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Intraocular pressure control over 24 hours using travoprost and timolol fixed combination administered in the morning or evening in primary open-angle and exfoliative glaucoma

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ABSTRACT.

Purpose: **To evaluate intraocular pressure (IOP) control over 24 hours using travoprost and timolol fixed combination (TTFC) administered in the morning or evening in primary open-angle and exfoliative glaucoma.**

Methods: **Patients were randomized to TTFC administered in either the morning or evening for 8 weeks. Previously treated patients underwent an untreated washout period of 4–6 weeks, after which baseline IOP was required to be > 25 mm Hg and < 38 mmHg (in two readings taken at 10.00 ± 1 hours). During the treatment period, IOP was measured at 10.00, 14.00, 18.00, 22.00, 02.00 and 06.00 hours. Patients were then treated with the opposite dosing regimen for 8 weeks and IOP measurements were repeated.**

Results: **In 32 subjects who completed the study, the untreated baseline IOP following washout was 27.7 ± 3.5 mmHg. Both dosing regimens reduced IOP from baseline at each time-point and throughout the 24-hour diurnal curve ($p < 0.0001$). When treatments were compared directly, evening dosing (18.4 ± 3.3 mmHg) provided a statistically significant lower 24-hour curve than morning dosing (19.2 ± 3.5 mmHg; $p = 0.001$). Evening dosing also resulted in a lower 24-hour IOP fluctuation (3.8 ± 1.6 mmHg) than morning dosing (5.1 ± 1.6 mmHg; $p = 0.0002$) and lower peak IOP ($p = 0.0003$).**

Conclusions: **Both morning and evening administration of TTFC provide effective 24-hour IOP reduction, but evening dosing demonstrates better 24-hour pressure control.**

Key words: travoprost/timolol fixed combination – morning dosing – evening dosing – primary open-angle glaucoma – exfoliative glaucoma

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Introduction

Travoprost 0.004%/timolol maleate 0.5% fixed combination (TTFC) (DuoTrav™; Alcon, Inc., Fort Worth, TX, USA) recently gained regulatory approval in the EU. This new fixed combination is indicated for the treatment of patients with open-angle glaucoma or ocular hypertension who need further intraocular pressure (IOP) reduction than provided by a beta-blocker or prostaglandin analogue.

Barnebey et al. (2005) showed that IOP in patients treated with TTFC dosed in the morning dropped from baseline by 1.9–3.3 mmHg more than with timolol monotherapy and by 0.9–2.4 mmHg more than with travoprost alone. Further, Schuman et al. (2005) demonstrated mean IOP in the range of 16.2–17.4 mmHg with TTFC dosed in the morning compared with 15.4–16.8 mmHg with concomitant travoprost and timolol. In a similar study, Hughes et al. (2005) noted mean IOP in the range of 15.2–16.5 mmHg in patients using

TTFC compared with 14.7–16.1 mmHg in a concomitant therapy group. Consequently, morning administration of TTFC should provide incrementally better IOP control than prior beta-blocker or prostaglandin analogue monotherapy and almost identical levels of control as concomitant therapy with these same products.

Although TTFC in Europe is labelled for morning or evening dosing, little information on the efficacy of evening versus morning dosing is available. Previous research has suggested that prostaglandin analogues dosed in the evening may provide lower daytime mean IOP and less fluctuation in pressure over 24 hours (Konstas et al. 1999, 2002, 2006).

The purpose of the current study was to evaluate the efficacy of morning and evening dosing of TTFC in 24-hour IOP control in primary open-angle glaucoma (POAG) or exfoliative glaucoma patients.

Materials and Methods

Patients

The study design was a prospective, randomized, double-masked, active-controlled, crossover comparison. Patients were recruited from the glaucoma unit of the First University Department of Ophthalmology, AHEPA Hospital, Thessaloniki, Greece. All patients were examined by the study investigators (AGPK, ST, ANV, MBN). Consecutive newly diagnosed or suitably washed-out patients were enrolled.

