)
Photophobia	1 (1)	1 (1)	2 (2)
Redness, eye	2 (2)	2 (2)	1 (1)
Stickiness, eye	4 (4)	1 (1)	0 (0)
Stinging eye†	25 (22)	19 (17)	9 (8)
Tearing eye‡	11 (10)	6 (6)	1 (1)
Vision cloudy	6 (5)	6 (6)	4 (4)

* Combination versus timolol, $P < 0.001$.

† Combination versus timolol, $P = 0.023$.

‡ Combination versus timolol, $P = 0.005$.

ences between the combination and dorzolamide groups in the proportion of patients reporting any ocular symptom; however, significantly more patients reported ocular symptoms in the combination group than in the timolol group (61% vs. 31%, $P < 0.001$). Specifically, when compared to the timolol group, the combination group had a significantly greater incidence of blurred vision, burning eye, stinging eye, and tearing eye. Of the 71 reports of burning eye in this study, 66 (93%) were graded mild by investigators, 3 (4%) were graded moderate, and only 2 (3%) were graded severe. Of the 53 reports of stinging eye, 42 (79%) were mild, 11 (21%) were moderate, and none were severe.

There were no statistically significant differences among the groups with regard to any specific laboratory adverse experience or the incidence of adverse events noted on physical examination. Additionally, there were no statistically significant differences between the treatment groups when they were compared for emergent or worsening ocular signs, visual acuity, visual field results, optic nerve cup-to-disc ratio, blood pressure and pulse rate, or laboratory measures.

Discussion

The primary objective of this study was to compare the IOP-lowering effect of the dorzolamide–timolol combination to that of each of its components administered in their usual monotherapy dose regimens in untreated patients. This was accomplished by evaluating the combination at morning trough (hour 0, the primary timepoint of interest) and at morning peak (hour 2). The results showed that the combination had a superior IOP-lowering effect relative to either of its individual components at the primary timepoint and at all other timepoints measured during the study. For patients receiving the combination, IOP was lowered, on average, an additional 1.5 to 3 mmHg compared to patients receiving timolol alone. Compared to patients receiving dorzolamide, additional IOP lowering of at least 3 mmHg was gained at both peak and trough for patients receiving the combination. This additional reduction in IOP could be clinically valuable for many patients. The fixed combination solutions of timolol 0.5% and pilocarpine, 2% and 4%, also have been compared to monotherapy with the individual components.[9] These studies defined adequate IOP control as an IOP less than or equal to 21 mmHg and found that the combination was superior to either of its components since a significantly greater proportion of patients receiving the combination had an IOP less than or equal to 21 mmHg than did patients receiving either of its components. Interestingly, if the same definition of adequate IOP were applied to this study, the mean IOP achieved with the dorzolamide–timolol combination meets this definition at all timepoints during the study. However, dorzolamide does not meet it at any study timepoint, and timolol does not meet this definition for three of the four trough timepoints (week 2, months 2 and 3).

A previous study of the combination showed the value of the combination in patients inadequately controlled on timolol alone (Strohmaier et al. Invest Ophthalmol Vis Sci 1996;37:S1102), whereas this study extends those findings by showing that the combination is also superior to its components in patients not receiving or discontinued from previous ocular hypotensive therapy. The additive effect of dorzolamide and timolol is perhaps not surprising since each component of the combination drug affects inflow by a different mechanism. Dorzolamide decreases aqueous humor secretion by inhibiting carbonic anhydrase isoenzyme-II in the ciliary process of the eye; this presumably slows the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport into the posterior chamber of the eye.[10] Although the precise mechanism of the ocular hypotensive action of timolol is not established clearly, it appears to be mediated via decreased production of cyclic adenosine monophosphate. This decreases active ion transport, which has been linked to decreased aqueous humor production.[11,12]

The safety profile of the combination was also evaluated closely in this study and was compared to that of its components administered as monotherapy. Overall, incidence rates of specific adverse experiences were similar for all three treatment groups with the exception of burning and stinging, which occurred more frequently in the combination and dorzolamide groups than in the timolol group. The adverse events attributed to the combination are essentially the sum of those of the components, with no adverse effects observed that were unique to the combination. The mild nature of the symptoms and the low number of discontinuations for burning and stinging indicate that these symptoms are not a significant limitation to the use of the combination product.

In summary, the dorzolamide–timolol combination, when dosed twice a day, has been shown to be a highly effective and generally well-tolerated therapy for the treatment of elevated IOP. As such, it represents a valuable alternative to concomitant therapy in patients in whom aggressive lowering of IOP is indicated.

Appendix

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A Randomized Trial in Patients Inadequately Controlled with Timolol Alone Comparing the Dorzolamide–Timolol Combination to Monotherapy with Timolol or Dorzolamide

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Objective: To compare the dorzolamide–timolol fixed combination twice daily to its components, timolol maleate and dorzolamide hydrochloride, given in their usual monotherapy regimens in patients whose intraocular pressure (IOP) was not controlled on timolol twice daily alone.

Design: Parallel, randomized, double-masked, and active-controlled study.

Participants: Enrolled were 253 patients from 22 sites throughout the United States.

Intervention: After a 3-week run-in of timolol (TIMOPTIC; Merck & Co., Inc., Whitehouse Station, NJ) twice daily, eligible patients received either the combination (COSOPT; Merck & Co., Inc., Whitehouse Station, NJ) twice daily (plus placebo to ensure masking), timolol twice daily (plus placebo to ensure masking), or dorzolamide (TRUSOPT; Merck & Co. Inc., Whitehouse Station, NJ) three times daily for 3 months.

Main Outcome Measures: Intraocular pressure taken at hours 0 (trough) and 2 (peak) after week 2 and months 1, 2, and 3 was compared to baseline within each treatment group and between the combination and each component group. The safety profile of the combination was compared to each component.

Results: The combination was numerically superior at all study timepoints and was statistically superior at all timepoints except for month 2, hour 0 for timolol, and month 2, hour 2 for dorzolamide. The safety profile of the combination reflected those of its two components. The number of patients reporting ocular or local adverse experiences was greater for the combination (45%) and dorzolamide (45%) than for timolol (27%), with burning and/or stinging eye being the most frequently reported.

Conclusion: The dorzolamide–timolol combination provides additional IOP lowering compared to either of its individual components and generally is well-tolerated. *Ophthalmology 1998;105:1952–1959*

The goal of treatment for patients with ocular hypertension or glaucoma is to reach a level of intraocular pressure (IOP) compatible with preservation of optic nerve function and stability of visual fields. Achieving this is most likely if the medication is harmonious with the patient's lifestyle. Treatment that is inconvenient or causes undesirable side effects encourages noncompliance. For example, it has been reported that patients take only approximately 76% of prescribed doses of pilocarpine drops, with 6% of patients taking fewer than one fourth and 15% taking fewer than half of the prescribed doses.[1] There appears to be no underlying patient characteristic that will make one patient compliant and another one noncompliant; age, gender, initial IOP, and ethnic background appear to have little influence.[2,3] However, noncompliance is a significant factor in the failure of medical therapy.[4] The practitioner often assumes that the patient is complying properly with the prescribed treatment and interprets the progression of disease as an indication of medication failure.

Whether because of noncompliance or medication failure, many patients are prescribed multiple medications to re-establish control of their IOP when there is evidence of disease progression or loss of IOP control. Dorzolamide is prescribed often as add-on therapy for patients inadequately controlled while taking timolol monotherapy.

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Ms. Clineschmidt, Dr. Adamsons, Dr. Snyder, and Dr. Reines are employees of Merck & Co., Inc., the manufacturer of the dorzolamide–timolol combination. The other authors have no proprietary interest in the dorzolamide–timolol combination or in Merck.

* Members of the Dorzolamide–Timolol Combination Study Group are listed in the Appendix at the end of this article.

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The availability of a combination formulation containing both timolol maleate and dorzolamide hydrochloride would have considerable clinical value for the predominately elderly glaucoma patient population. Compared to concomitant therapy, the combination would require fewer daily drops that, through improved convenience, may increase patient compliance, and the potential risk of confusion between the two bottles is overcome, which may also improve patient compliance.[3] The risk of elimination of the first drop from the cul-de-sac by instillation of the second drop is avoided completely.

Even though equivalence of the combination to concomitant therapy with its two components had been shown (Clineschmidt CM. Invest Ophthalmol Vis Sci 1995; 36[Suppl]:736), it was important to confirm that the combination was superior to each of the components given as monotherapy. In this article, we report the results of a study that compared the efficacy and safety of the combination to monotherapy with either timolol twice daily or dorzolamide three times daily in patients whose IOP was inadequately controlled while taking timolol twice daily alone.

Materials and Methods

This parallel, randomized, double-masked, active-controlled study was conducted in 22 sites throughout the United States, consistent with applicable local requirements regarding ethical committee review and informed consent. Patients eligible were older than 21 years of age with bilateral open-angle glaucoma or ocular hypertension who completed a 3-week run in taking 0.5% timolol twice daily monotherapy (days -21 to -1). For entry into the study on day 1, IOP was required to be 22 mmHg or higher in one eye (same eye) at 9:00 AM (hour 0), immediately before receiving 0.5% timolol, and at 11:00 AM (hour 2), 2 hours after receiving 0.5% timolol. The main exclusion criteria were best-corrected visual acuity worse than 20/80 in both eyes, contraindication to the use of beta-blockers, history or evidence of acute or chronic angle-closure glaucoma, intraocular surgery or trauma less than 6 months from study start, laser surgery less than 3 months from study start, and concomitant medications known to affect IOP. Candidates with a history of severe or serious hypersensitivity to sulfonamides were to be discussed by the sponsor's medical monitor and the investigator before entry.

During the timolol run-in period, patients underwent screening evaluations, which included external and anterior segment examination, IOP, and visual acuity. The screening examination also included a gonioscopy, automated static visual field (Humphrey Instruments program 24–2 or 30–2, or Octopus program G–1), and a dilated examination of the lens and fundus.

Women of childbearing potential had a negative pregnancy test result (urine human chorionic gonadotropin) before admission to the study that was confirmed at the final study visit.

Emphasis was placed on the role of the study coordinator in ensuring compliance by educating patients at the start of the study about the importance of following study procedures and by closely monitoring medication use throughout the study. All bottles were inspected at each visit and collected at the end of the study; the amount remaining in each bottle was recorded. To further ensure compliance, the coordinator called each patient on the evening before a study visit to remind the patient to administer the bedtime drops, not to administer the morning drops, and to bring all bottles of medication to the clinic the next day. Finally, patients were queried about any doses missed; these then were noted on the case report form.

