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CLINICAL STUDY

Brimonidine 0.2% *vs* unoprostone 0.15% both added to timolol maleate 0.5% given twice daily to patients with primary open-angle glaucoma or ocular hypertension

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Abstract

Purpose **To compare the efficacy and safety of brimonidine 0.2% *vs* unoprostone 0.15%, both added to timolol maleate 0.5% each given twice daily.**

Methods **In this prospective, multi-centred, double-masked, crossover comparison, patients were randomized to one treatment group for a 6-week treatment period, and then crossed over to the opposite treatment. Measurements were performed at 0800, 1000, 1600, 1800, and 2000 h at baseline and at the end of each treatment period.**

Results **In all, 33 patients entered this trial and 29 completed. The baseline trough intraocular pressure (IOP) was 23.3 ± 2.4 and the diurnal curve IOP was 22.0 ± 1.3 mmHg. For the brimonidine and timolol maleate treatment group, the trough IOP was 21.6 ± 3.3 and the diurnal curve IOP was 19.8 ± 2.1 mmHg, while the timolol and unoprostone treatment showed a trough IOP of 20.9 ± 3.8 and a diurnal curve IOP of 19.3 ± 2.4 mmHg. There was no significant difference between treatment groups at any time point for the diurnal curve, or in the reduction from baseline ($P > 0.05$). Both treatments failed to statistically reduce the IOP from baseline at 1800 h. There was no difference between treatment groups regarding ocular and systemic unsolicited adverse events, but patients admitted to more dryness ($P = 0.02$) and burning upon instillation ($P < 0.0001$) with unoprostone by survey.**

Conclusion **Brimonidine 0.2% or unoprostone 0.15% added to timolol maleate 0.5% provide similar efficacy and safety throughout the daytime diurnal curve.**

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Introduction

Patients with primary open-angle glaucoma or ocular hypertension are typically treated with medication to reduce the intraocular pressure (IOP) to prevent the onset or progression of optic nerve damage. Over the past several decades, timolol maleate has been the most commonly used primary therapy to lower the IOP.[1,2] However, many patients need a second medication to help further reduce the IOP. Over the past several years, brimonidine 0.2% (Alphagan®, Allergan, Irvine, CA, USA) has been an important adjunctive medication added to timolol maleate. Another medication, unoprostone 0.15% (Rescula®, Novartis Ophthalmics, Basal, Switzerland), was released recently into the worldwide market and may also be used as adjunctive therapy to timolol maleate.[3]

Unfortunately, data are still limited that evaluate the diurnal curve efficacy of brimonidine *vs* unoprostone each added to timolol maleate. Stewart and associates recently evaluated brimonidine 0.2% *vs*

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unoprostone 0.15%, both given twice daily, over the diurnal curve as monotherapy.[4] This study showed that, although brimonidine was more effective at peak, it lost its ocular hypertensive efficacy at the end of the daytime dosing cycle at 1800 and 2000 h.[4] In contrast, unoprostone statistically maintained the mean pressure reduction throughout the dosing cycle, and was more effective than brimonidine at 1800 and 2000 h.[4]

The purpose of this study was to evaluate the daytime diurnal safety and efficacy with a larger number of measurements for the intraocular pressure and greater statistical power to detect a statistical difference between brimonidine 0.2% and unoprostone 0.15%, both added to timolol maleate 0.5%, each given twice daily in patients with primary open-angle glaucoma or ocular hypertension.

Materials and methods

Patients

Individuals were included in this four-centre prospective trial if they demonstrated the following criteria: 18 years of age or older; new or previous clinical diagnosis of primary open-angle glaucoma or ocular hypertension; at baseline on timolol maleate 0.5% twice daily the IOP was between 22 and 34 mmHg, inclusive in at least one eye at 0800, and the average of all baseline pressure measures (diurnal curve) was $\geqslant$20 mmHg in the same eye (visit 2); and visual acuity was 20/200 or better in the study eye(s).

Patients were excluded from this study for any of the following exclusions: any abnormality preventing reliable applanation tonometry in study eye(s); any opacity or patient uncooperativeness that restricted adequate ocular examination in the study eye; infectious/noninfectious conjunctivitis, keratitis or uveitis in either eye; any history of allergic hypersensitivity or poor tolerance to any components of the preparations used in this trial; females of childbearing potential not using reliable means of birth control; pregnant or lactating females; any serious medical or psychiatric condition; participation in any investigational drug or device trial within the previous 30 days prior to visit 1; intraocular conventional or laser surgery within the 3 months prior to visit 1; according to the investigator's best judgement risk of visual field or visual acuity worsening as a consequence of participation in the trial; inability to understand the trial procedures; any anticipated change in systemic hypotensive therapy during the active treatment portion of the trial (visits 2–6); and history of monoamine oxidase use; and bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree atrioventricular block, or overt cardiac failure.