We included patients with POAG or exfoliative glaucoma of ≥ 29 years of age. Baseline IOP without treatment was required to be > 25 mmHg and < 38 mmHg (in two readings taken at 10.00 ± 1 hours).

Additional inclusion criteria were: distance best corrected Snellen visual acuity (VA) > 0.1 (Snellen fraction with the denominator divided into the numerator); understanding of the study instructions; agreement to comply with the medication regimen; normal appearing angles, and a diagnosis of either POAG or exfoliative glaucoma as demonstrated by glaucomatous optic nerve head cupping (neural rim notching or saucerization) and potentially by glaucomatous visual field loss (nasal step, or arcuate, paracentral or Seidel's scotoma) determined by automated static threshold perimetry (Humphrey 24-2, Humphrey Field Analyzer; Humphrey Instruments, Inc., San Leandro, CA, USA). Additionally, patients diagnosed with exfoliative glaucoma were required to demonstrate typical features of this condition (Layden 1989). We included patients with exfoliative glaucoma in order to provide higher baseline pressures so that we could potentially show differences in the pressure curve between morning and evening dosing more clearly (Konstas et al. 1999).

We excluded patients with a previous history of unresponsiveness (deemed to be an IOP reduction of < 10%) to any antiglaucoma medication because we did not want the results of this crossover study, which had a limited sample size, to be influenced by a small number of outliers. Patients were also excluded if they had: a history of non-compliance; previous ocular surgery or trauma; previous chronic use of corticosteroids; contact lens use; severe dry eye; a corneal abnormality or any condition that prevented reliable applanation tonometry; secondary glaucoma apart from exfoliative glaucoma (i.e. pigment dispersion); evidence of ocular infection, except blepharitis; advanced cataract; uveitis; history of renal or hepatic impairment; a contraindication for topical use of a prostaglandin analogue or beta-blocker; advanced glaucoma, or a safety profile that would not allow washout of their glaucoma medication. We also excluded women of childbearing potential, lactating mothers and subjects who were unwilling to accept the risk of hyperchromia of the iris.

Methods

The methods for this study were similar to those described previously (Konstas et al. 2000, 2001a, 2001b, 2002, 2003a, 2003b, 2005). All patients signed an informed consent form approved by the Institutional Review Board, Bioethics Committee of Medical School before enrolment. Previously treated patients underwent an untreated washout period of 4 weeks for brimonidine or dorzolamide, 5 weeks for beta-blockers or dorzolamide/timolol fixed combination, and 6 weeks for prostaglandins or prostamides (Stewart et al. 2001b).

Patients with a qualifying baseline untreated 24-hour pressure curve were randomly assigned to receive one drop of travoprost 0.004%/timolol maleate 0.5% fixed combination (DuoTrav^{TM}) administered in either the morning or evening for the first 8-week treatment period. Patients in the evening dosing group were asked to instil the study medicine at 20.00 hours and placebo at 08.00 hours. By contrast, patients in the morning dosing group were asked to instil the study medicine at 08.00 hours and placebo at 20.00 hours. Patients were then crossed over to the second treatment period. During the last 24 hours of each treatment period, patients underwent 24-hour IOP monitoring. The 8-week treatment period was chosen to avoid a carryover effect of the medications under investigation (Stewart et al. 2001a). No washout period was included between treatment periods.

During the assessment of the 24-hour pressure curve, the investigator who performed the IOP measurements was masked to the treatment regimen and the same investigators used the same calibrated instruments (Goldmann applanation tonometer) to measure 24-hour IOP curves. The medication and the placebo bottles were identical (supplied by Alcon, Inc.). Patients were admitted to the hospital in the morning and seated IOP measurements were recorded at 10.00, 14.00, 18.00, 22.00, 02.00 and 06.00 hours. At the 22.00 hours measurement, patients were awake at bed rest. The 02.00 and 06.00 hours IOP measurements were performed 5–10 mins immediately after wakening and at the slit-lamp. Patients were encouraged to maintain their normal lifestyles as far as was possible within the hospital boundaries.