All study medication was packaged in identical bottles by allocation number and was labeled in blue print for morning and bedtime dosing and labeled in red print for afternoon dosing. Each of these bottles had a tearoff label that was fixed to an inventory form when the bottle was dispensed; this label could also be used to break the blind if needed. On day 1, if the IOP criterion was met, patients randomly (according to a computer-generated allocation schedule) received one of the following masked treatment regimens for 3 months: the 2.0% dorzolamide–0.5% timolol combination twice daily (at 9:00 AM and bedtime) and placebo once daily (at 3:00 PM); 0.5% timolol twice daily (at 9:00 AM and bedtime) and placebo once daily (at 3:00 PM); or 2.0% dorzolamide three times daily (at 9:00 AM, 3:00 PM, and bedtime). The first dose of study drug was at 3:00 PM on study day 1.

Patients returned to the clinic for visits at week 2 and at months 1, 2, and 3. On these days, the 9:00 AM dose of test drug was administered at the clinic. Examinations were performed at 9:00 AM (before drop administration; hour 0, trough) and 11:00 AM (hour 2, peak) and included visual acuity (at 9:00 AM only), symptomatology, external and anterior segment examination, and measurement of IOP.

Within 5 days of completing or discontinuing the study, each patient had a dilated ophthalmoscopy and a visual field examination. If these examinations were performed on the final study day, mydriatic agents were not instilled until after the last IOP measurement.

To adjust for variability in baseline values, ocular-hypotensive effect was assessed using percent change (instead of absolute change) in IOP from the time-matched baseline values (at hours 0 and 2) using the patient's "worse eye." The worse eye was defined as the eye with the higher morning trough IOP at day 1 (baseline). If the IOP measurements in both eyes were equal at this time, then the eye with the higher IOP at morning peak on day 1 was selected. If the IOP measurements in both eyes were equal at this time, then the right eye was selected.

The combination treatment group was compared to each of its components to determine whether it produced a greater reduction in IOP than either dorzolamide or timolol administered as monotherapy. Comparisons between treatment groups were made at both morning trough (hour 0) and at peak (hour 2) at week 2 and months 1, 2, and 3. However, the primary timepoint of interest was hour 0, month 3. The mean difference in percent IOP change from baseline between the combination and each monotherapy group was estimated using a weighted average of observed treatment differences in clinics where the weights were based on the number of patients enrolled at each clinic. Treatment differences were assessed with a two-way analysis of variance model with interaction fitted at each timepoint. The model included terms for treatment group, investigative site, and treatment-by-investigator interaction. Interaction between treatment and the concomitant factors (age, race, gender, and iris color) was also investigated using an analysis of variance model. The model included terms for treatment group, concomitant factor, and treatment-by-concomitant factor interaction.

A sample size of 200 patients (80 allocated to the combination group, 80 allocated to the 0.5% timolol group, and 40 allocated to the 2.0% dorzolamide group) provided 95% power for detecting a true difference of 8 percentage points between the combination group and the timolol group in percent change in IOP from baseline, assuming a standard deviation of 14 percentage points. The power was 80% to detect a true difference of 6 percentage points between these two treatment groups. The power was 99% for detecting a true difference of 12 percentage points between the combination group and the dorzolamide group. For the joint hy-

pothesis that the combination differed from both of its components, the overall power was 95%. The percentage point difference and standard deviation assumptions were based on the results of a prior study evaluating the combination.

Two approaches to the analysis were used: (1) all patients treated, last observation carried forward (APT–LOCF) and (2) per protocol, observed cases (PP–OC). In the APT–LOCF approach, all patients randomized to study medication with efficacy data for at least one visit after randomization were included. Missing data were estimated from previous time-matched observations occurring within the treatment phase of the study. Patients with missing data at the first visit were not included until a visit with data was reached. Observations were not carried forward from the baseline phase to the treatment phase. In the PP–OC approach, examinations associated with a serious violation of the protocol were excluded. These examinations were identified before the data were unmasked as to the patients' treatment assignments. Missing data points were not estimated. Because the results from both approaches were similar, data from the APT–LOCF method only will be presented.

All patients who received study medication were included in the evaluation of clinical adverse experiences, ocular signs and symptoms, pupil diameter, visual acuity, visual field defects, and cup-to-disc ratio. Treatment group comparisons with regard to adverse experiences, ocular signs and symptoms, and incidence of visual field defects were made using Fisher's exact test (two-tailed). All probability values were rounded to three decimal places, and statistical significance was declared if the rounded probability value was less than or equal to 0.050. The data were analyzed with a statistical software package (SAS, Version 6.12; SAS Institute Inc., Cary, NC).

Table 1. Baseline Demographic Characteristics by Treatment Group: No. (%)*

	Combination (N = 104)	Dorzolamide (N = 51)	Timolol (N = 98)	Total (N = 253)
Sex				
Male	42 (40)	22 (43)	47 (48)	111 (44)
Female	62 (60)	29 (57)	51 (52)	142 (56)
Race				
White	90 (87)	40 (78)	78 (80)	208 (82)
Black	13 (13)	9 (18)	17 (17)	39 (15)
Other	1 (1)	2 (4)	3 (3)	5 (2)
Iris color				
Dark brown	14 (13)	7 (14)	15 (15)	36 (14)
Brown	30 (29)	16 (31)	30 (31)	76 (30)
Hazel	19 (18)	6 (12)	15 (15)	40 (16)
Green	2 (2)	5 (10)	3 (3)	10 (4)
Blue	39 (38)	17 (33)	35 (36)	91 (36)
Age (yrs)				
Mean [SD]	63.6 [12.4]	64.4 [15.0]	63.4 [12.7]	63.7 [13.0]
Range	37–86	28–88	30–88	28–88
Baseline IOP – worse eye (mm Hg) hour 0				
Mean [SD]	25.6 [3.7]	25.5 [3.8]	25.2 [3.1]	25.4 [3.5]
Range	21–41	20–38	22–38	20–41
Hour 2				
Mean [SD]	24.9 [4.0]	24.7 [3.3]	24.3 [2.6]	24.6 [3.3]
Range	17–48	22–39	21–35	17–48

SD = standard deviation; IOP = intraocular pressure.

* No significant differences between treatment groups were found.

Table 2. Patient Accounting: No. (%)*

	Combination	Dorzolamide	Timolol
Entered	104	51	98
Completed	94 (90)	49 (96)	89 (91)
Discontinued	10 (10)	2 (4)	9 (9)
Clinical adverse experience	3 (3)	0	1 (1)
Protocol deviation	2 (2)	0	3 (3)
Patient withdrew	1 (1)	0	2 (2)
Therapy ineffective	4 (4)	2 (4)	3 (3)

* No significant differences between treatment groups were found.

Results

Demographic Data

The demographic profile of patients in the study is outlined in Table 1. The mean age of the 253 patients was 63.7 years, and 208 (82%) were white. The proportion of males and females in the three treatment groups was similar. One hundred eleven (44%) of the 253 patients were male and 142 (56%) were female. The groups also were comparable with respect to racial distribution. Similar distributions between treatment groups also were observed with regard to iris color, age, and baseline IOP (for the worse eye). No statistically significant differences were noted. Approximately 75% of the patients had a diagnosis of primary open-angle glaucoma, another 20% had ocular hypertension, with the balance having pigmentary glaucoma. The most frequent secondary diagnosis was systemic hypertension, seen in 40% to 53% of the patients depending on the treatment group.

There were occasional statistically significant differences between the treatment groups in the types of prior and concomitant therapies taken as well as in secondary diagnoses. However, these differences were not clinically meaningful.

Patient Accounting

Two hundred fifty-three patients were randomized to the 3 treatment groups. Of this total, 232 (92%) completed the study. Table 2 presents the number (percentage) of patients by treatment group who entered, completed, and discontinued the study. Although the proportion of patients who discontinued was smaller in the dorzolamide group (4%) as compared to the combination group (10%) or the timolol group (9%), these differences were not statistically significant; the treatment groups did not differ significantly in the proportion of patients discontinuing for any of the reasons shown. All but two patients who entered the study were included in the analysis of efficacy. These two patients were in the combination group and had no IOP measurements after baseline. All patients who entered the study were included in the analysis of safety.

Efficacy Results

The principal objective of this study was to compare the IOP-lowering effect of the combination twice daily to that of timolol twice daily or dorzolamide three times daily for up to 3 months.

Table 3 displays IOP summary statistics for each study visit. At week 2, the mean IOP reduction from the timolol baseline at hour 0 was 10.9% (−2.9 mmHg) for the combination group, whereas the mean IOP reductions for the dorzolamide and timolol groups were 6.6% (−1.9 mmHg) and 5.4% (−1.4 mmHg), respectively. At month 3, the mean IOP reductions at hour 0 were 10.6% (−2.8

Table 3. Intraocular Pressure Summary Statistics*: Mean (Standard Deviation)

Examination	Treatment	N	Baseline	Treatment	Change	Percent Change
Hr 0						
Wk 2	Combination	99	25.5 (3.4)	22.6 (3.4)	−2.9 (3.3)	−10.9 (11.7)
	Dorzolamide	51	25.5 (3.8)	23.7 (3.6)	−1.9 (3.4)	−6.6 (12.3)
	Timolol	96	25.3 (3.2)	23.9 (4.2)	−1.4 (3.2)	−5.4 (11.6)
Mo 1	Combination	102	25.5 (3.4)	22.5 (3.5)	−3.0 (3.4)	−11.3 (12.5)
	Dorzolamide	51	25.5 (3.8)	23.7 (4.0)	−1.8 (3.9)	−6.3 (14.2)
	Timolol	98	25.2 (3.1)	23.3 (4.4)	−2.0 (3.0)	−7.9 (11.2)
Mo 2	Combination	102	25.5 (3.4)	22.6 (3.6)	−2.9 (3.1)	−11.0 (11.9)
	Dorzolamide	51	25.5 (3.8)	23.8 (4.2)	−1.8 (4.3)	−6.0 (16.5)
	Timolol	98	25.2 (3.1)	23.3 (4.2)	−1.9 (3.1)	−7.5 (11.9)
Mo 3	Combination	102	25.5 (3.4)	22.7 (3.9)	−2.8 (3.4)	−10.6 (12.5)
	Dorzolamide	51	25.5 (3.8)	24.2 (5.1)	−1.4 (4.3)	−4.9 (16.7)
	Timolol	98	25.2 (3.1)	23.6 (4.3)	−1.7 (3.1)	−6.7 (11.9)
Hr 2						
Wk 2	Combination	100	25.0 (4.0)	21.0 (4.0)	−4.0 (3.1)	−15.8 (11.4)
	Dorzolamide	51	24.7 (3.3)	21.8 (3.4)	−2.8 (3.8)	−10.8 (13.3)
	Timolol	93	24.3 (2.6)	22.4 (3.7)	−1.9 (2.5)	−8.1 (10.5)
Mo 1	Combination	103	25.0 (3.9)	20.7 (4.3)	−4.4 (3.0)	−17.3 (11.5)
	Dorzolamide	51	24.7 (3.3)	22.4 (3.8)	−2.3 (4.5)	−8.5 (16.4)
	Timolol	95	24.3 (2.6)	22.3 (4.6)	−2.0 (3.3)	−8.7 (13.4)
Mo 2	Combination	103	25.0 (3.9)	20.6 (4.2)	−4.4 (3.3)	−17.1 (12.5)
	Dorzolamide	51	24.7 (3.3)	21.2 (3.5)	−3.5 (4.3)	−13.3 (15.5)
	Timolol	95	24.3 (2.6)	22.0 (4.2)	−2.4 (3.2)	−9.8 (13.2)
Mo 3	Combination	103	25.0 (3.9)	20.7 (4.5)	−4.4 (3.3)	−17.3 (12.9)
	Dorzolamide	51	24.7 (3.3)	22.7 (3.8)	−2.0 (4.1)	−7.4 (15.8)
	Timolol	95	24.3 (2.6)	22.8 (4.6)	−1.6 (3.7)	−6.6 (15.3)