Procedures

Before any procedures were performed, the patients signed an Institutional Review Board approved informed consent form. At the screening visit (visit 1, day −28), and, at each subsequent visit, patients had slit-lamp biomicroscopy, Early Diabetic Treatment Retinopathy Study (ETDRS) visual acuity, and Goldmann applanation tonometry performed. At visit 1, patients had the inclusion and exclusion criteria reviewed, medical history obtained, and gonioscopy, dilated funduscopy, and a visual field (Program 24-2, Humphrey Visual Field Analyzer, Humphrey Instruments, Dublin, CA, USA) performed.

Qualified patients were placed on timolol 0.5% solution twice daily for 28 days and asked to return for the baseline visit (visit 2, day 0). At this visit and at each subsequent visit, unsolicited adverse events were recorded. Also, at visit 2, as well at the other efficacy visits (visits 4 and 6), an ocular symptom query (dry eye, pain in or around eyes, blurred vision, tearing, stinging or burning, crusting, itching, sandy or gritty feeling, or irritation), a systemic symptom survey (fatigue, dizziness, despondency, depression, or dry mouth), and a diurnal curve of the intraocular pressure at 0800, 1000, 1600, 1800, and 2000 h were performed. Following the trough pressure at the baseline and efficacy visits, patients had study medicines instilled by an unmasked dosing coordinator (who performed no other procedures) before the remainder of the diurnal curve was completed.

Patients who met the intraocular pressure requirements described above were randomized into the trial. Patients received either the brimonidine 0.2% and timolol maleate 0.5% to be instilled twice daily at 0800 and 2000 h, or timolol maleate 0.5% and unoprostone 0.15% to be instilled twice daily at 0800 and 2000 h with 5 min separating drop instillations. The patient, physician, and study personnel (apart from the unmasked dosing coordinator) were masked to the medicines.

Patients returned for the Period 1 safety check (visit 3, week 2) and then returned for the Period 1 efficacy visit (visit 4, week 6). Patients were then placed on the opposite treatment and returned for the Period 2 safety check (visit 5, week 8) and for the Period 2 efficacy visit (visit 6, week 12) performed the same way as visit 4.

Statistics

Data analyses were two-sided and a 0.05 alpha level was used. The primary efficacy variable was the IOP difference at Hour 0 between visits 4 and 6. This was analysed by a paired *t*-test for intragroup analysis.[5] The standard deviation used to determine the power was 2.8 mmHg.[6–9] This study provided with 27 patients at least an 80% power that a 1.5 mmHg difference could be excluded between groups. The secondary efficacy variable, intraocular pressure at each time point as well as diurnal IOP (the average of the five individual time points), was also analysed by a paired *t*-test.[5]

Safety parameters for intragroup analysis were evaluated with the Wilcoxon sign rank test including the ocular and systemic symptom queries.[5] Visual acuity was analysed by a paired *t*-test.[5] Adverse events were evaluated with a McNemar test.[10]

Results

Patients

In all, 33 patients were enrolled, who met the inclusion and exclusion criteria. Of these, 29 patients completed the study. The average age was 61.0 ± 11.0 years. Of these patients, 21 were Caucasian and eight were African American; 13 were male and 16 were female. A total of 20 patients had primary open-angle glaucoma and nine had ocular hypertension.

Intraocular pressure

The individual IOP and diurnal curves are shown in Table 1 and in diagrammatical form in Figure 1. The baseline trough pressure was 23.3 ± 2.4 and the baseline diurnal curve was 22.0 ± 1.3 mmHg on timolol alone. This study found that both study treatments caused a significant reduction for the diurnal curve, from baseline and at each time point ($P > 0.05$), except at 1800 h following dosing ($P > 0.05$).

The brimonidine and timolol maleate therapy showed a trough IOP of 21.6 ± 3.3 mmHg and a diurnal curve of 19.8 ± 2.1 mmHg. In contrast, timolol maleate and unoprostone showed a trough IOP of 20.9 ± 3.8 mmHg ($P = 0.49$) and a diurnal curve pressure of 19.3 ± 2.4 mmHg ($P = 0.45$). There was no difference between treatment groups at any time point in the absolute pressure value or in the reduction of the IOP from baseline ($P > 0.05$) (Table 1).

Adverse events

Ocular adverse events are shown in Table 2 and systemic adverse events in Table 3. There was no significant difference for any individual adverse event between the two treatments evaluated in this trial. The most frequent ocular adverse events were burning and conjunctival hyperaemia. There were no significant differences in systemic adverse events between the two treatment groups ($P > 0.05$). There were no serious adverse events.