Patients were instructed about correct medication instillation and compliance. In this study all patients were instructed to perform nasolacrimal occlusion for 1 min after instillation of each study eyedrop. At each visit adverse events were recorded according to the patient's unsolicited complaints or following a general query (such as: 'How are you doing?').

Statistics

Statistical analyses comparing the primary efficacy variable, 24-hour IOP (average IOP for the six time-points evaluated), was performed using a repeated measures of analysis because of the contiguous nature of the data and the repeated measures analysed over the 24-hour pressure curve. In addition, because the data pertained to a crossover design, a matched pairs platform was used. Individual time-points were evaluated with a paired *t*-test within the ANOVA (Book 1978; Konstas et al. 1997a, 1997b; Orzalesi et al. 2003). We used a modified Bonferroni correction ($\alpha/4$) to adjust the significance levels for multiple comparisons for the individual time-points. The significance level was set at 5% and a two-way analysis was used for all tests. This study had an 80% power to identify a 1.5-mmHg difference between individual time-points and between mean 24-hour IOP assuming a standard deviation of 2.8 mmHg between treatments (Duff 1987; Mundorf et al. 1998; Stewart et al. 2001a; Konstas et al. 2002). In a patient with bilateral glaucoma, one eye was randomly chosen at the time of enrolment for analysis.

The mean 24-hour IOP fluctuation (average of the highest pressure reading minus the lowest pressure reading within the 24-hour curve for each patient), as well as mean maximum and minimum IOP readings were analysed by a paired *t*-test within an ANOVA. The number of patients who suffered individual adverse events between treatment groups was evaluated by a McNemar test (Siegel 1956).

Results

Patients

A total of 34 open-angle glaucoma patients (23 with primary open-angle glaucoma and 11 with exfoliative glaucoma) were included in this study. Their average age was 64.9 ± 10.6 years. Seventeen patients (50%) were male and 17 (50%) were female. All were of Greek ethnic origin. Average corneal pachymetry was 552.6 ± 23.6 μm and average Snellen VA was 0.9 ± 0.2 (range 0.3–1.0). Average cup : disc ratio was 0.6 ± 0.1 (range 0.4–0.8) and average mean deviation was − 7.0 ± 4.5 dB (range − 1.0 dB to −19.7 dB). Two patients (6%) had been treated previously but were on no therapy at inclusion, seven (20%) were new to treatment and 25 (74%) had received and were using previous treatment for elevated pressure, with the most common being dorzolamide/timolol fixed combination (n = 10) and latanoprost/timolol fixed combination (n = 4). Thirty-two patients completed the study. Two patients were discontinued from study medication prior to the 24-hour IOP assessment while taking TTFC in the morning, one as a result of headaches and gastro-intestinal disturbance and one as a result of ocular intolerance.

Intraocular pressure

Mean IOP and pressure reductions are shown in Tables 1 and 2 and Fig. 1. Intraocular pressure was significantly reduced from baseline at each individual time-point and for the mean 24-hour pressure, for both morning and evening administration of TTFC ($p < 0.0001$).

When both treatments were compared directly, evening dosing demonstrated statistically significant lower absolute IOP levels for the 24-hour curve as well as for individual daytime time-points following a modified Bonferroni correction at 06.00, 10.00 and 14.00 hours ($p \leq 0.002$). No significant differences were observed at 22.00 and 02.00 hours, although morning dosing provided a slightly lower non-significant pressure difference ($p \geq 0.20$).

Table 2. Intraocular pressure reduction from baseline (mmHg ± standard deviation).