* All patients treated analysis (last observation carried forward) – worse eye.

mmHg), 4.9% (−1.4 mmHg), and 6.7% (1.7 mmHg) for the combination, dorzolamide, and timolol groups, respectively.

In all three treatment groups, the reduction in IOP at hour 2 was greater than at hour 0 at all visits with the exception of month 3 for the timolol group, which had nearly the same reduction in IOP at hours 0 and 2. At week 2, the mean IOP reduction from baseline at hour 2 was 15.8% (−4.0 mmHg), 10.8% (−2.8 mmHg), and 8.1% (−1.9 mmHg) for the combination, dorzolamide, and timolol groups, respectively. At month 3, the mean IOP reduction at hour 2 from baseline was 17.3% (−4.4 mmHg), 7.4% (−2.0 mmHg), and 6.6% (−1.6 mmHg) for the combination, dorzolamide, and timolol groups, respectively.

Figure 1 displays the IOP treatment means and standard errors by treatment group across all visits. The three treatment groups were, in general, comparable at baseline. At all visits, the combination group showed a numerically greater reduction in IOP from baseline than either of its components at hour 0 as well as at hour 2. The differences between the combination and each component were statistically significant at hours 0 and 2 at the primary visit (end of month 3) and at nearly all of the earlier timepoints. There was no evidence to suggest an interaction between treatment and the clinic (i.e., there was no inconsistency in treatment difference across clinics). There also was no evidence to suggest an interaction between treatment and any of

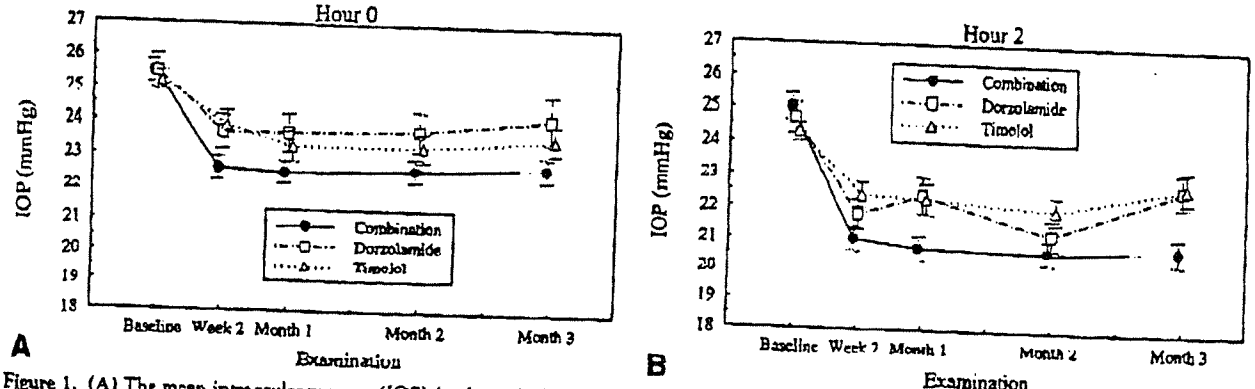

Figure 1. (A) The mean intraocular pressure (IOP) (and standard errors) at hour 0, morning trough and (B) hour 2, morning peak is presented for each treatment group at all study visits. At both timepoints and at all study visits, the patients receiving the combination experienced a numerically greater drop in IOP than did the patients receiving either timolol or dorzolamide monotherapy. Statistical significance was reached at all timepoints except hour 0 month 2 vs. timolol and hour 2 month 2 vs. dorzolamide.

Table 4. Point Estimates and Confidence Intervals for Difference between Treatments: Mean Percent Change in Intraocular Pressure (IOP) from Baseline*

Examination	Treatment Groups (N)	Estimated Difference between Treatment Means	Standard Error of Estimated Difference	95% Confidence Intervals for Difference between True Means
Hr 0				
Wk 2	Combination (99)–Dorzolamide (51)	−4.04	2.002	−7.99, −0.09
	Combination (99)–Timolol (96)	−5.48	1.663	−8.76, −2.20
	Timolol (96)–Dorzolamide (51)	1.64	2.014	−2.34, 5.61
Mo 1	Combination (102)–Dorzolamide (51)	−4.89	2.097	−9.03, −0.76
	Combination (102)–Timolol (98)	−3.43	1.729	−6.84, −0.02
	Timolol (98)–Dorzolamide (51)	−1.45	2.110	−5.61, 2.71
Mo 2	Combination (102)–Dorzolamide (51)	−4.67	2.239	−9.08, −0.25
	Combination (102)–Timolol (98)	3.46	1.846	−7.10, 0.18
	Timolol (98)–Dorzolamide (51)	−1.27	2.253	−5.72, 3.17
Mo 3	Combination (102)–Dorzolamide (51)	−5.63	2.289	−10.15, −1.12
	Combination (102)–Timolol (98)	−3.91	1.887	−7.63, −0.19
	Timolol (98)–Dorzolamide (51)	−1.53	2.303	−6.07, 3.01
Hr 2				
Wk 2	Combination (100)–Dorzolamide (51)	−4.72	1.962	−8.59, −0.85
	Combination (100)–Timolol (93)	−7.74	1.646	−10.98, −4.49
	Timolol (93) Dorzolamide (51)	3.24	1.992	−0.69, 7.16
Mo 1	Combination (103)–Dorzolamide (51)	−8.55	2.381	−13.25, −3.86
	Combination (103)–Timolol (95)	−8.68	1.983	−12.59, −4.77
	Timolol (95)–Dorzolamide (51)	0.17	2.418	−4.60, 4.94
Mo 2	Combination (103) Dorzolamide (51)	−3.92	2.347	−8.55, 0.71
	Combination (103)–Timolol (95)	−7.51	1.955	−11.37, −3.66
	Timolol (95)–Dorzolamide (51)	3.87	2.384	−0.83, 8.57
Mo 3	Combination (103)–Dorzolamide (51)	−9.71	2.570	−14.78, −4.64
	Combination (103)–Timolol (95)	−11.13	2.140	−15.35, −6.90
	Timolol (95)–Dorzolamide (51)	1.25	2.610	−3.90, 6.40

* All patients treated analysis (last observation carried forward) – worse eye. The estimated difference between treatments was a weighted average of the mean difference within each clinic based on the number of patients entered at each clinic.

the following concomitant factors: age, race, gender, and iris color.

Table 4 provides the point estimates and 95% confidence intervals for the difference between treatments in the mean percent change in IOP from baseline. At the primary timepoint of interest, month 3, hour 0, the treatment difference between the combination and dorzolamide was −5.63 percentage points (−10.15, −1.12). The treatment difference between the combination and timolol was −3.91 percentage points (−7.63, −0.19). The negative limits of the above confidence intervals indicate that the combination has a greater IOP-lowering effect than both dorzolamide and timolol administered as monotherapy.

Table 5. Clinical Adverse Experience Summary: No. (%) of Patients

	Combination	Dorzolamide	Timolol
Patients evaluated	104	51	98
With any adverse experience*	65 (63)	30 (59)	42 (43)
Drug-related adverse experience†,‡	43 (41)	21 (41)	23 (23)
Serious adverse experience	4 (4)	0	1 (1)
Patients who died	1 (1)	0	0
Discontinued due to adverse experience	3 (3)	0	1 (1)

* Combination versus timolol, (63% versus 43%, $P = 0.007$).

† Combination versus timolol, (41% versus 23%, $P = 0.007$).

‡ Drug-related implies possibly, probably, or definitely related to therapy.

Safety Results

Table 5 provides a summary of the clinical adverse experiences reported during this study. Of the 253 patients in the study, 137 (54%) had a clinical adverse experience: 65 (63%) while receiving the combination, 30 (59%) while receiving dorzolamide, and 42 (43%) while receiving timolol. A significantly greater proportion of patients in the combination group had an adverse experience as compared with those of the timolol group (63% vs. 43%, $P = 0.007$). A significantly greater proportion of patients in the combination group had a drug-related adverse experience as compared with those in the timolol group (41% vs. 23%, $P = 0.007$).

The most frequently reported adverse experiences were those relating to the eye and to taste (Table 6). The proportion of patients with these ocular or local adverse experiences was significantly greater in the combination group than in the timolol group (45% vs. 27%, $P = 0.008$). Burning and/or stinging eye was the most frequently reported adverse experience. Specifically, the proportion of patients with burning and/or stinging eye was significantly greater in the combination group than in the timolol group (30% vs. 8%, $P = 0.001$) but not in the dorzolamide group (24%). Of the 51 patients with the adverse experience of burning and/or stinging eye, 37 (73%) reported that the maximum intensity was mild. Taste perversion, usually a bitter or sour taste, was the next most frequently reported. Other than ocular or local adverse experi-

Table 6. Number (%) of Patients with Ocular or Local Adverse Experiences by Specific Adverse Experience (Incidence ≥3% in Any Treatment Group)

Adverse Experience	Combination (N = 104)			Dorzolamide (N = 51)			Timolol (N = 98)		
	n	(%)	[n]*	n	(%)	[n]*	n	(%)	[n]*
Ocular or local combined†	47	(45)	[40]	23	(45)	[18]	26	(27)	[21]
Blepharitis	0			2	(4)	[1]	0		
Blurred vision	2	(2)	[2]	2	(4)	[2]	7	(7)	[5]
Burning and/or stinging, eye‡	31	(30)	[30]	12	(24)	[12]	8	(8)	[8]
Conjunctivitis§	0			3	(6)	[1]	0		
Erosion, cornea	1	(1)	[1]	2	(4)	[1]	5	(5)	[4]
Foreign body sensation	3	(3)	[3]	0			2	(2)	[2]
Irritation, eye	1	(1)		2	(4)		0		
Itching, eye	2	(2)	[1]	1	(2)	[1]	3	(3)	[2]
Pain, eye	4	(4)	[1]	0			0		
Taste, bitter	8	(8)	[8]	7	(14)	[7]	2	(2)	[2]
Photophobia	1	(1)		2	(4)	[2]	0		
Tearing	3	(3)	[3]	1	(2)		2	(2)	[1]

* Values are no. of patients with adverse experiences possibly, probably, or definitely drug-related.

