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. They show minimal intrinsic sympathomimetic activity and membrane stabilising effect. 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 slitlamp 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...
with 170 µg 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 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 the mean blood pressure, pulse, and pupil diameters at pretreatment and following each therapy 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 ± SEM (n = 20)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Timolol 0.25%</th>
<th>Metipranolol 0.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-3.1±1.0</td>
<td>-4.0±1.0</td>
</tr>
<tr>
<td>3</td>
<td>-3.2±0.7</td>
<td>-3.1±0.5</td>
</tr>
<tr>
<td>7</td>
<td>-2.9±0.9</td>
<td>-4.7±0.7</td>
</tr>
<tr>
<td>11</td>
<td>-2.4±0.8</td>
<td>-3.0±0.8</td>
</tr>
<tr>
<td>24</td>
<td>-5.4±0.9</td>
<td>-5.0±1.1</td>
</tr>
<tr>
<td>27</td>
<td>-2.8±0.7</td>
<td>-3.2±0.6</td>
</tr>
<tr>
<td>31</td>
<td>-1.4±0.8</td>
<td>-2.3±0.8</td>
</tr>
<tr>
<td>35</td>
<td>-2.8±1.3</td>
<td>-4.0±1.2</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th></th>
<th>Timolol 0.25%</th>
<th>Metipranolol 0.3%</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right eye</td>
<td>2.7(1.2)</td>
<td>3.4(1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Left eye</td>
<td>3.1(1.0)</td>
<td>4.0(0.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Timolol 0.25%</th>
<th>Metipranolol 0.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>147 (17-67)</td>
<td>142 (12-95)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>84 (8-96)</td>
<td>78 (6-69)</td>
</tr>
<tr>
<td>Pulse, beats/S</td>
<td>86 (13-7)</td>
<td>76 (4-53)</td>
</tr>
<tr>
<td>Pupil diameter, mm</td>
<td>2.55 (0.44)</td>
<td>2.6 (0.52)</td>
</tr>
</tbody>
</table>

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 timolol. Denffer\(^\text{10}\) 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


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