Adrenaline 1% combined with guanethidine 1% versus adrenaline 1%: a randomised prospective double-blind cross-over study

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SUMMARY The hypotensive effect of a combination of guanethidine 1% with adrenaline 1% was compared with adrenaline 1% alone on the eyes of 20 patients with ocular hypertension in a randomised double-blind cross-over trial. The patients received 8 weeks of treatment with each preparation. A significant increase in the hypotensive effect was found by adding guanethidine 1% to adrenaline 1%. This hypotensive effect was maintained over the 8-week period of the trial.

Paterson and Paterson¹ introduced clinicians to the potentiating effect of adding guanethidine to adrenaline. Dose dilution studies suggested that a ratio of guanethidine 5:1 adrenaline was most effective. As a result different strengths of guanethidine with adrenaline were formulated; initially concentrations of 5:1 and then 5:0.5 and 3:0.5 were used. These strengths caused an appreciable incidence of side effects. Later Nagasubramanian and others² demonstrated that adrenaline 0.2% with guanethidine 1% had a sustained hypotensive effect. However, double-blind studies showed that this lower concentration did not have a greater hypotensive effect than 1% adrenaline alone, while the incidence of side effects was approximately the same.³ More recently guanethidine 1% with adrenaline 1/2% was shown to have a greater hypotensive effect than adrenaline 1% without producing a greater incidence of side effects.⁴ It seemed worthwhile, therefore, to see whether a further increase in the hypotensive effect could be obtained by combining guanethidine 1% with adrenaline 1%, and to see whether patients easily tolerated this combination.

Patients and methods

Twenty ocular hypertensive patients were drawn from the glaucoma clinic at Moorfields Eye Hospital, High Holborn. The basis of the study was explained and informed consent obtained.

The study design was as follows:

(1) An initial 7-day washout period off all anti-glaucoma treatment (where necessary).

(2) Twice-a-day instillation of coded sympathomimetic preparation prepared and dispensed by the Moorfields Eye Hospital Pharmacy.

(3) Intraocular pressures were measured before treatment, and then at 1, 3, and 8 weeks after starting treatment on the first preparation. Intraocular pressures were measured at the same time of day. Care was taken to ensure that a repeatable intraocular pressure was obtained; the right eye was always measured first.

(4) At the end of the first 8-week period there was a further washout period lasting 7 days without any hypotensive therapy.

(5) The alternative coded sympathomimetic treatment was dispensed and the procedure repeated for a further 8 weeks as in no. 3 above.

(6) Throughout the study the patients' subjective comments were noted, as were observations of conjunctival hyperaemia, alterations in visual acuity, and ocular irritation.

Results

Twenty patients entered the trial. Seven patients could not complete one or other half of the trial. Each patient who wished to withdraw was restarted on his normal antiglaucoma treatment (where applicable) and re-entered the study at the time of the prescribed second washout period. After this period they were started on the alternative sympathomimetic preparation. One patient failed to re-enter the study.

Only two patients failed to complete both halves of

Table 1 Analysis of the paired results for each eye: Student's *t* test

<i>Comparison of pretrial washout IOP with IOP on adrenaline</i>			
<i>Week</i>	<i>I</i>	<i>III</i>	<i>VIII</i>
Mean IOP fall (mmHg)	($\bar{x}$)=1.89 mmHg SD=3.33 n=19 eyes t=2.47 p=<0.05	$\bar{x}$ =1.89 SD=2.59 n=19 t=3.18 p=<0.01	$\bar{x}$ =0.79 SD=2.14 n=19 t=1.61 p=>0.10
<i>Comparison of pretrial washout IOP with IOP on guanethidine and adrenaline</i>			
<i>Week</i>	<i>I</i>	<i>III</i>	<i>VIII</i>
Mean IOP fall (mmHg)	($\bar{x}$)=3.17 SD=4.09 n=19 eyes t=3.38 p=<0.005	$\bar{x}$ =4.46 SD=4.31 n=15 t=4.01 p=<0.002	$\bar{x}$ =4.78 SD=4.16 n=15 t=4.45 p=<0.001

the trial. Three patients completed the adrenaline half but not the combination-drop half, while one patient completed the combination-drop but not the adrenaline half of the trial. In each case withdrawal was caused by intolerance to the drug in question. No patient was withdrawn because of high intraocular pressures.