† Significantly greater incidence in the combination group (versus timolol), $P = 0.008$.

‡ Significantly greater incidence in the combination group (versus timolol), $P = 0.001$.

§ Significantly greater incidence in the dorzolamide group (versus combination), $P = 0.034$.

ences, there were no significant differences between the combination and its components for any other body system or for any other specific adverse experience.

The proportion of patients having any adverse experience that was considered possibly, probably, or definitely drug related was significantly greater in the combination group than in the timolol group (41% vs. 23%, $P = 0.007$). The proportion of patients with any drug-related ocular or local adverse experience was significantly greater in the combination group than in the timolol group (38% vs. 21%, $P = 0.009$). Specifically, the proportion of patients with drug-related burning and/or stinging eye was significantly greater in the combination group than in the timolol group (30% vs. 8%, $P < 0.001$).

Of the three patients who discontinued while receiving the combination, two discontinued because of drug-related adverse experiences that resolved after discontinuation; one patient had eye pain, and the other had dizziness, nausea, and tremor. The remaining patient who discontinued from the combination group did so because of a nonocular adverse experience (neoplasm) that was not drug related. No patients discontinued while receiving dorzolamide. One patient in the timolol group discontinued because of urinary frequency that was considered to be probably drug related and that resolved.

There were no statistically significant differences between the combination group and its components in the proportion of patients with serious adverse experiences, discontinuations due to an adverse experience, or those who died.

Ocular complaints and observations were collected as symptoms and signs and, if found to be clinically significant by the investigator, also were recorded as adverse experiences. The most frequently reported ocular symptoms in all three treatment groups were blurred vision, burning and/or stinging eye, and tearing eye. There were no significant differences between the combination and dorzolamide or timolol groups in the proportion of patients reporting any specific ocular symptom. Bitter taste was the most commonly reported nonocular symptom. The combination group had a significantly greater incidence of bitter taste than did the timolol group (16% vs. 5%, $P < 0.020$). There were no other significant differences among the treatment groups. There were no statistically significant differences among the groups with regard to the incidence of any sign. The most frequently reported ocular sign was conjunctival hyperemia, reported for nine patients (9%) in the combination group, six patients (12%) in the dorzolamide group, and eight patients (8%) in the timolol group.

Data also were collected on pupil diameter, visual acuity, visual field defects and progression, and cup-to-disc ratio. No significant changes would have been expected in these parameters and none were found.

Discussion

Elevated IOP is a major risk factor for glaucomatous optic nerve damage and subsequent visual field loss or blindness. Therefore, the treatment of elevated IOP, whether or not it is associated with optic nerve damage and visual field loss, is well-accepted. Reduction of IOP is frequently achieved with topical medication; the beta-blocker timolol maleate is the most commonly prescribed first-line therapy. However, because ocular hypertension and glaucoma are chronic progressive diseases, many patients eventually require more than one medication for IOP control. As adjunctive therapy to timolol, dorzolamide hydrochloride provides additional IOP lowering and generally is well-tolerated.[5] It has become one of the most commonly prescribed add-on agents.

Dorzolamide and timolol both lower IOP by decreasing aqueous humor production. However, they do so by different mechanisms, which suggests that a greater IOP-lowering effect would be achieved with concomitant use of these agents than with the use of either agent alone.[6] This has indeed been found to be the case. When dorzolamide was given concomitantly with timolol in previous studies, clinically significant additional IOP reductions were observed that were comparable to those observed when 2% pilo-

carpine was added to timolol.[5,7] The dorzolamide–timolol combination has not been studied in a direct comparison to other fixed combination therapies. However, studies have shown that the timolol–pilocarpine fixed combination (TIMPILO; Merck & Co., Inc., Whitehouse Station, NJ) is as effective in lowering IOP as concomitant therapy with timolol plus pilocarpine. By extrapolation, therefore, the dorzolamide–timolol combination should be equivalent in efficacy to the timolol–pilocarpine combination.[5,8,9]

The primary objective of this study was to compare the IOP-lowering effect of the 2.0% dorzolamide–0.5% timolol combination administered twice daily to that of each of its components administered in their usual monotherapy dose regimens in patients whose IOP was not adequately controlled with timolol alone. The combination was numerically superior at all study timepoints and was statistically superior at all timepoints except for month 2, hour 0 for timolol and month 2, hour 2 for dorzolamide. The combination achieved an additional 3 to 4 mmHg lowering of IOP over the timolol baseline. This additional IOP effect was maintained consistently throughout the study (Fig 1) and would be valuable for many patients. The additional efficacy shown by the combination (relative to timolol monotherapy) in this study is consistent with that noted in previous studies evaluating the additivity of dorzolamide to timolol.[5,10] The safety profile of the combination drug was evaluated closely in this study, and no unexpected findings were detected. In large part, the tolerability of the combination drug reflected that of its dorzolamide component with mild, transient burning and/or stinging and bitter taste being the most commonly reported adverse experiences and symptoms, as has been seen in other studies of dorzolamide.[5,10]

To minimize problems with compliance within this study due to the seemingly complicated dosing regimen, emphasis was placed on patient education.[11,12] The importance of correctly administering all of the study drops was discussed with patients who knew that all medication bottles were to be returned for inventory. Relatively few doses were reported as being missed, and the disposition of all bottles was known. Thus, patient compliance with study medication appears to have been good.

The results presented us with a point to explore further. In two previous studies that investigated the additivity of dorzolamide, dosed either twice daily or three times daily, to that of placebo added to TIMOPTIC-XE (Merck & Co., Inc., Whitehouse Station, NJ), patients underwent a 2-week, prestudy run-in on TIMOPTIC-XE (Merck & Co., Inc.).[13] Those patients randomized to placebo experienced an additional drop in IOP of approximately 2 mmHg compared to the baseline IOP measured at the end of the timolol run-in. This could have been caused by a placebo effect or by an inadequate run-in period. Therefore, in the current study, we increased the run-in by 1 week, hoping to achieve a stable baseline. However, on average, the IOP for the patients who continued to receive timolol after the 3-week timolol run-in dropped another 2 mmHg by week 2 and continued at around that level for the remainder of the study. If the IOP had been stable at the end of baseline, then a priori, the IOP should have remained at the baseline level for all of the measurements thereafter. Perhaps a 3-week run-in is not long enough to establish a stable baseline for timolol, perhaps there was a "placebo effect" in those patients who continued to receive timolol, or perhaps regression to the mean occurred to a greater extent than predicted in this trial.

Overall, the current study shows that the IOP-lowering effect of the combination is superior to that of either of its components administered as monotherapy. Furthermore, the safety profile of the combination reflected that of its components and showed the generally good tolerability of the product. Therefore, the dorzolamide–timolol combination represents a promising new ocular-hypotensive therapy that may provide increased convenience and compliance in the clinical treatment of elevated IOP.

Appendix

The Dorzolamide–Timolol Combination Study Group

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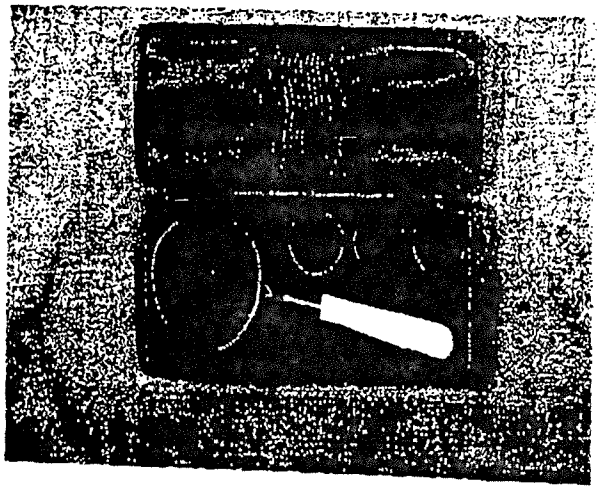
Historical Image

Small Liebreich's reflecting ophthalmoscope and case, ca 1900.*



*Courtesy of the Museum of Ophthalmology, Foundation of the American Academy of Ophthalmology, San Francisco, California.

The Efficacy and Safety of the Dorzolamide–Timolol Combination versus the Concomitant Administration of its Components

*Kim Strohmaier, BS,[1] Ellen Snyder, PhD,[2] Harvey DuBiner, MD,[3] Ingrid Adamsons, MD, MPH,[1] the Dorzolamide–Timolol Study Group**

Objective: To evaluate whether a fixed combination of 2% dorzolamide and 0.5% timolol given twice daily showed equivalent efficacy to the concomitant administration of 2% dorzolamide given three times daily and 0.5% timolol given twice daily in patients whose intraocular pressure (IOP) remained elevated during monotherapy with 0.5% timolol twice daily.

Design: Multicenter, parallel, randomized, double-masked clinical trial with an open-label extension.

Participants and Intervention: In the masked phase, 242 patients received either the dorzolamide–timolol combination twice daily and placebo three times daily or dorzolamide three times daily and timolol twice daily for up to 3 months. In the open-label extension, 220 patients received the dorzolamide–timolol combination twice daily for up to 9 months.

Main Outcome Measures: The criterion for establishing treatment equivalency was a 95% or greater confidence that the absolute difference in the mean change in IOP from baseline was less than 1.5 mmHg between treatments.

Results: During 3 months of treatment, the dorzolamide–timolol combination reduced IOP relative to the 0.5% timolol baseline by approximately 14% at hour 0 (just before the morning dose), 20% at hour 2, and 15% at hour 8. The IOP-lowering effect of concomitant therapy with dorzolamide and timolol was approximately 16% at hour 0, 20% at hour 2, and 17% at hour 8. At hours 0, 2, and 8, there was greater than 97% confidence that the treatments were equivalent. During the open-label extension, the mean IOP reduction ranged from 14% to 15% at hour 0 and from 20% to 21% at hour 2. The treatment groups were generally comparable in terms of adverse events, symptoms, ocular signs, visual acuity, visual fields, physical examination, and laboratory measures.

