A blind randomised cross-over trial comparing metipranolol 0.3% with timolol 0.25% in open-angle glaucoma: a pilot study

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SUMMARY A blind randomised cross-over study was conducted on 10 patients (20 eyes) to compare the effect in patients with open-angle glaucoma of metipranolol 0.3% with that of timolol 0.25% on intraocular pressure following one month's topical instillation with each preparation alone. There was no statistically significant difference in intraocular pressure reduction between these two preparations, and the ocular tolerance of both was good. There was no significant difference in the blood pressure, pulse, or pupil diameters of patients receiving either preparation.

Both timolol and metipranolol are non-selective beta-adrenergic blocking agents effective in lowering the intraocular pressure in both normal and glaucomatous eyes.¹⁻⁶ They show minimal intrinsic sympathomimetic activity and membrane stabilising effect.^{7,8} In contrast to timolol, which has been intensively investigated, metipranolol is a relative newcomer to the field of ophthalmology and as yet is not freely available commercially. The present study was undertaken to compare the effect on intraocular pressure and systemic parameters (such as blood pressure and pulse) of these two compounds in the short term.

Patients and methods

Patients with characteristic discs and field changes of primary open-angle glaucoma, either controlled on single antiglaucoma therapy or presenting as new patients, were considered for inclusion. Patients with, or with a history of, cardiovascular disease or constrictive airways disease (whether receiving systemic therapy or not) were excluded from consideration. Patients with existing corneal disease or corneal scarring or a previous history of ocular surgery were also excluded from the study.

Ten patients (20 eyes) were included in the trial (six female, four male, mean age 71.8 years, range 53-84 years). Following a five-day wash-out period for those individuals already using antiglaucoma

topical therapy (a five-day wash-out period was considered to be sufficient, as those patients who were already receiving topical antiglaucoma therapy were receiving either adrenaline or pilocarpine) each patient had a two-day intraocular pressure curve measured (at times 0, 3, 7, 11, 24, 27, 31, and 35 hours, where time 0 was 0900 h on day 1 of the curve) by Goldmann applanation with the Haag-Streit slit-lamp while an inpatient in hospital and receiving no antiglaucoma medication. Pulse and blood pressure (after three minutes sitting) and pupil diameters were measured at 0900 h on the second day of each phasing.

Each patient was then randomly allocated with timolol 0.25% or metipranolol 0.3% to be instilled topically twice daily into each eye. Each patient was readmitted to hospital after four weeks therapy, and a further two-day phasing curve with blood pressure, pulse, and pupil diameter was measured as before.

The second preparation was then allocated to each patient (without a second wash-out period) and again instilled topically twice daily for a further four weeks, after which time the patients were readmitted for a final two-day phasing curve and repeat measurements of blood pressure, pulse, and pupil diameter.

The code, which was held in the Pharmacy Department, was not broken until the trial was completed. Any subjective side effects were noted. Metipranolol was provided as the drop Beta-Ophtiole (metipranolol hydrochloride pH 5.5 with benzalkonium chloride and PVP tear film stabiliser

Table 1 Pretreatment and post-treatment mean intraocular pressures for two patients showing poor or no response to therapy. Intraocular pressure is the mean of data during two-day phasing period ($\pm$ SD)

Patient number	Eye	Intraocular pressure (mmHg)		
		Pretreatment	Timolol 0.25%	Metipranolol 0.3%
5	Right	24.3 $\pm$ 1.98	28.5 $\pm$ 2.67	24.8 $\pm$ 2.75
	Left	26.0 $\pm$ 1.41	27.5 $\pm$ 4.38	25.9 $\pm$ 2.90
7	Right	22.9 $\pm$ 4.02	21.3 $\pm$ 2.87	21.1 $\pm$ 2.70
	Left	28.3 $\pm$ 3.84	25.0 $\pm$ 3.89	23.5 $\pm$ 3.51

Table 2 Intraocular pressure at pretreatment and after four weeks' therapy with timolol 0.25% or metipranolol 0.3%. Mean $\pm$ SEM (n=20)

Time (h)	Intraocular pressure (mmHg)		
	Pretreatment	Timolol 0.25%	Metipranolol 0.3%
0	25.7 $\pm$ 0.7	22.6 $\pm$ 1.0	21.7 $\pm$ 1.0
3	24.7 $\pm$ 0.8	22.4 $\pm$ 0.9	21.6 $\pm$ 0.6
7	25.1 $\pm$ 1.0	22.2 $\pm$ 0.8	20.4 $\pm$ 0.4
11	23.8 $\pm$ 1.1	21.4 $\pm$ 1.1	20.8 $\pm$ 0.7
24	25.9 $\pm$ 0.9	20.7 $\pm$ 0.7	20.9 $\pm$ 0.5
27	23.6 $\pm$ 0.6	20.8 $\pm$ 0.5	20.3 $\pm$ 0.4
31	22.4 $\pm$ 0.8	21.0 $\pm$ 0.8	20.1 $\pm$ 0.6
35	23.5 $\pm$ 1.1	20.7 $\pm$ 0.8	19.5 $\pm$ 0.9

with 170 μ g of metipranolol in one drop of 0.3% solution).