On the systemic query, no significant difference existed between groups for any solicited systemic adverse event. However, on the ocular symptom survey, more patients reported dryness ($n = 7$) with unoprostone than brimonidine ($n = 1$, $P = 0.02$). Also, a greater number of patients indicated more stinging upon instillation with unoprostone ($n = 26$) than brimonidine ($n = 8$, $P < 0.001$). No difference in visual acuity was observed between treatment periods ($P = 0.93$).

Table 1 Mean intraocular pressures ± standard deviation (mmHg) and reduction (number of patients = 29)

	Baseline	*Brimonidine and timolol*	*Unoprostone and timolol*	P-*value**
Mean intraocular pressures				
Trough (0800)	23.3 ± 2.4	21.6 ± 3.3	20.9 ± 3.8	0.49
1000 h	22.0 ± 2.5	18.4 ± 2.8	17.1 ± 5.7	0.28
1600 h	21.8 ± 2.4	18.8 ± 2.5	19.3 ± 2.1	0.37
1800 h	21.2 ± 1.7	20.4 ± 3.2	20.5 ± 2.9	0.93
2000 h	21.6 ± 2.7	19.9 ± 3.0	18.9 ± 2.5	0.17
Diurnal[a]	22.0 ± 1.3	19.8 ± 2.1	19.3 ± 2.4	0.45
Reduction from baseline				
Trough (0800)		1.7 ± 3.0	2.3 ± 3.2	0.42
1000 h		3.6 ± 3.2	4.9 ± 5.8	0.30
1600 h		3.1 ± 2.3	2.5 ± 3.0	0.43
1800 h		0.8 ± 3.4	0.7 ± 2.8	0.93
2000 h		1.8 ± 4.0	2.8 ± 3.6	0.31
Diurnal		2.2 ± 2.1	2.7 ± 2.4	0.20

**P*-value is a comparison between treatment groups by a paired *t*-test.
[a]The mean diurnal curve is calculated as an average of the five individual measured time points.

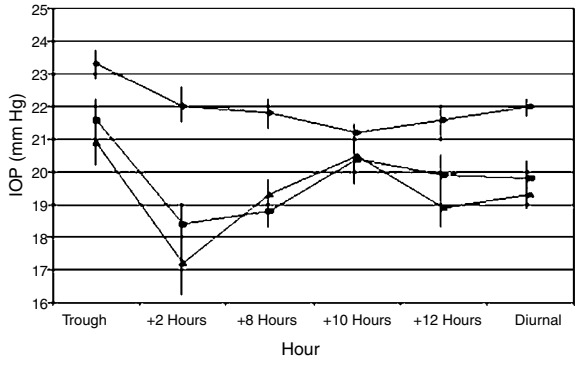

Figure 1 Baseline IOP (diamonds) at each time point *vs* brimonidine added to timolol maleate (squares) and unoprostone added to timolol maleate (triangles).

Table 2 Unsolicited ocular adverse events (number of events, two or more events included)

	Brimonidine and timolol	*Unoprostone and timolol*	P-*value**
Burning/stinging on instillation	2	7	0.06
Conjunctival hyperaemia	4	4	0.13
Decreased vision	2	2	>0.999
Itching	2	2	>0.999
Tearing	1	2	>0.999
Corneal abrasion	1	1	>0.999
Flare in anterior chamber	1	1	>0.999
Dryness	1	1	>0.999
Stickiness	1	1	>0.999
Photophobia	1	1	>0.999
Toxic epitheliopathy	1	1	>0.999

**P*-value determined by the McNemar test.

Table 3 Unsolicited systemic adverse events (number of events)

	Brimonidine and timolol	*Unoprostone and timolol*	P-*value**
Upper respiratory tract infection	1	1	>0.999
Dermatitis	1	0	>0.999
Nausea	1	0	>0.999
Overactive bladder	1	0	>0.999
Right knee inflammation	1	0	>0.999
Sleepiness	1	0	>0.999
Diagnosed with hypertension	0	1	>0.999
Infection in left leg	0	1	>0.999
Joint stiffness	0	1	>0.999
Tooth ache	0	1	>0.999

**P*-value determined by the McNemar test.

Discontinued patients

In all, 29 patients completed both the trough time points of the study. Two patients were excluded from data analysis because of a site administrative error. One patient was not used due to incorrect dosing and one patient was exited early from a treatment period because of dermatitis of the eyelid while on brimonidine.