Conclusions: The IOP-lowering effect of the dorzolamide–timolol combination is comparable to that of dorzolamide three times daily plus timolol twice daily and is maintained for up to 1 year. The dorzolamide–timolol combination provides clinically important reduction in IOP relative to baseline treatment with timolol alone and is generally well-tolerated for up to 1 year. *Ophthalmology 1998;105:1936–1944*

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Ms. Strohmaier and Drs. Snyder and Adamsons are employees of Merck & Co., Inc, the manufacturer of the dorzolamide–timolol combination. Dr. DuBiner has no proprietary interest in the dorzolamide–timolol combination or Merck.

* Members of the Dorzolamide–Timolol Study Group are listed in the Appendix at the end of this article.

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Open-angle glaucoma is a chronic, progressive disease characterized by visual field loss and optic nerve damage, often in the presence of elevated intraocular pressure (IOP).[1] Lowering the IOP is recognized to retard or prevent additional damage to the optic nerve.[1] Patients with open-angle glaucoma are usually treated initially with monotherapy to reduce their IOP; however, many patients eventually require more than one medication. Dorzolamide hydrochloride, a topical carbonic anhydrase inhibitor, is among the most commonly used add-on agents in the treatment of glaucoma worldwide. In patients with ocular hypertension or open-angle glaucoma, the IOP-lowering activity of dorzolamide monotherapy is comparable to that of betaxolol.[2] As adjunctive therapy to timolol, the IOP-lowering activity of 2% dorzolamide is similar to that of 2% pilocarpine.[3] Dorzolamide is generally well-tolerated, both as monotherapy[2,4] and as adjunctive therapy.[3]

Noncompliance with recommended medical therapy is a major problem in the treatment of glaucoma because the disease is chronic and often asymptomatic, whereas the treatment provides no subjective improvement and may cause ocular or systemic side effects or both.[4] Patient interviews suggest that mid-day doses are more likely to be missed than morning or evening doses and that patients are more compliant with twice-daily medications than with those prescribed three or four times a day.[5] Studies using electronic medication monitors confirm that noon-time doses are frequently missed[7] and that compliance is improved by reducing the frequency with which a medication must be taken.[8,9] Similar studies have shown that the daytime doses of three times daily and four times a day regimens are not spaced adequately 20% to 30% of the time.[10,11] Complicated dosing regimens may also reduce compliance. For example, patients taking more than one drop at the same time of day should space the instillation of any two medications by at least 5 to 10 minutes to avoid diluting or washing each other from the cul-de-sac.[5] Fixed combination drugs may improve compliance by reducing the number of daily doses and by simplifying the dosing regimen.

A fixed combination of 2% dorzolamide hydrochloride and 0.5% timolol maleate has been developed. The pH of the fixed combination is the same as the pH of 2% dorzolamide (approximately 5.6), whereas the pH of 0.5% timolol maleate is 6.8; all three products are isotonic solutions. In the pigmented rabbit eye, concentrations of dorzolamide and timolol in the cornea, aqueous humor, and iris–ciliary body were very comparable after instillation of the drugs individually or in combination (Sugrue MF, et al. Invest Ophthalmol Vis Sci 1998;39:5926). Early work in normal subjects confirmed that the dorzolamide–timolol combination was generally well-tolerated (Strahlman ER, et al. Invest Ophthalmol Vis Sci 1992;33:1122). In two studies of patients with ocular hypertension or open-angle glaucoma, the IOP-lowering effect of the combination was superior to that of either of its components given alone (articles accepted for publication). It was also important to confirm that the efficacy of the combination was equivalent to that of the concomitant administration of its components and that combining dorzolamide and timolol in one bottle did not produce any unexpected effects. This article presents the results of a large-scale clinical trial that compared the efficacy and safety of the dorzolamide–timolol combination given twice daily to the concomitant administration of 2% dorzolamide hydrochloride three times daily and 0.5% timolol maleate twice daily in patients with elevated IOP. This concomitant regimen reflects the approved dosage for adjunctive use of dorzolamide in the United States. This study also evaluated the tolerability and IOP-lowering effect of the dorzolamide–timolol combination after 1 year of treatment.

Materials and Methods

Study Design

This randomized, double-masked, parallel study was conducted at 19 sites throughout the United States with approval from the appropriate institutional review boards; informed consent was obtained from all patients. Patients were men and nonfertile women, 21 to 85 years of age, with bilateral ocular hypertension or open-angle glaucoma. Patients with any of the following conditions were excluded from the study: any contraindications to the use of beta-blockers, hypersensitivity to carbonic anhydrase inhibitors or sulfonamides, corrected visual acuity worse than 20/80 in both eyes, clinically significant dry eye syndrome, previous intraocular surgery or laser treatment, laser trabeculoplasty within 3 months of study start, significant ocular trauma, recent ocular infection or inflammation, herpes simplex keratitis or corneal ulcer within 1 year, or current ocular symptoms such as photophobia, metamorphopsia, or diplopia. Contact lens use was not allowed during the study or for 3 weeks before study entry. Concomitant use of systemic or dermatologic medications known to affect IOP also was not allowed; however, oral beta-blockers were allowed if the dosage remained constant throughout the study. All patients were required to complete a 2-week prestudy run-in on 0.5% timolol twice daily alone. To enter the study, baseline IOP was required to be 22 mmHg or higher in at least one eye immediately before and 2 hours after the morning dose of timolol at the end of the run-in period (study day 1).

Patients who met the IOP entry criteria were randomized to 3 months of double-masked therapy with either the dorzolamide–timolol combination twice daily (and placebo three times daily) or concomitant administration of 0.5% timolol twice daily and 2% dorzolamide three times daily. Treatment assignment was determined by a computer-generated allocation schedule that was prepared by a statistician who was not involved in the analysis of the study results. All study medications for the masked phase were provided by the sponsor (Merck & Co., Inc., West Point, PA) as sterile ophthalmic solutions in identical containers labeled with the patient's allocation number. Patients were instructed to administer the twice-daily medications at 8:30 AM and bedtime and to administer the three-times-daily medications at 8:40 AM, 2:30 PM, and bedtime (10 minutes after the twice-daily medication). A 9-month extension was available to patients who completed the masked phase successfully; all patients received open-label dorzolamide–timolol twice daily (at 8:30 AM and bedtime) during the extension. Patients were called the night before each study visit to remind them to administer the evening dose, not to administer the next morning dose, and to bring all bottles of study medication to the study visit. All bottles of study medication were inspected at each visit and were collected at the end of the study, when the amount remaining in each bottle was recorded. At each study visit, patients were asked to report the date and time of the last dose of study medication as well as any doses that were missed since the previous visit.

Intraocular pressure was measured immediately before the morning dose of study medication (hour 0) as well as 2 hours later (hour 2) and 8 hours later (hour 8) on days 1, 15, 30, 60, and 90 of the masked phase. During the open-label extension, IOP was measured at hours 0 and 2 on days 180, 270, and 365. Ocular examinations consisting of symptom evaluation, visual acuity measurement, and slit-lamp examination were also performed at all study visits during both phases of the study. The following examinations were performed at the screening visit and on completion or discontinuation of each phase of the study: automated static threshold perimetry (either the Humphrey 24-2 or Octopus G1 program), dilated examination of the lens and fundus, physical examination, and laboratory tests (blood chemistry, hematology, and urinalysis). The same perimeter was used throughout the study for each patient, and the investigator provided an assessment of the intensity and loca-

tion of any visual field defects that were present. Clinically significant changes in any of the study examinations also were reported as adverse experiences.

Statistical Analyses

The hypothesis of the study was that the dorzolamide–timolol combination given twice daily would have an ocular-hypotensive effect equivalent (within 1.5 mmHg) to that of the concomitant administration of 0.5% timolol twice daily and 2% dorzolamide three times daily. Ocular-hypotensive effect was assessed using the change in IOP from the time-matched baseline value obtained on day 1. The change from baseline was calculated using the patient's "worse eye," which was defined as the eye with the higher IOP at hour 0 on day 1. If both eyes were equal at hour 0, the eye with the higher IOP at hour 2 on day 1 was selected. If both eyes were equal at hour 2, the eye with the higher IOP at hour 8 on day 1 was selected. If both eyes were equal at hour 8, the right eye was selected. The criterion for establishing treatment equivalence was 95% or greater confidence that the difference between treatments in mean change in IOP lies between −1.5 and 1.5 mmHg. A sample size of 120 patients per treatment group provided 79% power to detect equivalence, assuming a standard deviation of 4.0 mmHg.

The effect of baseline covariates on treatment response was explored using a two-way analysis of variance model with interaction. The following baseline factors were examined: investigator, age (<65 years, ≥65 years), race (white, other), gender (male, female), and iris color (dark, light). Three approaches to the analysis were performed for the masked phase: (1) all patients treated, observed cases (APT–OC); (2) all patients treated, last observation carried forward (APT–LOCF); and (3) per protocol, observed cases (PP–OC). The APT–OC approach was used for the primary assessment of treatment equivalence, which was based on the change in IOP from baseline averaged across months 2 and 3 to utilize both visits at which the IOP-lowering effect was most likely to have been established. All randomized patients with efficacy data at month 2 or month 3 or both were included; missing data were not estimated because averaging data that have been estimated from previous examinations could underestimate the variability of the data. The APT–LOCF approach was used for descriptive summary statistics of the IOP data and for the assessment of treatment equivalence at the individual visits. All patients randomized to study medication with efficacy data for at least one visit after randomization were included. Missing data were estimated from previous time-matched observations occurring within the same phase of the study. The PP–OC approach was used for secondary analyses of the data. Examinations associated with a serious violation of the protocol (e.g., failure to instill all doses of study medication the day before, or the morning and afternoon of, an examination) were excluded, and missing data points were not estimated. Examinations to be excluded were identified before unmasking the data.

Maintenance of effect was assessed at months 6, 9, and 12 among the patients who received the dorzolamide–timolol combination during both phases of the study. In addition, the change in IOP was compared between this group of patients and those who were switched from concomitant therapy during the masked phase to the dorzolamide–timolol combination during the extension. The APT–LOCF approach was used for these analyses.

