A double blind comparison of guanethidine-and-adrenaline drops with 1% adrenaline alone in chronic simple glaucoma

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SUMMARY We present the results of a double-blind trial comparing the efficacy of a single dose combination of guanethidine 3% and adrenaline 0.5% with that of adrenaline 1% alone in reducing the intraocular pressure of eyes suffering from chronic open-angle glaucoma. The mean fall in ocular tension with the combined therapy was 10.67 mmHg, and with adrenaline 1% 6.31 mmHg, 24 hours after the commencement of phasing. The combined drop produced satisfactory control of ocular tension in all cases. These results indicate that a combined drop of guanethidine 3% and adrenaline 0.5% is a promising topical therapy for the control of chronic open-angle glaucoma.

Adrenaline is effective in controlling the intraocular pressure of some patients with open-angle glaucoma in concentrations of 0.5–2.0% (Becker and Ley, 1958; Becker et al., 1961). Guanethidine also lowers intraocular pressure and controls some cases of chronic simple glaucoma (Oosterhuis, 1962; Bonomi and Di Comite, 1967; Anselmi et al., 1968). It has been shown to supersensitise tissue to catecholamines (Boura and Green, 1962; Sneddon and Turner, 1967), and the 2 drugs act as synergists, producing an enhanced effect when used in combination. A combination of guanethidine 5% and adrenaline (0.5 to 1%) has been found to be more effective in controlling intraocular pressure than either alone (Paterson and Paterson, 1972; Roth, 1973; Gloster, 1974). A long-term study of 1% guanethidine and 0.05 to 0.5% adrenaline on patients with glaucoma simplex produced encouraging results (Nagasubramanian et al., 1976).

The present study has been undertaken to evaluate treatment of chronic open-angle glaucoma with guanethidine 3% and adrenaline 0.5% and to compare the effect of that of adrenaline 1% alone. A recent study (Hoyng et al., 1977) using the above combination produced promising results but was based only on a single-dose diurnal intraocular pressure curve.

Methods

Seventeen patients (34 eyes) with the disc and field changes of open-angle glaucoma (including 3 of the ‘low-tension’ type) either presenting for the first time or already with intraocular pressures controlled on topical instillation only were admitted to the trial after their informed consent had been obtained. There were 8 males and 9 females, their average age being 69 years with a range of 54 to 79.

Adrenaline 1% was provided in the commercial preparation Simplene, in unmarked coded bottles identical to those containing a pharmaceutically acceptable mixture of guanethidine 3% and adrenaline 0.5% (Ganda). The distribution of the bottles was randomised and the contents of each known only to the pharmacist.

The mean of 3 intraocular pressure measurements with the Goldmann applanation tonometer was taken. Patients stopped their present antiglaucoma therapy (if any). They were supplied with one of the above preparations in random order and double blind to us. They instilled 1 drop into each eye twice daily for 1 month.

They were then admitted to hospital for 48 hours, during which time intraocular pressures were measured 4 times per day at 9.30 a.m., 12.30 p.m., 4.30 p.m., and 8.30 p.m. During phasing they received their drops at 8.30 a.m. and 4.0 p.m. They then received the alternative preparation and were re-admitted in a further 1 month for another 48 hours’ phasing. The key to the code was not revealed by the pharmacist until all recordings were complete.

Results

One patient was removed from the trial as the side effects of discomfort and blurring of vision while
Table 1  Mean intraocular pressures obtained on Ganda drops and adrenaline 1% drops during phasing

<table>
<thead>
<tr>
<th>Time</th>
<th>Right eye</th>
<th>Left eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment pressures</td>
<td>26.56 ± 2.20</td>
<td>25.06 ± 1.31</td>
</tr>
<tr>
<td>1% Adrenaline</td>
<td>3% Guanethidine</td>
<td>1% Adrenaline</td>
</tr>
<tr>
<td>0 Hours (First reading of phasing)</td>
<td>22.89 ± 1.98</td>
<td>18.00 ± 1.34</td>
</tr>
<tr>
<td>3 Hours</td>
<td>21.40 ± 1.46</td>
<td>17.87 ± 1.24</td>
</tr>
<tr>
<td>7 Hours</td>
<td>20.06 ± 1.56</td>
<td>16.94 ± 1.05</td>
</tr>
<tr>
<td>11 Hours</td>
<td>19.38 ± 2.45</td>
<td>17.63 ± 1.95</td>
</tr>
<tr>
<td>24 Hours</td>
<td>20.00 ± 1.76</td>
<td>15.07 ± 1.07</td>
</tr>
<tr>
<td>27 Hours</td>
<td>19.75 ± 1.82</td>
<td>14.56 ± 1.09</td>
</tr>
<tr>
<td>31 Hours</td>
<td>19.44 ± 1.69</td>
<td>14.25 ± 1.43</td>
</tr>
<tr>
<td>35 Hours</td>
<td>18.63 ± 2.39</td>
<td>14.63 ± 1.48</td>
</tr>
</tbody>
</table>

Table 2  Mean reductions in intraocular pressures during phasing with Ganda drops and adrenaline 1% drops

