

British Journal of Ophthalmology, 1981, **65**, 50-52

Double-masked cross-over comparison of Ganda 1.02 (guanethidine 1% and adrenaline 0.2% mixture) with gutt. adrenaline 1% (Simplene 1%) and with pilocarpine 1% (Sno-Pilo 1%)

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SUMMARY A trial of the efficacy of low-concentration nonmiotic therapy was carried out, the aim being to minimise the side effects produced by 1% adrenaline or pilocarpine. A total of 77 eyes with open-angle glaucoma were studied in both parts of the trial. Thirty-nine eyes had a base-line pressure of over 28 mmHg and 28 eyes a pressure of 30 mmHg or over. In the comparison between Ganda 1.02 and adrenaline 1% (Simplene) the mean lowering of intraocular pressure was 8.6 mmHg with Ganda and 7.69 mmHg with Simplene. In the comparison between Ganda 1.02 and pilocarpine 1% (Sno-Pilo) the mean decrease was 6.34 mmHg with Ganda and 6.13 mmHg with Sno-Pilo. The resulting falls in intraocular pressure were highly significant statistically, but the differences between the effects of the 3 drugs were not significant. No significant side effects were reported with Ganda 1.02, and in particular no ptosis or superficial punctate staining of the cornea was noted.

Recent studies have established the efficacy in controlling glaucoma of combined treatment with low-concentration guanethidine (1-3%) and adrenaline (0.05-0.5%), especially when administered as a single formulation.¹⁻⁶ In a long-term study over 12 to 42 months in nearly 100 patients combined treatment with 1% guanethidine and 0.25/0.5% adrenaline was found to be effective in a large number of patients without the development of tolerance to either of the drugs.⁷ The present study was undertaken to compare the ocular hypotensive effect of a commercial preparation of a 1% guanethidine and 0.2% adrenaline mixture (Ganda 1.02) with a 1% adrenaline (Simplene 1%) and a 1% pilocarpine (Sno-Pilo 1%) preparation in patients with chronic open-angle glaucoma.

Material and methods

The study was carried out on 40 patients (77 eyes) with open-angle glaucoma attending the Glaucoma Unit at Moorfields Eye Hospital, City Road, London. Cases of various degrees of severity were included, 39 eyes having untreated intraocular pressures of 28 mmHg or over and 28 eyes a pressure of 30 mmHg or over. The series comprised patients

already on topical treatment and newly diagnosed untreated cases.

The patients were randomly allocated to the Ganda/Simplene trial (38 eyes in 20 subjects) or to the Ganda/Sno-Pilo trial (39 eyes in 20 subjects).

PROTOCOL OF DOUBLE-MASKED CROSS-OVER TRIAL

Random allocation of the next available patient number determined which of the 2 drugs was to be prescribed first. The drops were issued in plain bottles, marked with the letter A or B to designate the preparation used during the first and second period of the trial respectively, and patients were instructed to use the drops twice daily, at 12-hourly intervals.

Duration of the trial: 8 weeks.

Initial visit: Establishment of the correct diagnosis and recording of the following parameters: baseline untreated intraocular pressure at the time of diagnosis; nature and frequency of medication in the treated cases; mean intraocular pressure on the previous treatment; measurement of the pulse and blood pressure. Estimation of the visual acuity on the Snellen 6-meter chart, intraocular pressure by the Goldmann applanation tonometer on the Haag-Streit 900 slit-lamp.

Pupil diameter measured on the Goldmann

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perimeter under constant illumination at 31·50 apostilb.

Slit-lamp examination of the cornea for superficial punctate staining and measurement of the palpebral aperture for the detection of ptosis. The patient was issued with vial A and instructed to return after 14 days. The same parameters were assessed. The patient was asked to return after a fortnight, when the cross-over to vial B was carried out, and after a further fortnight a final assessment was carried out.

Results

These are given in Tables 1 and 2.

Discussion

INTRAOCULAR PRESSURE

The fall in the mean intraocular pressure from the baseline pressure was greater with Ganda 1.02 than with either adrenaline 1% or pilocarpine 1%. The difference, about 1 mmHg in the case of adrenaline and 0·21 mmHg for pilocarpine, was not statistically significant. However, this fact does indicate that Ganda 1.02 is at least as effective as either of the two time-tested therapeutic agents it was being compared with, and possibly more effective. All 3 agents produced a considerable and significant fall in the intraocular pressure during the time of the trial.

