*British Journal of Ophthalmology*, 1989, **73**, 827–831

# 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%

G M MACLURE, R VOGEL, A STURM, AND B BINKOWITZ

*From North Riding Infirmary, Middlesbrough, Cleveland*

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% ($TP_2$) twice daily. By comparing full 24-hour diurnal curves on timolol with those on $TP_2$ it was possible to show that all patients except one (at a single timepoint) had an IOP <22 mm Hg when changed to $TP_2$. The mean IOPs, the area under the diurnal pressure curve, and the diurnal variation were all significantly lower on $TP_2$ twice daily than on timolol 0·5% twice daily.

It has been reported[1-3] 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[4] 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.

Correspondence to Mr G M Maclure, North Riding Infirmary, Newport Road, Middlesbrough, Cleveland TS1 5JE

## Materials and methods

The timolol and pilocarpine combination contained timolol 0·5% and pilocarpine 2% ($TP_2$) 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 $TP_2$ 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 $TP_2$ 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 throughout the study were taken 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 $TP_2$ instilled in both eyes at 0615 (after the 0600 IOP readings). They were given a bottle of $TP_2$ 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. $TP_2$ 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 $TP_2$, 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 $TP_2$ 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 $TP_2$. 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[4] 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 $TP_2$ with 80% power ($\alpha$=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 ($\alpha$=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 ($\alpha$=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 treatments 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 $TP_2$) measured the 12-hour efficacy of T. the 12-hour efficacy of $TP_2$ 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 $TP_2$ is significant ($p \leq 0{\cdot}01$) 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 $TP_2$. The mean difference was significant ($p \leq 0{\cdot}01$).

Smoothness of diurnal control was indicated by the diurnal variation. Only one patient (no. 6) did not have a smoother curve while on $TP_2$ 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 ($p \leq 0{\cdot}05$): the mean diurnal variation for T was 4·9 mm Hg and for $TP_2$ was 1·9 mm Hg.

Table 1 *Worse eye data (IOP mm Hg)*

| *No.* | *Treatment Group* | *0600* | *1000* | *1400* | *1800* | *2400* | *0600* | *Number of Controlled Timepoints (IOP <22 mm Hg)* | *AUC** | *Range of IOP (mm Hg)* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $TP_2$ | 20 | 18 | 18 | 17 | 18 | 20 | 6 | 437 | 3 |
| | T 0·5† | 25 | 22 | 21 | 21 | 22 | 25 | 2 | 534 | 4 |
| | Change | − 5 | − 4 | − 3 | − 4 | − 4 | − 5 | | | |
| 2 | $TP_2$ | 22 | 21 | 20 | 21 | 21 | 21 | 5 | 502 | 2 |
| | T 0·5 | 26 | 24 | 22 | 23 | 29 | 38 | 0 | 609 | 7 |
| | Change | − 4 | − 3 | − 2 | − 2 | − 8 | − 7 | | | |
| 3 | $TP_2$ | 20 | 18 | 18 | 18 | 20 | 19 | 6 | 451 | 2 |
| | T 0·5 | 28 | 25 | 23 | 24 | 23 | 27 | 0 | 587 | 5 |
| | Change | − 8 | − 7 | − 5 | − 6 | − 3 | − 8 | | | |
| 4 | $TP_2$ | 20 | 18 | 19 | 19 | 20 | 20 | 6 | 463 | 2 |
| | T 0·5 | 26 | 24 | 22 | 22 | 26 | 27 | 0 | 583 | 5 |
| | Change | − 6 | − 6 | − 3 | − 3 | − 6 | − 7 | | | |
| 5 | $TP_2$ | 15 | 16 | 15 | 16 | 16 | 16 | 6 | 378 | 1 |
| | T 0·5 | 26 | 22 | 22 | 22 | 25 | 26 | 0 | 566 | 4 |
| | Change | −11 | − 6 | − 7 | − 6 | − 9 | −10 | | | |
| 6 | $TP_2$ | 17 | 15 | 14 | 16 | 17 | 17 | 6 | 383 | 3 |
| | T 0·5 | 25 | 23 | 22 | 25 | 25 | 25 | 0 | 580 | 3 |
| | Change | − 8 | − 8 | − 8 | − 9 | − 8 | − 8 | | | |
| 7 | $TP_2$ | 18 | 18 | 18 | 19 | 19 | 18 | 6 | 443 | 1 |
| | T 0·5 | 28 | 25 | 23 | 22 | 24 | 27 | 0 | 583 | 6 |
| | Change | −10 | − 7 | − 5 | − 3 | − 5 | − 9 | | | |
| 8 | $TP_2$ | 16 | 15 | 16 | 15 | 15 | 16 | 6 | 369 | 1 |
| | T 0·5 | 26 | 23 | 22 | 22 | 23 | 27 | 0 | 561 | 5 |
| | Change | −10 | − 8 | − 6 | − 7 | − 8 | −11 | | | |

*Area under curve. †T 0·5 = timolol 0·5%.