<table>
<thead>
<tr>
<th>Time</th>
<th>Right eye</th>
<th>Left eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Hours</td>
<td>3.67 ± 0.79</td>
<td>8.56 ± 1.10</td>
</tr>
<tr>
<td>3 Hours</td>
<td>5.16 ± 0.52</td>
<td>8.69 ± 0.69</td>
</tr>
<tr>
<td>7 Hours</td>
<td>6.50 ± 0.51</td>
<td>9.62 ± 0.68</td>
</tr>
<tr>
<td>11 Hours</td>
<td>7.18 ± 1.29</td>
<td>8.93 ± 1.38</td>
</tr>
<tr>
<td>24 Hours</td>
<td>6.56 ± 0.64</td>
<td>11.49 ± 0.84</td>
</tr>
<tr>
<td>27 Hours</td>
<td>6.81 ± 0.63</td>
<td>12.00 ± 0.82</td>
</tr>
<tr>
<td>31 Hours</td>
<td>7.12 ± 0.62</td>
<td>12.31 ± 0.82</td>
</tr>
<tr>
<td>35 Hours</td>
<td>7.93 ± 1.36</td>
<td>11.93 ± 1.68</td>
</tr>
</tbody>
</table>

using the trial drops were considered to be intolerable.

The mean intraocular pressure at the initial diagnosis was 26.56 ± 2.20 mmHg in the right eye and 25.06 ± 1.31 in the left eye. Mean values obtained during phasing are as in Table 1. These are expressed graphically in Figs. 1 and 2. The average falls in intraocular pressures are shown in Table 2.

Table 1 shows that at the beginning of phasing Ganda-treated eyes had markedly lower mean intraocular pressures than adrenaline-treated eyes. Comparison of these values with those obtained before treatment, that is, at initial diagnosis, shows that they are highly significant for Ganda-treated eyes (P > 0.001) but not for eyes treated with adrenaline 1% (P > 0.1).

Comparison of the intraocular pressures found at the beginning of phasing showed that right eyes had significantly lower starting values on Ganda than on adrenaline (0.05 > P > 0.02). For left eyes the difference was just not significant at the 5% level.

With both drugs the intraocular pressure appeared to fall during the phasing period, being significantly lower 24 hours after phasing began except in the case of the left eyes treated with Simplene (for right eyes treated with Ganda 0.01 > P > 0.002).

Discussion

Guanethidine acts as a depletor of noradrenaline from sympathetic nerve endings by increasing its liberation and inhibiting the normal process of re-uptake (Hendley and Eakins, 1965). It lowers intraocular pressure initially by increasing aqueous outflow but later by decreasing aqueous production.
Bonomi and Di Comite, 1967). Paterson and Paterson (1972), studying dose response curves on patients treated with 5% and 3% guanethidine found an average decreased ocular tension of 7.3 mmHg and 9.7 mmHg, respectively, 8 hours after instillation. However, the same authors showed that this hypotensive effect of guanethidine alone is not maintained after 1 month.

The exact mechanisms by which adrenaline reduces intraocular tension remains obscure, but it has been shown that topical catecholamines reduce aqueous flow by decreasing aqueous production.

Figs. 1 and 2. Mean intraocular pressure in Simplene-treated eyes and Ganda-treated eyes respectively. Mean intraocular pressure without treatment obtained at first hospital visit also shown at top left corner of graph.

Key:
- = Right eye.
--- = Left eye.
□ = Standard error of mean.
↑ = Dosed.
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and increasing aqueous outflow (Weekers et al., 1954; Becker and Ley, 1958; Garner et al., 1959). Harris et al. (1970) found 0.5% adrenaline to lower ocular tension by 5.00±0.52 mmHg after 4 weeks. Becker and Ley (1958) recorded a mean reduction in ocular tension with adrenaline 1% of 4.8 mmHg after 3 months. Our results show a fall in intraocular pressure at 24 hours of phasing of 6.31 mmHg on pairing the mean of both eyes.

The mean fall in ocular tension on Ganda of 10.67 mmHg (both eyes taken together) 24 hours after the beginning of phasing compares favourably with a fall of 10.1 mmHg with a similar combination reported by Hoyng et al. (1977), though, as mentioned above, this latter reading was for a single-dose diurnal intraocular pressure curve. Nagasubramanian et al. (1976) reported a fall in intraocular pressure of 9 mmHg in 95% of patients receiving topical guanethidine 1% and adrenaline 0.05 to 0.5%.

Six patients complained of sore irritable eyes while receiving Ganda (including the 1 who was withdrawn from the trial). Three of these also complained of blurred vision after the instillation of their drops lasting for about 30 minutes. Four patients reported an improved visual acuity subjectively, but we could record no objective verification. This incidence of side effects compares favourably with that reported by Hoyng et al. (1977), though Nagasubramanian et al. (1976) reported very few side effects to lower concentrations.

With adrenaline 1% 2 patients complained of red irritable eyes associated with some blurring of vision. Five patients remarked that subjectively their vision had improved.

In this study all the patients maintained intraocular pressures below 21 mmHg while on combined treatment with guanethidine 3% and adrenaline 0.5% twice daily. However, 3 patients failed to maintain pressures below this level while on adrenaline 1% alone, and this finding together with the significantly greater pressure-lowering effect of Ganda as compared with adrenaline suggests that the combined preparation is the more effective.

Our thanks are due to Mr Steven Freeborn, pharmacist, and Mrs R. Gibbs and Mrs A. Molloy, glaucoma technicians, at the Manchester Royal Eye Hospital, for their help in the completion of this project. We also thank Dr J. Lamble and colleagues of Smith & Nephew Research for their considerable assistance with this project and for providing the material for the study.

References


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