Of the 20 patients entered one failed to complete even one half of the trial. Analysis has therefore been restricted to the 19 remaining patients. The intraocular pressures for the right eye are tabulated.

The mean pretrial washout IOP was 23.38 mmHg, SD 4.68.

The hypotensive effect of adrenaline alone and in combination with guanethidine has been set out in

Table 2 Comparison of IOP fall on adrenaline with IOP fall on guanethidine with adrenaline; shown as the extra hypotensive effect of guanethidine and adrenaline. Analysis of paired results by Student's *t* test

Week	I	III	VIII
Mean extra hypotensive effect (mmHg)	($\bar{x}$)=1.61	$\bar{x}$ =1.80	$\bar{x}$ =3.33
	SD=3.16	SD=2.0	SD=4.40
	n=18	n=15	n=15
	t=2.16	t=3.49	t=2.93
	p=<0.05	p=<0.005	p=<0.05

Table 1. The comparison has been made with the pretrial washout IOP. A comparison of the hypotensive effect of the 2 drugs has been set out in Table 2. Table 3 lists the noted side effects.

Table 3 Side effects

Symptom	No. of patients	
	Guanethidine and adrenaline	Adrenaline
Headache/brow ache	4	1
Red eye	7	2
Burning	0	0
Ptosis	0	0
Ocular pain	1	0
Blurred vision	2	1

Discussion

The results presented here show that by adding guanethidine 1% to adrenaline 1% there is a marked and sustained increase in the hypotensive effect in the ocular hypertensive patients studied. This effect lasted for the full 8 weeks of the trial. There was an

Fig. 1 Comparison of the hypotensive effect of varying combinations of adrenaline combined with 1% guanethidine with adrenaline 1% alone. This has been recorded as the pressure difference between the different combination drops and adrenaline 1% alone for 3 different studies, for each study at 1, 3, or 4, and 8 weeks of treatment. There was a significant difference ($p<0.05$) between the intraocular pressures recorded on treatment with adrenaline 1% alone compared with varying strengths of the combination drops as follows: preparation A, week 1; B, week 8; C, week 1, 3, and 8. A=adrenaline 1/4%; B=adrenaline 1/2%; C=adrenaline 1%.

increase in the side effects seen with the combination drop. However, not every patient intolerant of adrenaline was going to be intolerant of the combination drop and vice versa. Three-quarters of the patients found that the guanethidine and adrenaline drop was easily tolerated for the duration of the trial.

Further analysis of the results that were obtained by Murray *et al.*,⁴ who conducted similar double-blind prospective studies, allowed a comparison of the additional hypotensive effect of adding guanethidine 1% to various strengths of adrenaline ($\frac{1}{4}$, $\frac{1}{2}$, or 1%) compared with adrenaline 1% alone. This analysis may be seen in Fig. 1. It will be seen that combining adrenaline 0.25% with guanethidine gives a combination drug of equivalent hypotensive effect to adrenaline 1% alone. Combining adrenaline $\frac{1}{2}$ % with guanethidine 1% gives a combination drop which by the eighth week of the trial gave significant extra hypotensive effect on the patients studied. However, the combination of adrenaline 1% with guanethidine 1% gave an immediate and sustained increased hypotensive effect when compared with adrenaline 1% alone and appeared the most potent hypotensive combination of the 3.

CONCLUSION

From this study it is suggested that combining guanethidine 1% with adrenaline 1% gives a useful

antiglaucoma preparation which has a greater hypotensive effect than adrenaline 1% alone and also than weaker adrenaline concentrations combined with 1% guanethidine. Approximately 25% of the patients studied in this trial were not prepared to tolerate it for the 8-week period. This was a slightly greater number than those who were not prepared to tolerate adrenaline alone. However, the remaining patients were happy to use it in the long term. It is suggested that those patients with an inadequate hypotensive response to adrenaline alone could well benefit by being changed to a combination of adrenaline 1% with guanethidine 1%.

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References

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