Effect on the 24-hour diurnal curve of intraocular pressure of a fixed ratio combination of timolol 0.5% and pilocarpine 2% in patients with COAG not controlled on timolol 0.5%

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SUMMARY Eight patients with chronic open-angle glaucoma who had an intraocular pressure >24 mm Hg at some time during the day while taking timolol 0.5% twice daily were given the fixed ratio combination of timolol 0.5% with pilocarpine 2% (TP2) twice daily. By comparing full 24-hour diurnal curves on timolol with those on TP2 it was possible to show that all patients except one (at a single timepoint) had an IOP <22 mm Hg when changed to TP2. The mean IOPs, the area under the diurnal pressure curve, and the diurnal variation were all significantly lower on TP2 twice daily than on timolol 0.5% twice daily.

It has been reported that up to 30% of patients with chronic open-angle glaucoma (COAG) will not experience fully adequate reduction of intraocular pressure (IOP) on timolol 0.5% twice daily. The commonest and most rational additional agent used with timolol is pilocarpine. Pilocarpine is usually prescribed three or four times a day because its duration of action is only 6-8 hours. In a previous study it was shown that, whereas timolol 0.5% plus pilocarpine 2% or 4% twice daily both improved IOP control significantly in patients not controlled (<22 mm Hg) on timolol 0.5% twice daily, increasing the frequency of the pilocarpine from twice to four times a day had no beneficial effect on the level of control or on its smoothness. Thus it was shown that it was possible to combine timolol with pilocarpine in a twice daily regimen. The present study was undertaken to evaluate the efficacy of a fixed ratio combination of timolol and pilocarpine twice daily in patients with COAG whose IOP was not controlled by timolol 0.5% twice daily. In particular we wished to compare the diurnal variation on the two regimens, since this would best confirm or negate the value of this fixed combination in glaucoma management.

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Materials and methods

The timolol and pilocarpine combination contained timolol 0.5% and pilocarpine 2% (TP2) at pH 6-8 produced by mixing a ready mixed timolol and pilocarpine solution with a buffering solution to raise the pH of the mixture just prior to being issued to the patients. It is known that formulated in this way the TP2 mixture is stable for four weeks.

Patients with primary open-angle glaucoma (POAG) were selected who had been on timolol 0.5% (T) alone twice daily for at least two weeks and had an IOP in both eyes greater than 24 mm Hg at one point during a 24-hour period. Males or females were to be over the age of 18 years, with no evidence of acute ocular infection or inflammation and no history of ocular surgery or trauma. Other exclusions were current or recent contact lens wear within one month, a history of embedded corneal foreign body within one month, active herpetic keratitis or active corneal ulcer within three months, any corneal abnormality preventing reliable applanation tonometry, diseases known to affect retinal function acutely or to produce acute visual field loss, and abnormalities of the peripheral retina which might lead to retinal detachment while on a miotic.

Since there is no way of masking an ophthalmolo-
gist to the miosis caused by pilocarpine, this was an
open study requiring eight patients to complete the
protocol. All patients consented to participate after
the objectives and procedures of the study had been
explained fully to them and a full ophthalmological
examination carried out. On the day before the TP2
was to be given (day −1) all patients had 24-hour
diurnal IOP measurements while still continuing
to receive T twice daily in both eyes. The IOP was
measured on day −1 at 0600, 1000, 1400, 1800, 2400,
and 0600 the next morning (the morning of study
day 1). Only patients with an IOP greater than 24 mm
Hg for at least one timepoint entered the treatment
period. All intraocular pressures were measured
during the study by the same ophthalmologist (GMM) using the same applanation tonometer.
Patients were admitted to hospital for the diurnal
curve recordings.

On day 1 patients had one drop of TP2 instilled in
both eyes at 0615 (after the 0600 IOP readings). They
were given a bottle of TP2 with instructions to
administer one drop into each eye at 0615 and 1815
daily until they returned in two weeks. The timolol
0·5% was discontinued.

On day 14 the patients had an ophthalmological
examination on arrival at 0600; the diurnal curve of
IOP was measured at the same times as on day −1.
TP2 was instilled at 0615 and finally at 1815 on day 14.

Adverse experiences were sought throughout the
study. The investigator was asked to evaluate their
severity and their relationship to the test medication.
Any patient reporting photopsias or an increase in
floaters during the study was to be taken off TP2,
excluded from further participation in this study,
fully examined, and assigned to appropriate clinical
follow-up.