Fisher's exact test (two-tailed) was used to compare the treatment groups with regard to dichotomous patient characteristics as well as the incidence of adverse experiences and emergent or worsening ocular signs, ocular symptoms, and visual field defects. Age at entry and baseline IOP were compared between the treatment groups using a two-way analysis of variance model with investigator and treatment as main effects and no interaction. The statistical software package used for the analyses was SAS, Version 6.10 (SAS Institute Inc, Cary, NC). All probability values are two-tailed and were rounded to three decimal places; statistical significance was declared if the rounded probability value was less than 0.050.

Table 1. Baseline Demographic Characteristics by Treatment Group: No. (%)

	Combination (N = 121)	Concomitant (N = 121)	Total (N = 242)
Sex*			
Male	50 (41)	71 (59)	121 (50)
Female	71 (59)	50 (41)	121 (50)
Race			
White	88 (73)	92 (76)	180 (74)
Black	29 (24)	29 (24)	58 (24)
Hispanic	3 (2)	0 (0)	3 (1)
Chinese	1 (1)	0 (0)	1 (0)
Iris color			
Dark brown	30 (25)	24 (20)	54 (22)
Brown	29 (24)	33 (27)	62 (26)
Hazel	17 (14)	19 (16)	36 (15)
Green	3 (2)	5 (4)	8 (3)
Blue	42 (35)	40 (33)	82 (34)
Age (yrs)			
N	121	121	242
Mean [SD]	60.7 [11.6]	61.7 [13.0]	61.2 [12.3]
Median	63	65	64
Range	22–81	25–84	22–84
Baseline IOP (mmHg)			
Worse Eye			
Hour 0			
N	121	121	242
Mean [SD]	26.1 [3.0]	26.1 [3.8]	26.1 [3.4]
Median	25	26	26
Range	22–34	20–48	20–48
Hour 2			
N	121	121	242
Mean [SD]	25.0 [3.3]	25.0 [3.7]	25.0 [3.5]
Median	24	24	24
Range	19–39	18–48	18–48
Hour 8			
N	119	120	239
Mean [SD]	23.7 [3.8]	23.3 [4.2]	23.5 [4.0]
Median	23	23	23
Range	15–36	14–47	14–47

SD = standard deviation; IOP = intraocular pressure.

* p = 0.010, significantly more females in the combination group.

Results

Demographic Data

The baseline demographic characteristics of the patients are presented in Table 1. Of the 242 patients in this study, 121 (50%) were male. The racial distribution was 74% white, 24% black, and 1% Hispanic. Fifty-two percent of the patients had light irides (blue, green, or hazel). The mean age of the patients was 61.2 years; approximately 74% were older than 54 years of age and approximately 49% were older than 64 years of age. The majority (83%) of patients had open-angle glaucoma; the remaining patients (17%) had ocular hypertension. The most common secondary

diagnosis was systemic hypertension, which occurred in 42% of the patients. More women were randomized to the combination group than to the concomitant therapy group (59% vs. 41%, $P = 0.01$); however, there was no gender effect on IOP reduction when baseline covariates were analyzed. The treatment groups were similar with respect to all other baseline characteristics, including the mean and median baseline IOP values. However, baseline IOP was very high in one patient in the concomitant therapy group (48, 48, and 47 mmHg at hours 0, 2, and 8, respectively). The next highest baseline IOP values in this group were 40, 40, and 34 mmHg. Adjustment for baseline IOP was accomplished by using the mean change in IOP from baseline as the variable to assess treatment effect.

Patient Accounting

Of the 242 patients enrolled in the study, 220 (91%) completed the masked phase and entered the open-label extension; 203 (92%) of these patients completed the extension. The most common reasons for discontinuation were clinical adverse events (4% during the masked phase and 4% during the extension) and lack of therapeutic effect (3% during the masked phase and 1% during the extension). Other reasons for discontinuation were protocol deviation, patient withdrawal, and patient lost to follow-up; these reasons accounted for no more than 1% of the patients in either phase. More patients in the combination group than in the concomitant therapy group discontinued from the masked phase (12% vs. 7%), but this difference was not statistically significant.

Efficacy

Figure 1 displays the mean IOP for each treatment group at each study visit during the masked phase of the study. Table 2 presents the IOP summary statistics for this phase. Throughout the masked phase, the mean IOP reduction was very similar between treatment groups at hour 2 (2 hours after the morning dose of both regimens) but was slightly greater in the concomitant therapy group than in the combination group at hour 0 (just before the morning dose of both regimens) and at hour 8 (2 hours after the afternoon dose of dorzolamide in the concomitant therapy group). The maximum IOP-lowering effect of both regimens was achieved by week 2, the first study visit after treatment was initiated. At month 3, the dorzolamide–timolol combination reduced IOP by 13.8% at hour 0, 19.7% at hour 2, and 14.9% at hour 8. In the concomitant therapy group, the mean IOP reduction at month 3 was 15.5% at hour 0, 19.1% at hour 2, and 17.4% at hour 8.

Table 3 presents the estimated difference between treatments for the mean change in IOP from baseline, as well as the 95% confidence interval and the estimated confidence (probability) that the true difference lies between −1.5 mmHg and 1.5 mmHg. A negative difference indicates a greater IOP reduction in patients receiving concomitant therapy than in those receiving the fixed combination. Throughout the masked phase of the study, the difference between treatments was greater at hour 0 and at hour 8 than at hour 2. Using the average of the month 2 and month 3 data, the estimated treatment difference was −0.67 mmHg at hour 0, −0.05 mmHg at hour 2, and −0.73 mmHg at hour 8; at each timepoint, there was greater than 97% confidence that the treatments met the definition of equivalence. Using the data from the individual visits, the estimated difference between treatments at month 3 was −0.52 mmHg at hour 0, 0.17 mmHg at hour 2, and −0.69 mmHg at hour 8. In support of the primary analysis, there was greater than 96% confidence that the treatments met the definition of equivalence at all timepoints and all visits.

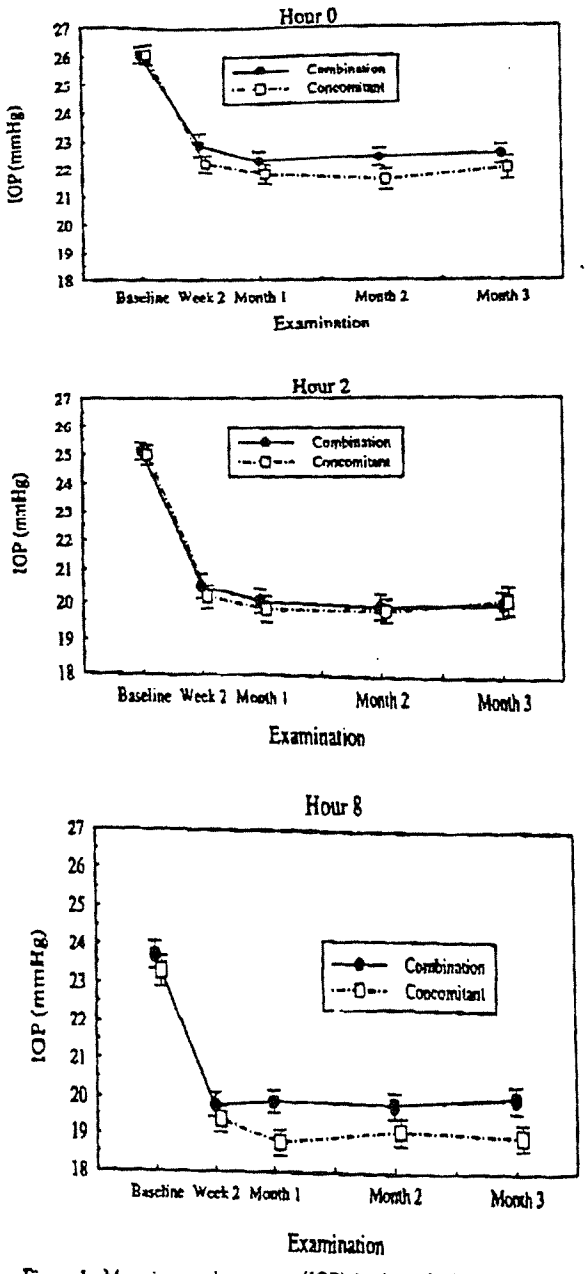

Figure 1. Mean intraocular pressure (IOP) (and standard errors) by treatment group at baseline and at each study visit in the masked phase. At hours 0 and 8, mean IOP was slightly lower in the concomitant therapy group than in the combination group; at hour 2, mean IOP was virtually the same for both treatments.

Using the secondary PP–OC approach, the difference between treatments was slightly larger at all timepoints. For the average of the month 2 and month 3 data, the estimated treatment difference was −0.90 mmHg at hour 0, −0.21 mmHg at hour 2, and −0.85 mmHg at hour 8. The treatments were equivalent at hour 2 (confidence >99%) but not at hour 0 or hour 8 (confidence 94%). For the individual visits, the estimated treatment difference at month 3 was −0.71 mmHg at hour 0, −0.03 mmHg at hour 2, and −0.88 mmHg at hour 8. Treatment equivalence was shown for hour 2 at all visits, for hour 0 at half of the visits (months 1 and 3), and for hour 8 at half of the visits (week 2 and month 2). In all cases, however, the difference between treatments was less than 1.0 mmHg.