Time-points	Morning dosing	Evening dosing	p-value
10.00	9.8 ± 2.9	11.0 ± 3.0	0.002
14.00	8.7 ± 3.1	10.0 ± 3.4	0.0005
18.00	8.9 ± 3.2	9.8 ± 2.9	0.03
22.00	8.5 ± 3.3	8.1 ± 3.1	0.20
02.00	7.0 ± 2.3	6.7 ± 2.2	0.45
06.00	8.4 ± 2.9	10.2 ± 2.7	< 0.0001
24-hour mean	8.6 ± 2.1	9.3 ± 2.0	0.001

In addition, when the reductions in pressure from untreated baseline levels were compared between morning and evening dosing, there was a significantly greater difference with evening administration, in terms of both the 24-hour curve as well as individual daytime time-points at 06.00, 10.00 and 14.00 hours ($p \leq 0.002$).

Further, the mean 24-hour IOP fluctuation (highest minus lowest IOP reading within the 24-hour pressure curve for every patient) was significantly lower with evening dosing of TTFC (3.8 ± 1.6 mmHg) compared with morning dosing (5.1 ± 1.6 mmHg; $p = 0.0002$). Additionally, the mean peak (maximum) pressure was significantly lower with evening dosing ($p = 0.0003$). By contrast, there was no difference in minimum pressure between the groups ($p = 1.0$).

Adverse events

Adverse events are listed in Table 3. There was no difference between dosing regimens for frequency of any adverse event. The most common adverse event was conjunctival

Table 1. Absolute intraocular pressure (IOP) levels (mmHg ± standard deviation).

Time-points	Baseline IOP	IOP after morning dosing	IOP after evening dosing	p-value*
10.00	29.5 ± 3.2	19.7 ± 3.5	18.5 ± 3.4	0.002
14.00	28.3 ± 4.1	19.6 ± 3.9	18.3 ± 3.5	0.0005
18.00	28.1 ± 4.2	19.2 ± 4.0	18.3 ± 4.1	0.03
22.00	26.4 ± 4.5	17.9 ± 3.6	18.3 ± 3.6	0.20
02.00	25.3 ± 3.8	18.3 ± 3.9	18.6 ± 3.5	0.45
06.00	28.8 ± 4.3	20.4 ± 4.2	18.6 ± 3.5	< 0.0001
24-hour mean	27.7 ± 3.5	19.2 ± 3.5	18.4 ± 3.3	0.001
Maximum	31.1 ± 3.9	21.7 ± 3.9	20.4 ± 3.8	0.0003
Minimum	24.4 ± 3.0	16.6 ± 3.0	16.6 ± 3.1	1.0
Fluctuation	6.6 ± 2.6	5.1 ± 1.6	3.8 ± 1.6	0.0002

* Between treatments.

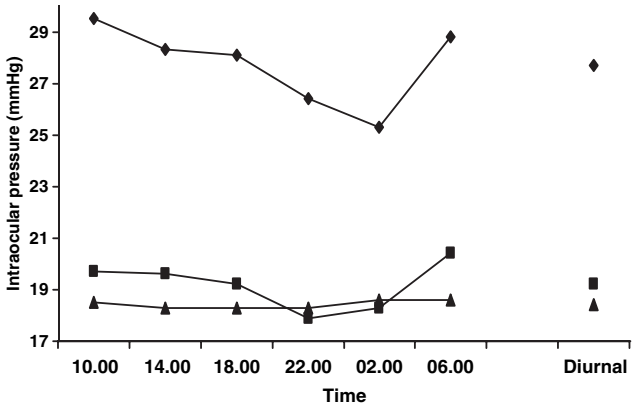

Fig. 1. Mean intraocular pressure at each time-point and mean 24-hour pressure for untreated baseline IOP (♦) and with morning (■) and evening (▲) administration of the travoprost/timolol fixed combination.

Table 3. Adverse events.

Event	Morning dosing	Evening dosing	p-value
Conjunctival hyperaemia	7	7	1.0
Foreign body sensation	4	0	0.15
Ocular discomfort	1	4	0.15
Stinging	2	3	0.64
Itchiness	3	2	0.64
Hypertrichosis	2	1	0.55
Headache	0	1	0.23
Watering	0	1	0.23
Dry eye sensation	0	1	0.23

hyperaemia, which was found in 21% (n = 7) of patients with both morning dosing and evening dosing (p = 1.0). In all, 19 adverse events were noted for morning dosing and 20 for evening dosing.