Discussion

Brimonidine 0.2% was commercially released by Allergan in late 1996. It is a highly selective α_2-adrenergic agonist, and reduces the IOP primarily by decreasing aqueous production. It has become a popular adjunctive agent for glaucoma and, when prescribed, it is frequently given as monotherapy. It reduces the IOP at the 0800 trough level approximately 15–16% from baseline.[11–14] It is labelled three times a day, but is most frequently dosed twice daily. Brimonidine may cause side effects, including ocular allergy with an incidence approximately 10% presenting 3 months or later after initiation of therapy.[15] Also, systemic side effects of dry mouth, fatigue, and blood pressure changes may occur.[16,17]

Unoprostone 0.15% was released onto the commercial market in October 2000. This medicine demonstrates the structural characteristics of an $F_2\alpha$ prostaglandin, but may not be active at the FP-receptor in humans (internal data, Novartis Ophthalmics). It is labelled as a docosanoid by the United States regulatory agency. Unoprostone reduces the IOP by increasing outflow.[17] However, the exact pathway by which it acts, uveoscleral or conventional, has not yet been clarified.

Regulatory trials in the United States and Europe have shown that unoprostone reduces the IOP from baseline between 14 and 19%, with a consistent pressure reduction maintained over the 12-h daytime diurnal curve (internal data, Novartis Ophthalmics).[18] However, in these studies, unoprostone was not as effective statistically in reducing the IOP as timolol maleate. In addition, several reports have recently shown that latanoprost reduces the IOP statistically more than unoprostone.[19,20] Ocular stinging upon instillation is the most common side effect.[21]

This current report evaluated brimonidine 0.2% and timolol maleate 0.5% therapy given twice daily *vs* concomitant timolol maleate 0.5% and unoprostone 0.15%, each given twice daily in patients with primary open-angle glaucoma or ocular hypertension.

This study found that both treatments caused a significant reduction at each time point and for the diurnal curve from baseline, except at 1800 h after dosing. The reason why both medications did not reduce IOP at 1800 h after dosing, but at each other time point including 2000 h after dosing, is not clear from the results.

For brimonidine, the results at the end of the dosing cycle were consistent with several past studies. In two

separate diurnal curve studies, Stewart and coworkers[4] showed no effect from brimonidine as monotherapy when given twice daily at 1800 and 2000 h.[4] Stewart and associates also noted, in contrast, that a small effect was shown at both time points when brimonidine was added to timolol maleate (1.0 mmHg decrease).[22]

Unoprostone typically demonstrates a 12-h effect with twice daily dosing, and does not typically demonstrated a peak effect.[21,23] In a previous study (mentioned above), the effect of unoprostone monotherapy at peak was shown to be less than that of brimonidine (1200 h after dosing).[4] In contrast, unoprostone maintained a reduced pressure effect for the 12-h daytime dosing cycle. In this current study, an ocular hypotensive effect was seen throughout the dosing cycle, except at 1800 h when unoprostone was added to timolol. The reason for the lack of effect at 1800 h in this trial is not clear.

When the two treatment groups were compared, there was no significant difference in the IOP between treatments at each time point and for the diurnal curve of the pressure. Timolol and unoprostone showed a slight trend to be better at morning trough, whereas brimonidine and timolol showed a tendency to be better 8 h after dosing. In addition, there was no significant difference between treatments at each time point for the amount of reduction of the IOP.

Both brimonidine and unoprostone statistically reduced the IOP compared to timolol alone, but only by approximately 2 mmHg. This is less than that observed with the addition of latanoprost compared to timolol alone, and slightly more than that observed with the dorzolamide/timolol fixed combination compared to timolol alone (1.2 mmHg).[24–27] The results of this study are similar, but slightly less, to those of Hommer and associates,[28] in which approximately a 3 mmHg further reduction was found when adding brimonidine or unoprostone to timolol. The reason for the differences in the extent of the reduction between the current trial and Hommer's study is not readily apparent.

Safety results were similar between treatment results. The most common ocular adverse events were conjunctival hyperaemia and ocular stinging upon instillation, for which there was no significant difference between treatments. Stinging has been noted previously with unoprostone.[21,23] On the solicited ocular symptom survey, stinging upon instillation and dryness was noted more commonly with unoprostone. No differences in unsolicited or solicited systemic events were noted. There were no serious adverse events in this trial.

This study suggests that brimonidine 0.2% or unoprostone each added to timolol maleate 0.5% provide similar efficacy and safety throughout the daytime diurnal curve.

This study did not evaluate other types of glaucoma or nighttime IOPs with these medications. In addition, the study did not evaluate the efficacy of brimonidine *vs* unoprostone dosed per label (three times daily for brimonidine). Further research may help clarify any important medical differences between brimonidine and unoprostone as monotherapy or adjunctive therapy.

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