Table 2. Intraocular Pressure Summary Statistics* of Masked Phase: Mean (Standard Deviation)

Examination	Treatment	N	Baseline (mmHg)	Treatment (mmHg)	Change (mmHg)	% Change
Hr 0						
Wk 2	Combination	115	26.0 (3.0)	22.9 (4.2)	−3.1 (3.1)	−12.0 (11.8)
	Concomitant	120	26.1 (3.8)	22.2 (3.6)	−3.9 (3.0)	−14.6 (10.6)
Mo 1	Combination	120	26.1 (3.0)	22.3 (4.1)	−3.8 (3.0)	−14.8 (11.5)
	Concomitant	121	26.1 (3.8)	21.8 (3.7)	−4.2 (3.1)	−15.9 (11.1)
Mo 2	Combination	120	26.1 (3.0)	22.4 (3.8)	−3.7 (2.7)	−14.3 (10.3)
	Concomitant	121	26.1 (3.8)	21.6 (3.9)	−4.4 (3.6)	−16.6 (12.6)
Mo 3	Combination	120	26.1 (3.0)	22.5 (4.1)	−3.6 (3.0)	−13.8 (11.1)
	Concomitant	121	26.1 (3.8)	22.0 (4.4)	−4.1 (3.7)	−15.5 (13.8)
Hr 2						
Wk 2	Combination	114	25.1 (3.3)	20.5 (3.9)	−4.6 (3.2)	−18.1 (12.2)
	Concomitant	119	25.1 (3.7)	20.2 (3.7)	−4.8 (3.5)	−18.9 (12.8)
Mo 1	Combination	119	25.1 (3.3)	20.1 (3.5)	−5.0 (3.3)	−19.6 (12.1)
	Concomitant	120	25.0 (3.7)	19.9 (3.7)	−5.2 (3.1)	−20.3 (11.3)
Mo 2	Combination	119	25.1 (3.3)	20.0 (3.8)	−5.0 (3.4)	−19.9 (12.3)
	Concomitant	120	25.0 (3.7)	19.9 (3.5)	−5.2 (3.3)	−20.2 (11.8)
Mo 3	Combination	119	25.1 (3.3)	20.1 (3.8)	−5.0 (3.5)	−19.7 (12.9)
	Concomitant	120	25.0 (3.7)	20.2 (4.2)	−4.9 (3.8)	−19.1 (14.4)
Hr 8						
Wk 2	Combination	111	23.6 (3.9)	19.8 (3.8)	−3.8 (3.3)	−15.5 (12.9)
	Concomitant	115	23.3 (4.2)	19.4 (3.6)	−3.9 (3.9)	−15.6 (15.3)
Mo 1	Combination	116	23.7 (3.9)	19.9 (3.6)	−3.8 (3.3)	−15.2 (12.8)
	Concomitant	118	23.3 (4.2)	18.8 (3.6)	−4.5 (3.4)	−18.5 (13.0)
Mo 2	Combination	116	23.7 (3.9)	19.8 (3.7)	−3.9 (3.4)	−15.6 (13.4)
	Concomitant	118	23.3 (4.2)	19.1 (3.9)	−4.3 (3.9)	−17.3 (15.2)
Mo 3	Combination	116	23.7 (3.9)	20.0 (3.9)	−3.7 (3.4)	−14.9 (13.2)
	Concomitant	118	23.3 (4.2)	19.0 (3.5)	−4.3 (3.8)	−17.4 (14.8)

* All patients treated analysis (last observation carried forward) — worse eye.

Figure 2 displays the mean IOP for each treatment group at each study visit during the extension phase of the study. Table 4 presents the IOP summary statistics for this phase. Among patients who received the combination during both phases of the study, the mean IOP reduction during the extension, relative to the timolol baseline, ranged from 3.5 to 3.8 mmHg (14%–15%) at hour 0 and

Table 3. Intraocular Pressure (IOP) Estimates and Confidence Levels for Difference between Treatments—Mean Change in IOP from Baseline in Masked Phase

Examination	Sample Size		Difference between Treatments† (mmHg)	Standard Error (mmHg)	95% Confidence Interval	Confidence Level‡
	Combination	Concomitant				
APT-OC*						
Hr 0	112	116	−0.67	0.37	−1.41, 0.06	0.986
Hr 2	112	115	−0.05	0.39	−0.81, 0.71	>0.999
Hr 8	110	114	−0.73	0.41	−1.53, 0.07	0.971
APT-LOCF						
Hr 0						
Wk 2	115	120	−0.78	0.39	−1.55, −0.02	0.967
Mo 1	120	121	−0.42	0.37	−1.15, 0.32	0.998
Mo 2	120	121	−0.72	0.40	−1.50, 0.07	0.975
Mo 3	120	121	−0.52	0.42	−1.34, 0.31	0.990
Hr 2						
Wk 2	114	119	−0.23	0.43	−1.08, 0.62	0.998
Mo 1	119	120	−0.11	0.41	−0.92, 0.69	>0.999
Mo 2	119	120	−0.14	0.43	−0.98, 0.71	0.999
Mo 3	119	120	0.17	0.47	−0.75, 1.10	0.997
Hr 8						
Wk 2	111	115	−0.15	0.47	−1.08, 0.79	0.963
Mo 1	116	118	−0.74	0.43	−1.58, 0.10	0.989
Mo 2	116	118	−0.44	0.46	−1.34, 0.46	0.967
Mo 3	116	118	−0.69	0.44	−1.55, 0.18	

* The APT-OC approach was based on the change in IOP from baseline averaged over month 2 and month 3.

† Concomitant − combination; a negative difference indicates a greater decrease in IOP in the concomitant group.

‡ The confidence is 0.950 or more that the difference between treatment means lies between −1.5 and 1.5 mmHg.

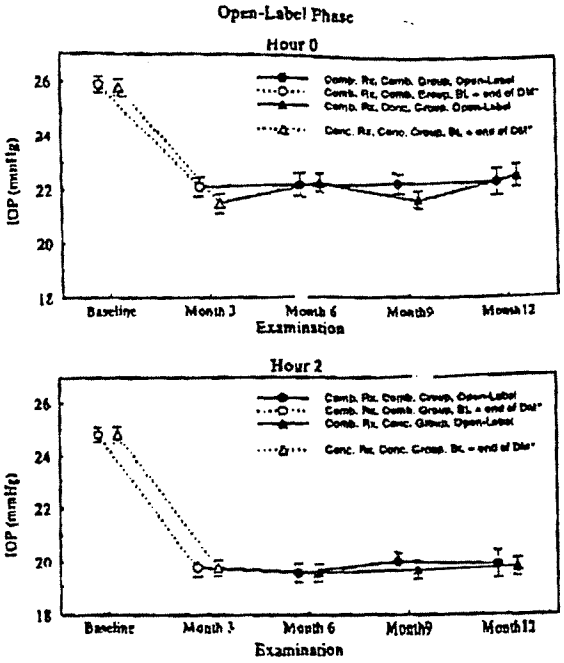

Figure 2. Mean intraocular pressure (IOP) (and standard errors) by initial treatment assignment at baseline, the end of the masked phase, and each study visit in the extension phase. From months 3 to 12, mean IOP at hour 0 remained constant in patients who continued to receive the combination and remained similar in patients who switched from concomitant therapy to the combination; mean IOP at hour 2 remained constant in both groups.

from 5.0 to 5.4 mmHg (20%–21%) at hour 2. These reductions are very similar to those measured at the end of the masked phase, indicating that the IOP-lowering effect of the dorzolamide–timolol combination was maintained over the 12 months of therapy. Among patients who were switched from concomitant therapy to the combination, the mean IOP reduction during the extension, relative to the original timolol baseline, ranged from 3.2 to 4.1 mmHg (12%–16%) at hour 0 and from 5.0 to 5.2 mmHg (20%–21%) at hour 2. Patients who entered the extension also were evaluated to determine whether their initial treatment assignment affected their response to the fixed combination during the open-label phase. At all timepoints, the confidence was greater than 98% that the treatment groups were equivalent in their IOP response to the fixed combination during the extension. Thus, the initial treatment assignment did not affect treatment response during the extension.

Safety

Symptoms reported by more than 3% of the patients in either treatment group during the masked phase or by more than 3% of the patients during the extension are displayed in Table 5. During both phases of the study, the most commonly reported symptoms were bitter taste, blurred vision, and ocular burning. The incidence of most symptoms was very similar between treatment groups. Eyelid pain or discomfort was the only symptom that occurred with a significantly higher incidence in the combination group than in the concomitant therapy group (6% vs. 1%, $P = 0.036$); the majority of these cases were mild in severity (5 cases in the combination group and 1 in the concomitant therapy group) and the remaining cases were moderate (2 cases in the combination group). Symptoms tended to occur less frequently during the extension than during the masked phase.

The ocular signs observed most frequently during the masked phase were conjunctival hyperemia (12% in the combination group, 14% in the concomitant group) and punctate epithelial erosions or superficial punctate keratitis (13% in both groups). There were no statistically significant differences between the treatment groups with regard to the incidence of any ocular sign. The ocular signs observed most frequently during the extension phase were punctate epithelial erosions or superficial punctate

Table 4. Intraocular Pressure Summary Statistics* of Extension Phase: Mean (Standard Deviation)

Examination	Treatment‡	N	Baseline	Treatment	Change	Percent Change
Hr 0						
Mo 3†	Combination	107	25.9 (2.9)	22.1 (3.8)	−3.8 (2.8)	−14.6 (10.7)
	Concomitant	113	25.8 (3.3)	21.5 (3.8)	−4.4 (3.4)	−16.6 (12.8)
Mo 6	Combination	105	26.0 (2.9)	22.2 (4.3)	−3.8 (3.2)	−14.8 (12.6)
	Concomitant	111	25.8 (3.3)	22.3 (3.5)	−3.5 (3.7)	−12.9 (13.3)
Mo 9	Combination	105	26.0 (2.9)	22.3 (3.9)	−3.6 (3.1)	−13.9 (11.6)
	Concomitant	112	25.8 (3.3)	21.7 (3.7)	−4.1 (3.5)	−15.6 (13.0)
Mo 12	Combination	105	26.0 (2.9)	22.4 (5.1)	−3.5 (4.3)	−13.7 (15.5)
	Concomitant	112	25.8 (3.3)	22.6 (4.2)	−3.2 (4.1)	−12.1 (14.8)
Hr 2						
Mo 3†	Combination	107	24.8 (2.9)	19.7 (3.5)	−5.1 (3.4)	−20.3 (12.8)
	Concomitant	113	24.8 (2.9)	19.7 (3.2)	−5.1 (3.4)	−20.2 (12.4)
Mo 6	Combination	105	24.9 (2.9)	19.5 (3.4)	−5.4 (3.4)	−21.4 (12.5)
	Concomitant	108	24.6 (2.5)	19.5 (3.3)	−5.2 (3.4)	−20.7 (13.1)
Mo 9	Combination	105	24.9 (2.9)	19.9 (3.3)	−5.0 (3.3)	−19.7 (12.7)
	Concomitant	108	24.6 (2.5)	19.6 (3.5)	−5.1 (3.2)	−20.5 (12.5)
Mo 12	Combination	105	24.9 (2.9)	19.8 (5.1)	−5.1 (4.5)	−20.5 (16.4)
	Concomitant	108	24.6 (2.5)	19.7 (3.5)	−5.0 (3.5)	−20.0 (12.9)

* All patients treated analysis (last observation carried forward) — worse eye.

† Summary statistics for month 3 (final visit of the double masked phase) for patients who continued into the open-label phase are included for reference.

‡ Combination and concomitant refer to the initial treatment group assignments; all patients received 0.5% timolol/2.0% dorzolamide fixed combination twice daily during the open-label phase.