Discussion

The purpose of this study was to evaluate the quality of 24-hour IOP control between morning and evening administrations of TTFC in open-angle glaucoma patients.

Several previous studies have indicated differences in daytime control of IOP according to whether latanoprost is dosed in the morning or evening (Konstas et al. 1999; Konstas et al. 2000). Although both dosing regimens are effective, Alm & Stjernschantz (1995) showed daytime pressure to be 0.7–1.5 mmHg lower when latanoprost was dosed in the evening compared with in the morning. Further, Konstas et al. (1999) showed that evening dosing of latanoprost resulted in lower daytime IOP (17.9–18.6 mmHg) than morning dosing (18.7–21.6 mmHg). Konstas et al. (2002) also demonstrated that when latanoprost was given with timolol, but in separate bottles, evening dosing resulted in lower daytime pressure (16.4 ± 18.2 mmHg) compared with morning dosing (17.3 ± 19.0 mmHg).

Travoprost (Travatan™, Alcon, Inc.) is a newer prostaglandin analogue that has demonstrated similar to slightly improved efficacy in the afternoon, relative to the morning, as latanoprost when dosed in the evening (Netland et al. 2001; Parrish et al. 2003; Orzalesi et al. 2006; Konstas et al. 2007). Konstas et al. (2006) recently showed that patients dosed with travoprost in the evening demonstrated statistically significant lower pressures at 10.00 hours compared with those dosed in the morning (17.7 ± 2.1 mmHg versus 19.1 ± 2.5 mmHg), as well as less fluctuation in pressure over 24 hours (3.2 mmHg versus 4.0 mmHg). In addition, evening dosing resulted in a trend towards lower pressures at 06.00 and 14.00 hours.

Denis et al. (2006) recently evaluated morning versus evening dosing of TTFC in a parallel, 6-week study and found no daytime difference with morning (16.5–16.7 mmHg) versus evening (16.1–17.2 mmHg) dosing. Little further information is available regarding the comparative efficacy of morning and evening administrations of TTFC.

This study showed that both morning and evening dosing of TTFC provided a statistically significant reduction from untreated baseline IOP for each time-point and for the 24-hour pressure curve. However, when both treatment regimens were compared, evening dosing demonstrated a lower absolute IOP, and a significantly greater reduction from untreated baseline IOP, for both the 24-hour pressure curve and individual daytime time-points at 06.00, 10.00 and 14.00 hours. By contrast, morning dosing provided a slightly lower, non-significant reduction in pressure at 22.00 and 02.00 hours.

These results are consistent with those of past studies by Konstas et al. (1999, 2002, 2006), which have indicated that prostaglandins (latanoprost, travoprost or latanoprost added to timolol) administered in the evening consistently provide lower daytime pressures compared with those administered in the morning. This may reflect the fact that prostaglandins demonstrate their peak efficacy 12–24 hours after dosing. Consequently, a prostaglandin administered in the evening generally provides its maximum pharmacological effect, and its best ocular hypertensive control, in the daytime (Konstas et al. 1999, 2002, 2006). This fact is important clinically because most studies indicate that IOP is usually higher in the daytime (Shields 1987).

Further, this study also demonstrated a narrower fluctuation in 24-hour pressure control, and a lower maximum (peak) pressure, with evening dosing compared with morning dosing of the fixed combination. Previous 24-hour studies by Konstas et al. (1999, 2002, 2006) consistently show that evening dosing with a prostaglandin, with or without timolol, provides a lower 24-hour fluctuation in pressure than morning dosing. Reduced IOP fluctuation may be important in helping to prevent long-term progressive visual field loss (Asrani et al. 2000; Advanced Glaucoma Intervention Study Investigators 2002; Stewart et al. 2006). Therefore, the reduced 24-hour fluctuation offered by the evening dosing of this fixed combination could be advantageous in reducing longterm fluctuations in pressure and consequently improve prognosis in glaucoma. As prostaglandins demonstrate peak efficacy 12–24 hours after dosing, applying this peak efficacy to the time period during the 24-hours when pressure is generally higher may allow

for lower peak pressures throughout the day and, consequently, less fluctuation.