All analyses were performed using the patient's
worst eye defined as the eye with the greater IOP on
day 1 at 0600 (the last diurnal curve measurement
before TP2 was administered). If the IOP was the
same in both eyes, the right eye was chosen. To
evaluate efficacy the baseline (T) diurnal curve was
compared with that on TP2. Comparisons were made
by comparing the area under the diurnal curves, by
timepoint analysis of differences in IOP, by the
smoothness of the diurnal curves (<5 mm Hg range
being used as a reference point).

POWER AND SAMPLE SIZE
From a previous study it was calculated that, with
a standard deviation for IOP change of 3·0 mm Hg,
eight patients would be sufficient to detect a 3·5 mm
Hg difference in IOP between T and TP2 with 80% power (α=0·05, two tailed). In fact in this study the
actual pooled standard deviation of the change from
baseline of 2·2 mm Hg gave 80% power to detect a
change of 2·5 mm Hg (α=0·05, two tailed). Similarly
it was calculated that if the range of patients’ IOPs
over a 24-hour period had a standard deviation of 2·2
mm Hg, eight patients would suffice to detect a 2·5
mm Hg difference from the hypothesised range of 5
mm Hg with 80% power (α=0·5, two tailed). The
actual deviation found in the study was only 0·8 mm
Hg, which gave the study 80% power to detect a 0·9
mm Hg difference from the 5 mm Hg range.

Results

Eight patients gave informed consent, entered, and
completed the study. There were six males and two
females with a median age of 60·5 years, range 51 to
70 years. All patients had both eyes treated in the
study. No patients withdrew or were removed from
the study. There were no protocol violators and no
missing data. The mean of the IOPs on presentation—(that is, prior to timolol therapy)—was 27·87
mm Hg (range 18·26 mm Hg) for the right eyes and
30·25 mm Hg (range 24·36 mm Hg) for the left eyes.
Five patients had an arcuate scotoma in at least one
eye. The remainder had enlargement of the blind
spot or general depression of light threshold. All eyes
had one or more of the above visual field defects as
measured on the Octopus 2000, program 33.

Analyses were performed as described above. The
analysis of IOPs at each timepoint for both
reatments addresses the efficacy 12 hours after the
previous dose both at night and in the morning.
Examinations on day −1 (the last day on timolol
0·5% twice daily as single therapy) at 1800 and on day
1 at 0600 (12 hours after the last dose of timolol 0·5%
and immediately prior to the first dose of TP2) measured the 12-hour efficacy of T. The 12-hour
efficacy of TP2 was measured on day 14 at 1800 and
day 15 at 0600.

The data for all patients are shown in Table 1. The
mean IOPs at each timepoint are summarised in
Table 2 and shown graphically in Fig. 1. The difference
between the mean IOP on T and that on TP2 is
significant (p≤0·01) at all timepoints. This is reflected
further by the means of the areas under the diurnal
curves. The mean area under the curves for the worst
eye was 575·4 (SD 22·1) mm Hg/h on T and 428·3 (SD
47·1) mm Hg/h on TP2. The mean difference was
significant (p≤0·01).

Smoothness of diurnal control was indicated by the
diurnal variation. Only one patient (no. 6) did not
have a smoother curve while on TP2 than on T,
having a range of 3 mm Hg for each (Table 1). The
mean reduction in diurnal variation for the eight
patients’ worst eyes was significant (p≤0·05): the
mean diurnal variation for T was 4·9 mm Hg and for
TP2 was 1·9 mm Hg.
Fixed ratio combination of timolol and pilocarpine

Table 1  Worse eye data (IOP mm Hg)

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*Area under curve. †T0-5=timolol 0.5%.

No adverse experiences were reported, but five patients reported a total of 10 ocular symptoms when receiving TP2. There were three instances of headache, three of ‘night blindness’ (difficulty in seeing in reduced light due to miosis), two of blurred vision, and one each of phanopsias and eye irritation. Except for one report of ‘night blindness’ all the ocular symptoms occurred on the first day of treatment with TP2 and had disappeared by day 14. One case of ‘night blindness’ was not reported on day 1 but was

Table 2  IOP means (mm Hg): worse eye

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*Significant change from base line, p ≤0.01. T0-5=timolol 0.5%.