Results

All patients completed the study. Two patients complained of a slight and short-lasting burning sensation following topical instillation of metipranolol. There was a poor or no lowering of

Table 3 Mean intraocular pressure ($\pm$ SEM) using the average of the recordings made during the two-day phasing period for each patient

Eye (n)	Intraocular pressure (mmHg)		
	Pretreatment	Timolol 0.25%	Metipranolol 0.3%
Right eye (10)	23.9 $\pm$ 1.0	21.3 $\pm$ 1.0	20.5 $\pm$ 0.7
Left eye (10)	24.8 $\pm$ 0.9	21.6 $\pm$ 0.9	20.9 $\pm$ 0.7
Both eyes (20)	23.34 $\pm$ 0.69	21.47 $\pm$ 0.66	20.65 $\pm$ 0.48

intraocular pressure with metipranolol and timolol in two patients (Table 1). However, good control of intraocular pressure was achieved with both preparations in the remaining eight patients (16 eyes).

Table 2 shows the intraocular pressures (both eyes taken together) at pretreatment and after four weeks' therapy with either timolol 0.25% or metipranolol 0.3% during the two-day phasing period. These results are expressed graphically in Fig. 1. Table 3 shows the mean intraocular pressure (by eye) after four weeks' treatment with timolol 0.25% or metipranolol 0.3%.

Table 4 shows the mean reduction in intraocular pressure (both eyes taken together) during the two-day phasing period after treatment with timolol 0.25% and metipranolol 0.3%. The overall reduction in intraocular pressure for right and left eyes after four weeks' treatment with either of the two topical preparations (the mean of the two-day phasing results being taken) is shown in Table 5. The paired *t* test showed no statistically significant difference between the intraocular pressure reduction between metipranolol 0.3% and timolol 0.25%.

The mean blood pressure, pulse, and pupil diameters at pretreatment and following each therapy period are shown in Table 6. There was no statistically significant difference (paired *t* test) in

Fig. 1 Intraocular pressure at pretreatment and after four weeks' therapy with either timolol 0.25% or metipranolol 0.3% during the two-day phasing period.

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Table 4 Reduction in intraocular pressure during two-day phasing after treatment with timolol 0.25% or metipranolol 0.3%. Mean $\pm$ SEM (n=20)

Time (h)	Change in intraocular pressure from pretreatment values (mmHg)	
	Timolol 0.25%	Metipranolol 0.3%
0	-3.1 $\pm$ 1.0	-4.0 $\pm$ 1.0
3	-2.3 $\pm$ 0.7	-3.1 $\pm$ 0.5
7	-2.9 $\pm$ 0.9	-4.7 $\pm$ 0.7
11	-2.4 $\pm$ 0.8	-3.0 $\pm$ 0.8
24	-5.4 $\pm$ 0.9	-5.0 $\pm$ 1.1
27	-2.8 $\pm$ 0.7	-3.3 $\pm$ 0.6
31	-1.4 $\pm$ 0.8	-2.3 $\pm$ 0.8
35	-2.8 $\pm$ 1.3	-4.0 $\pm$ 1.2

Table 5 The mean reduction in intraocular pressure by eye mmHg (with SEM) (the mean of the two-day phasing period being taken for each patient) and significance (by the paired t test)

	Timolol 0.25%	Metipranolol 0.3%	Significance
Right eye	2.7 (1.2)	3.4 (1.0)	NS
Left eye	3.1 (1.0)	4.0 (0.8)	NS

Table 6 The mean (with SD) blood pressure, pulse, and pupil diameter (both eyes being taken together) at pretreatment and following timolol 0.25% and metipranolol 0.3% therapy

	Pretreatment	Timolol 0.25	Metipranolol 0.3%
Systolic blood pressure, mmHg	147 (17.67)	142 (12.95)	151 (20.28)
Diastolic blood pressure, mmHg	84.5 (8.96)	78.5 (6.69)	81.1 (6.97)
Pulse, beats/S	86.4 (13.7)	76.4 (4.53)	82.3 (11.01)
Pupil diameter, mm	2.55 (0.44)	2.6 (0.52)	2.6 (0.48)

blood pressure, pulse, or pupil diameter between either metipranolol 0.3% or timolol 0.25% and pretreatment values.