In addition, the strength of the daytime effect of evening dosing of travoprost may have been minimized by the once daily instillation of timolol at the same time. Timolol has a peak effect approximately 2 hours after dosing and theoretically could demonstrate less 24-hour fluctuation when dosed in the morning, although this has never been shown.

However, the comparative fluctuation advantage for travoprost administered in the evening may not have been minimized by timolol in this trial. Our prior work with travoprost alone in a similarly designed study showed a 0.8-mmHg advantage in 24-hour fluctuation for evening dosing. By contrast, a 1.3-mmHg advantage for evening dosing was observed in the current trial with timolol added to travoprost. However, these trials are not exactly comparable because exfoliative patients were included in the current study and may have exaggerated the fluctuation differences between morning and evening dosing of the fixed combination (Konstas et al. 2006). More research is needed to elucidate 24-hour fluctuations with TTFC.

Our results do not agree with those of Denis et al. (2006), who found no significant difference in daytime pressures between morning and evening dosing. However, fluctuations were not evaluated specifically in their study. The reason for the different findings between the studies is not apparent from our data. Our study differed in that it used a crossover, rather than a parallel, design, included night-time and evening time-points, and was not designed to show equivalence. Our design allowed for an 80% power to exclude a 1.5-mmHg difference between groups, (assuming a standard deviation of 3.5 mmHg, which is typical of regulatory requirements) versus 2.5 mmHg in the study by Denis et al. (2006). This difference in power indicates it was easier to find a statistically significant difference in our study but does not explain the variances in daytime pressure findings between evening and morning dosing between studies. One partial explanation may be that baseline pressures were higher in the current study, which might have allowed it a greater opportunity to show a difference than the study by Denis et al. (2006).

The clinical importance of these findings indicates that in routine practice TTFC can provide an effective reduction in pressure, whether it is administered in the morning or the evening. However, for the majority of open-angle glaucoma patients who demonstrate higher pressures in the morning and during the daytime, evening administration may provide a better quality of 24-hour pressure control (Barnebey et al. 2005; Hughes et al. 2005; Schuman et al. 2005).

Relatively few adverse events were noted with either dosing regimen. Conjunctival hyperaemia was the most common side-effect observed in a minority of patients with essentially the same incidence for morning and evening administration (21%). Both dosing regimens were well tolerated throughout the study.

Patients performed nasolacrimal occlusion following installation of their eyedrops for this study. The fixed combination medicines currently available for the treatment of glaucoma all contain timolol, which is a beta-blocker. This class of medicine has been linked to pulmonary and cardiovascular side-effects leading, in rare cases, to death. Nasolacrimal occlusion may help prevent systemic absorption of the beta-blocker and potentially could help reduce systemic side-effects. Accordingly, no systemic side-effects related to beta-blocker usage were observed in this study. However, patients with a history of pulmonary or cardiovascular disease which might have been worsened with beta-blocker treatment were excluded from this study. Importantly, patients with reactive airway disease, second- or third-degree cardiac block and some patients with heart failure should not be treated with beta-blockers (Stewart & Garrison 1998).

This study suggests that both morning and evening dosing of TTFC provide effective 24-hour IOP reduction. However, evening dosing demonstrates a narrower range of 24-hour fluctuation and peak pressures as well as a lower 24-hour pressure curve and lower daytime pressures.

This study did not evaluate the efficacy and safety of TTFC versus other available fixed combinations for the treatment of glaucoma, such as fixed combinations with latanoprost, bimatoprost, dorzolamide and brimonidine adjunctive to timolol. This study also did not evaluate longterm visual outcomes of morning versus evening dosing of TTFC therapy. Further research is required generally to determine the most efficacious, safe and cost-efficient step-wise therapy for glaucoma.

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