No adverse experiences were reported, but five patients reported a total of 10 ocular symptoms when receiving $TP_2$. 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 photopsias and eye irritation. Except for one report of 'night blindness' all the ocular symptoms occurred on the first day of treatment with $TP_2$ 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*

| *Hour* | *Treatment Group* | *n* | *Mean* | *SD* | *Minimum* | *Median* | *Maximum* |
|---|---|---|---|---|---|---|---|
| 0600 | $TP_2$ | 8 | 18·5 | 2·4 | 15 | 19·0 | 22 |
| | T 0·5 | 8 | 26·3 | 1·2 | 25 | 26·0 | 28 |
| | Change | 8 | − 7·8* | 2·5 | −11 | − 8·0 | − 4 |
| 1000 | $TP_2$ | 8 | 17·4 | 2·0 | 15 | 18·0 | 21 |
| | T 0·5 | 8 | 23·5 | 1·2 | 22 | 23·5 | 25 |
| | Change | 8 | − 6·1* | 1·8 | − 8 | − 6·5 | − 3 |
| 1400 | $TP_2$ | 8 | 17·3 | 2·1 | 14 | 18·0 | 20 |
| | T 0·5 | 8 | 22·1 | 0·6 | 21 | 22·0 | 23 |
| | Change | 8 | − 4·9* | 2·1 | − 8 | − 5·0 | − 2 |
| 1800 | $TP_2$ | 8 | 17·6 | 2·0 | 15 | 17·5 | 21 |
| | T 0·5 | 8 | 22·6 | 1·3 | 21 | 22·0 | 25 |
| | Change | 8 | − 5·0* | 2·4 | − 9 | − 5·0 | − 2 |
| 2400 | $TP_2$ | 8 | 18·3 | 2·1 | 15 | 18·5 | 21 |
| | T 0·5 | 8 | 24·6 | 2·2 | 22 | 24·5 | 29 |
| | Change | 8 | − 6·4* | 2·2 | − 9 | − 7·0 | − 3 |
| 0600 | $TP_2$ | 8 | 18·4 | 1·9 | 16 | 18·5 | 21 |
| | T 0·5 | 8 | 26·5 | 1·1 | 25 | 27·0 | 28 |
| | Change | 8 | − 8·1* | 1·9 | −11 | − 8·0 | − 5 |

*Significant change from base line, $p \leq 0{\cdot}01$. T 0·5 = timolol 0·5%.

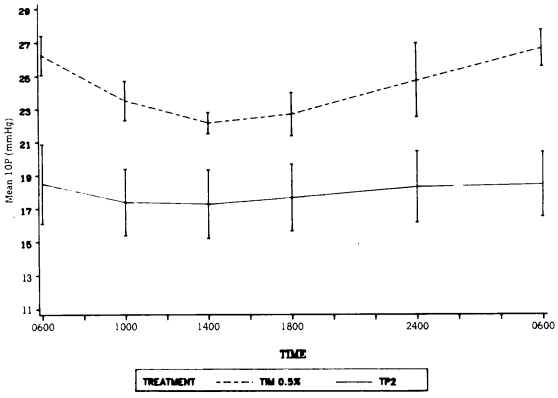


Fig. 1 *Plot of baseline (timolol) and $TP_2$ diurnal curves. Means (with SD) for all patients: worse eye IOP (mm Hg).*

reported on day 14. All of the ocular symptoms were mild in severity. There were no changes in visual acuity of either eye between day −1 (on T) and day 14 (on $TP_2$).

## Discussion

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 $TP_2$. 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 $TP_2$ with pilocarpine has been reported elsewhere.[5]

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 $TP_2$ 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 $TP_2$ 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 $TP_2$ 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 $TP_2$. For all patients there was significantly greater control of IOP after they received $TP_2$ 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 $TP_2$ 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 intraocular pressures obtained between doses. $TP_2$ 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 $TP_2$ 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 $TP_2$ 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 investigator[4] 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

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 $TP_2$ 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 $TP_2$ 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 $TP_2$ 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[8] it is likely that the use of a timolol pilocarpine combination twice daily will achieve better control and improved compliance in patients with glaucoma.

This study was supported by a grant from Merck Sharp and Dohme Research Labs (MSDRL). Mr G M Maclure has no commercial interest in Merck Sharp and Dohme or in the material discussed in this paper. Dr R Vogel, Ms A Sturm, and Mr B Binkowitz are employees of MSDRL.

**References**

1 Yalon M, Urinowsley E, Rothlcoff L, Treister G, Blumenthal M. Frequency of timolol administration. *Am J Ophthalmol* 1981; **92:** 526-9.
2 Rosenbaum LJ. A controlled clinical evaluation of timolol in the treatment of patients with elevated intraocular pressure. *Glaucoma* 1979; **1:** 21-4.
3 Soll DB. Evaluation of timolol in chronic open-angle glaucoma. *Arch Ophthalmol* 1980; **98:** 2178-81.
4 Maclure GM, Vogel R. The effect on diurnal control of IOP of coadministration of pilocarpine and timolol. *New Trends in Ophthalmology* 1987; **2:** 79-86.
5 Airaksinen PJ, Stenborg T, Takki K, Klemmetti A, Kontlcamen M, Oskala P. A double masked study of timolol and pilocarpine combined. *Am J Ophthalmol* 1987; **104:** 587-9.
6 Drance SM. The significance of diurnal variations in normal and glaucomatons eyes. *Arch Ophthalmol* 1960; **64:** 494.
7 Grant W. *Toxicology of the eye (Drugs Chemicals Plants and Venoms)*. Springfield: Thomas, 1974.
8 Kass M, Meltzer D, Gordon M, Cooper D, Goldberg J. Compliance with topical pilocarpine treatment. *Am J Ophthalmol* 1986; **101:** 515-23.

*Accepted for publication 15 May 1989.*