Table 5. Number (%) of Patients with Emergent or Worsening Symptoms (Incidence >3% in Any Treatment Group)

	Masked Phase		Extension (Combination) (N = 220)
	Combination (N = 121)	Concomitant (N = 121)	
Bitter taste	38 (32)	42 (35)	36 (17)
Blurred vision	14 (12)	15 (12)	16 (7)
Burning eye	17 (14)	12 (10)	20 (9)
Eyelid pain or discomfort*	7 (6)	1 (1)	5 (2)
Itching eye	9 (8)	8 (7)	11 (5)
Stinging eye	14 (12)	15 (12)	9 (4)
Tearing eye	7 (6)	4 (3)	8 (4)

* P = 0.036.

keratitis (9%), fluorescein staining (5%), conjunctival hyperemia (5%), and nuclear opacity of the lens (5%).

During the masked phase of the study, clinical adverse events occurred in 34% of the combination group and in 26% of the concomitant therapy group. There were no statistically significant differences between the treatment groups in the overall incidence of clinical adverse events, the incidence of drug-related clinical adverse events, or the incidence of any specific clinical adverse event. The most common clinical adverse events were headache (3%) and eye discharge (3%) in the combination group and eye irritation (3%) in the concomitant therapy group. Clinical adverse events that were considered drug related occurred in 10% of each treatment group. The most common drug-related adverse events in the combination group were dry mouth (2%), eye discharge (2%), and foreign body sensation (2%); in the concomitant therapy group, the most common drug-related adverse events were ocular burning or stinging or both (2%) and eye irritation (2%). During the extension phase, clinical adverse events occurred in 46% of the patients and were considered drug related in 6%. The most common clinical adverse events were upper respiratory infection (6%) and lens opacity (5%). All of the drug-related adverse events occurred in less than 1% of the patients in the extension.

Clinical adverse events caused ten patients to be discontinued from the masked phase, seven (6%) in the combination group and three (2%) in the concomitant therapy group (difference not significant), and nine patients (4%) to be discontinued from the extension phase. Drug-related ocular events, such as lid reactions, allergic reactions, and blurred vision, accounted for half of the treatment discontinuations during the masked phase and one third of the treatment discontinuations during the extension phase; all of these patients recovered completely after the study medication was stopped. Drug-related nonocular events, such as urolithiasis (see below), nausea, and depression, led to treatment discontinuation in three patients: only the patient with depression had not recovered at last follow-up, which was 10 months after the study medication was stopped. The remaining discontinuations were because of serious nonocular events that were not drug related (6 patients) or visual field defects that were not drug related (2 patients).

Three patients developed urolithiasis while receiving the dorzolamide–timolol combination. The first case occurred on day 20 of the study in a patient with no history of kidney stones; although this case was considered to be not drug related, the patient was discontinued from the study and the stone was removed surgically. The second case occurred on day 75 of the study in a patient with a 10-year history of kidney stones; the patient passed the stone and was discontinued from the study (as mentioned above) because the event was considered possibly drug related. The third case occurred on day 130 of the study in a patient with no history of kidney stones; although this case was considered possibly drug related, the patient continued in the study with no further problems after passing the stone. There were no cases of urolithiasis among patients in the concomitant therapy group.

Laboratory adverse events occurred in 4% of each treatment group during the masked phase of the study. There were no statistically significant differences between the treatment groups in the overall incidence of laboratory adverse events, the incidence of drug-related laboratory adverse events, or the incidence of any specific laboratory adverse event. The most common laboratory adverse events were increased leukocyte count (3%) in the combination group and hyperglycemia (2%) in the concomitant therapy group. Three patients had laboratory adverse events that were considered drug related: increased leukocyte count, decreased erythrocyte count, and decreased serum bicarbonate in one patient each. All three patients were in the combination group and recovered without treatment by the end of the extension phase. During the extension phase, laboratory adverse events occurred in 5% of the patients. The most common laboratory adverse event was hyperglycemia (2%). Two patients had laboratory adverse events that were considered drug related: crystalluria and oxaluria in one patient each. Both patients had a history of urine crystals before the study, and in both cases the crystals were no longer present 2 weeks after the patient completed the study. No patients were discontinued because of laboratory adverse events.

At the end of the masked phase, there were no statistically significant differences between the treatment groups with regard to emergent or worsening visual field defects or changes in visual acuity, blood pressure, or pulse rate. Changes in these parameters at the end of the extension were similar to those observed at the end of the masked phase. No clinically meaningful changes in mean laboratory values were observed during either phase of the study.

Discussion

In this study, a fixed combination of 2% dorzolamide and 0.5% timolol given twice daily showed ocular-hypotensive efficacy comparable to that of 2% dorzolamide given three times daily in addition to 0.5% timolol given twice daily. The criterion for establishing treatment equivalence was 95% or greater confidence that the difference between treatments in mean change in IOP lies between −1.5 and 1.5 mmHg. No epidemiologic studies are available to provide support for what a meaningful difference in IOP might be. Because 1.5 mmHg is the outside boundary in our definition of equivalence, the point estimate of the true difference between treatments would have to be much closer to zero. In our primary analysis, the point estimates ranged from −0.05 to −0.73 mmHg.

During 3 months of treatment, both regimens produced clinically significant reductions in IOP from the timolol baseline. Similar reductions in IOP have been observed in previous studies that evaluated the concomitant use of 0.5% timolol twice daily and 2% dorzolamide three times daily.[2–4] In the current study, the

largest difference in IOP reduction between the dorzolamide–timolol combination and the concomitant administration of its components was observed at hour 8; this measurement occurred 8 hours after the morning dose of all study medications and 2 hours after the afternoon dose of the three-times-daily medication (i.e., placebo for the combination group and dorzolamide for the concomitant therapy group). The difference between treatments observed at this timepoint may have been caused by the afternoon dose of dorzolamide received by the concomitant therapy group. However, the difference between treatments at hour 0 was only slightly less than the difference at hour 8. The reason for this difference is not clear since hour 0 represents the morning trough measurement for both treatment regimens. These results suggest that patients receiving dorzolamide three times daily and timolol twice daily may experience slightly greater IOP reductions during the afternoon and early morning than patients receiving the dorzolamide–timolol combination; however, these differences are likely to be very small.

Other studies comparing a fixed combination to concomitant therapy with its components have reported similar results. Soderstrom et al[12] compared a fixed combination of 0.5% timolol and 4% pilocarpine given twice daily to the concomitant administration of 0.5% timolol twice daily and 4% pilocarpine three times daily in patients whose IOP exceeded 21 mmHg after at least 1 week of receiving 0.5% timolol alone. Intraocular pressure was measured at 8:30 AM, 1:30 PM, and 4:30 PM (not more than 3 hours after the mid-day dose of pilocarpine) after 2 and 4 weeks of treatment. Significant reductions in IOP from baseline were observed at all timepoints in both groups, and there were no significant differences between the regimens at any timepoint. Demailly et al[13] compared twice-daily administration of a fixed combination of 2% carteolol and 2% pilocarpine to the concomitant administration of 2% carteolol twice daily and 2% pilocarpine three times daily in patients with IOP greater than 21 mmHg while receiving beta-blocker monotherapy. Intraocular pressure was measured at 12 noon and 7 PM after 15 days and 2 months of treatment. Although the difference between groups was not statistically significant at any timepoint, there was a trend toward better IOP control at 7 PM (4 hours after the mid-day dose of pilocarpine) in patients receiving concomitant therapy.

Among patients who received the dorzolamide–timolol combination during both phases of the current study, the reduction in IOP after 12 months was very similar to the reduction observed after 3 months. Thus, the IOP-lowering effect of the combination was maintained during long-term use. Furthermore, the mean IOP reduction in patients who were switched from concomitant therapy was equivalent to the mean IOP reduction in patients who received the combination during both phases of the study. This finding confirms that, as expected, prior use of concomitant therapy does not compromise the IOP-lowering effect of the dorzolamide–timolol combination. Moriarty et al[14] studied the IOP-lowering effect of a fixed combination of 0.5% timolol and 2% pilocarpine given twice daily in patients who previously were controlled taking timolol 0.25% or 0.5% twice daily and pilocarpine 2% four times a day. Intraocular pressure was measured at 10:00 AM (2 hours after the morning dose). At 1, 3, and 6 months after switching to the fixed combination, mean IOP was approximately 1 mmHg higher than at baseline. In our study, mean IOP was essentially unchanged at 3, 6, and 9 months after switching from concomitant therapy to the dorzolamide–timolol combination.

The safety profile of the dorzolamide–timolol combination was very similar to that of concomitant therapy with dorzolamide and timolol. The symptoms reported in this study have been observed in previous studies of dorzolamide used alone[2,4] or as adjunctive therapy to timolol.[3] The lower incidence of symptoms observed during the extension phase suggests that symptoms may become less noticeable to patients as therapy continues. The incidence of drug-related adverse events and the rate of discontinuation also were lower during the extension than during the masked phase of the study. Thus, extended use of the dorzolamide–timolol combination is well-tolerated.

Three patients developed renal stones during the course of this study. The first patient had received the drugs for only 20 days, far too little for any reasonable association with dorzolamide therapy. Insignificant amounts of dorzolamide are excreted for several weeks after initiation of therapy, due to storage in erythrocytes.[15] The second patient had a history of kidney stones, and the third patient continued taking study drug without further incident. Patients receiving chronic therapy with acetazolamide have a tenfold increase in the incidence of urolithiasis, probably secondary to metabolic acidosis with decreased urinary citrate and decreased solubilization of urinary calcium.[16] However, metabolic acidosis was not observed in this study or in other long-term clinical studies of dorzolamide.[2,4] Since its introduction to the marketplace, dorzolamide has been used by more than 1 million patients in the United States alone. Only 13 cases of renal stones or renal pain have been reported to the manufacturer during this time. By comparison, a recent study of diet and disease in men found 753 incident cases of kidney stones during 6 years of follow-up in a cohort of 45,289 men 40 to 75 years old with no history of kidney stones.[17]

In summary, this study has shown that the efficacy and safety of the dorzolamide–timolol combination are comparable to those observed with concomitant use of dorzolamide and timolol. The dorzolamide–timolol combination continues to be effective and well-tolerated for up to 12 months and is also effective in patients who previously have received concomitant therapy with dorzolamide and timolol. The dorzolamide–timolol combination is more convenient to use than concomitant therapy with these two agents since it requires fewer bottles and fewer daily doses (2 vs. 5). In addition, using the dorzolamide–timolol combination eliminates the need to wait 5 to 10 minutes between drug instillations. This greater convenience may lead to greater patient compliance, which is an important consideration in the treatment of a chronic and asymptomatic disease. Thus,

the dorzolamide–timolol combination may provide a clinically useful alternative for patients requiring multiple medical therapy for glaucoma.

Appendix

Dorzolamide–Timolol Study Group

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