Discussion

This short-term trial indicates that there is no significant difference in the intraocular pressure-lowering effect between timolol 0.25% and metipranolol 0.3%. Although there was an 11% reduction in intraocular pressure after four weeks' therapy with timolol 0.25% as compared with a 15% reduction in intraocular pressure after metipranolol 0.3%, this difference was not statistically significant. Many studies have shown a reduction in intraocular pressure with timolol and metipranolol eye drops to

be greater than that recorded in this study^{5,9,10} (an average reduction of about 25%). If one analyses the results from those eight patients showing a response to both metipranolol 0.3% and timolol 0.25%, the intraocular pressure reduction from pretreatment values approximates to that shown by the cited authors.^{5,9,10}

Although a reduction of pulse rate and blood pressure was recorded following therapy for four weeks with both these treatment regimens, it was not significantly different. However, the results from 10 patients may be insufficient to identify any systemic problems in the short term, and as this was a pilot study it was of insufficient duration to identify any systemic problems occurring in the long term. The mild burning sensation noticed after metipranolol 0.3% instillation in two patients (20%) has been recorded elsewhere and is likely to be due to the lower pH of metipranolol (5.5) than of timolol. Denffer¹⁰ recorded a burning sensation following topical instillation of metipranolol in 45% of patients, but this sensation was insufficient in intensity to warrant discontinuance of the drug in any patient.

This trial would suggest that metipranolol 0.3% is a well tolerated non-selective beta blocking agent which appears to be as effective as timolol 0.25% in the reduction of intraocular pressure following short-term administration. Further trials are in progress to assess its long-term effectiveness and patients' tolerance of it.

We express our gratitude to Mrs Margaret Hercules, of the Pharmacy Department at Manchester Royal Infirmary for her help in the randomisation and allocation of treatment schedules. We thank Dr Mann Pharma, of Berlin, for supplying metipranolol eye drops. We express our gratitude to Kath Shawley, of Smith and Nephew Research, for her help in statistical analysis.

References

- 1 Katz IM, Hubbard WA, Getson AJ, Gould AL. Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. *Invest Ophthalmol Visual Sci* 1976; **15**: 489-92.
- 2 Zimmerman TJ, Kaufman HE. Timolol: a beta-adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977; **95**: 601-4.
- 3 Ostbaum SA, Galin MA, Katz IM. Timolol: effect on intraocular pressure in chronic open-angle glaucoma. *Ann Ophthalmol* 1978; **10**: 1347-51.
- 4 Merte HJ, Mertz M, Stryz J. Augendruck unter Metipranolol-einwirkung. In: Kriegelstein GK, Leydhecker W, eds. *Medikamentöse Glaukomtherapie*. Munich: Bergmann, 1982: 189-93.
- 5 Bleckmann H, Pham Duy T, Grajewski O. Therapeutic efficiency of metipranolol eye drops 0.3% versus timolol eye drops 0.25%. A double blind cross-over study. In: Merte HJ, ed. *Metipranolol. Pharmacology of beta-blocking agents and use of metipranolol in ophthalmology*. Vienna: Springer, 1983: 106-120.

- 6 Dausch D, Brewitt H, Edelhoff R. Metipranolol eye drops: clinical suitability in the treatment of chronic open angle glaucoma. In: Merte HJ, ed. *Metipranolol. Pharmacology of beta-blocking agents and use of metipranolol in ophthalmology*. Vienna: Springer, 1983: 132–47.
- 7 Hall RA, Robson RD, Share NN. Timolol maleate: a new beta-adrenergic receptor blocking agent. *Arch Int Pharmacodyn Ther* 1975; **213**: 251–63.
- 8 Bartsch W, Sponer G, Strein K. Pharmacological spectrum of metipranolol and experience in clinical use. In: Merte HJ, ed. *Metipranolol. Pharmacology of beta-blocking agents and use of metipranolol in ophthalmology*. Vienna: Springer, 1983: 35–48.
- 9 Radius RL, Diamond GR, Pollak IP, Langham ME. Timolol: a new drug for management of chronic simple glaucoma. *Arch Ophthalmol* 1978; **96**: 1003–8.
- 10 Denffer H. Efficacy and tolerance of metipranolol. Results of multicentre long term study. In: Merte HJ, ed. *Metipranolol. Pharmacology of beta-blocking agents and use of metipranolol in ophthalmology*. Vienna: Springer, 1983: 121–5.

Accepted for publication 11 April 1985.