The objective of this study was to show that a fixed combination of timolol and pilocarpine used twice daily would allow better and smoother control of IOP than timolol twice daily in those patients not responding adequately to timolol alone. The effects of the drugs were assessed by examining the extent of IOP lowering and the duration of action, as shown by the smoothness of the diurnal curves.

There is a potential for bias in this study, since the investigator would be clearly aware that the patients were on the test medication TP2. There is no way of disguising a miosis to an ophthalmologist and thus no satisfactory way of controlling this study without introducing a third active agent, for example pilocarpine alone, which because of the time required for timolol washout would be to an undetermined extent additive and thus a rather confounded control agent. A comparison of activity of TP2 with pilocarpine has been reported elsewhere.1

From comparison with pretreatment IOPs all patients except patient 4 in the right eye had shown some reduction in IOP when treated with timolol 0.5% twice daily.

Comparison of the diurnal curves showed significant lowering of IOP at all timepoints when patients received TP2 in comparison with the same timepoints when patients received T. This held true when we examined the mean IOP of the worst eye and under the diurnal data curve. When all six timepoints for individual patients were examined, reductions in IOP at every timepoint were seen after patients had been on TP2 for 14 days; two patients had IOP reductions of as much as 11 mm Hg.

The value of this drug combination lies not in just the extent of the IOP lowering but also in the duration of the IOP lowering. It is important in the management of glaucoma that the IOP should be controlled (<22 mm Hg) throughout a 24-hour period. For many patients the pressure tends to be highest in the morning.6 Because TP2 was given twice daily (every 12 hours), the extent to which the IOP was controlled could be determined by looking at the measurements taken at 0600, 1800, and 0600 the following day. These measurements were taken immediately before patients received their eye drops. Only one patient had the IOP controlled at two timepoints while receiving T; however, every patient except one at one timepoint had the IOP controlled at all timepoints after receiving TP2. For all patients there was significantly greater control of IOP after they received TP2 than with T.

The smoothness of the diurnal curve was assessed by examining the range of IOPs along each curve. A smaller range of IOPs indicated a smoother or flatter diurnal curve. Patients receiving TP2 had a smoother curve than when they received T. Of importance in assessing the efficacy of a drug for glaucoma therapy is the range of IOPs obtained between doses. TP2 was significantly better than T in this regard as shown by the smaller range of IOPs over the diurnal curve. The fluctuation or 'spiking' of IOP was smaller with TP2 than with T.

The patients tolerated the combination well. No adverse symptoms or ocular signs were noted. Ten ocular symptoms were reported; all were mild and, except for one case of ‘night blindness’ had disappeared by day 14. ‘Night blindness’ is a descriptive term describing reduced visual function in poor illumination. In this study it is probable that, since all the patients were asymptomatic before receiving TP2, the symptoms experienced were due to the introduction of pilocarpine into their regimen. The symptoms reported have all been reported on pilocarpine.7

The results of this study confirm findings in a previous study conducted by the same investigator8 when 24 patients who had been on timolol received concomitant therapy of timolol 0.5% and pilocarpine 2% or if necessary pilocarpine 4%. Pilocarpine (2% or 4%) was administered twice or four times a day concomitantly with timolol 0.5% twice daily. In patients who received concomitant therapy the IOP was reduced significantly in comparison with timolol 0.5% alone. The patients receiving concomitant therapy also showed a smoother diurnal curve than when they received timolol 0.5%. In addition the study showed that there was no statistical difference between twice a day and four times a day dosing with...
Fixed ratio combination of timolol and pilocarpine

pilocarpine when used concomitantly with timolol.

In conducting the present study we hoped to show that a similar quality of IOP control could be obtained using a fixed combination of TP2 to that shown in the previous study using concomitant timolol pilocarpine. To make real comparisons a further study using combination and concomitant administration in a randomly allocated, double-masked design would be required. The present study does, however, confirm the smooth nature of IOP control on TP2 twice daily in patients whose IOP was inadequately controlled on timolol 0.5% twice daily.

Pilocarpine is usually administered every six hours; even if it is administered concomitantly only twice a day with timolol 0.5%, the patient is still required to administer four drops, that is, two of timolol and two of pilocarpine. With TP2 the patient administers only one drop twice a day. Since compliance with a pilocarpine regimen has been shown to be poor, with patients administering a mean of only 76% of the prescribed doses and 30% of patients compressing their doses into 12 hours of the day; it is likely that the use of a timolol pilocarpine combination twice daily will achieve better control and improved compliance in patients with glaucoma.

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