POSSIBLE PERSISTENCE OF GUANETHIDINE EFFECT

As no washout period was included in the protocol, we considered the possibility that a persistence of the effect of guanethidine enhanced the effect of adrenaline. In the Ganda/Simplene trial 14 patients that had been treated with guanethidine 1% and adrenaline 0·25% in the period immediately leading up to the trial and 9 patients who received Ganda first according to the protocol were studied. If a lingering effect were present, the first intraocular pressure reading on adrenaline would have been expected to be lower than the second reading a fortnight later. However, only 2 patients showed a substantial rise of intraocular pressure at the second visit; half of the rest showed no difference in pressure, and the other half had a higher second reading than the first.

PUPIL SIZE

The average pupil diameter on Ganda 1.02 was 3·0 mm in both trials. This compares with a mean diameter of 1·9 mm in the Sno-Pilo trial. Although this difference in mean pupil diameter is significant, the magnitude of the difference is less than that

Table 1 *Ganda/Simplene trial*

Mean baseline IOP	29·55 ± 7·44 mmHg
Mean IOP on Ganda 1.02	20·89 ± 4·83 mmHg P < 0·001
Mean IOP on Simplene	21·86 ± 4·48 mmHg P < 0·001
Fall of mean IOP on Ganda 1.02	8·66 mmHg
Fall of mean IOP on Simplene 1%	7·69 mmHg
Mean pupil diam. on Ganda	3·07 mm ± 0·92 mm
Mean pupil diam. on Simplene	3·5 mm ± 0·86 mm
Average pulse rate on Ganda	78·0/min ± 10·97
Average pulse rate on Simplene	77·0/min ± 10·06
Mean BP on Ganda	$\frac{147·3 \pm 23·57}{86·3 \pm 12·19}$ mmHg
Mean BP on Simplene	$\frac{147·22 \pm 19·79}{87·80 \pm 14·19}$ mmHg

IOP = intraocular pressure. BP = blood pressure.

Table 2 *Ganda/Sno-Pilo trial*

Mean baseline IOP	27·28 ± 4·68 mmHg
Mean IOP on Ganda 1.02	20·94 ± 3·89 mmHg P < 0·001
Mean IOP on Sno-Pilo	21·15 ± 3·52 mmHg P < 0·001
Fall of mean IOP on Ganda 1.02	6·34 mmHg
Fall of mean IOP on Sno-Pilo 1%	6·13 mmHg
Mean pupil diam. on Ganda 1.02	3·15 mm ± 0·98 mm
Mean pupil diam. on Sno-Pilo	1·90 mm ± 0·36 mm
Average pulse rate on Ganda 1.02	81/min ± 12·67
Average pulse rate on Sno-Pilo	80·58/min ± 14·35
Mean BP on Ganda 1.02	$\frac{150·35 \pm 21·5}{89·1 \pm 10·89}$ mmHg
Mean BP on Sno-Pilo 1%	$\frac{149·68 \pm 20·94}{90·37 \pm 8·65}$ mmHg

IOP = intraocular pressure. BP = blood pressure.

observed in clinical practice, where pupils of 2 mm diameter or less are not infrequently seen during treatment with pilocarpine.

The mean pupil diameter on Simplene 1% was 3·5 mm. Since the standard deviation was 0·86 mm, this would indicate that some of the pupils were kept dilated beyond the 4·0–4·25 mm which is considered to be within the 'dangerous zone' of mid-dilatation, in which possible angle closure could occur in predisposed eyes. In borderline anterior chamber depths and/or narrow angles it would thus be possible to use Ganda 1.02 with caution where adrenaline 1% might be considered to be too risky.

VISUAL ACUITY

In the majority of cases in both trials there was no change in the visual acuity when passing from one drug to the other (28 eyes in the Ganda/Simplene

Table 3 Side effects. The figures refer to numbers of patients

	Ganda/Simplene trial		Ganda/Sno-Pilo trial	
	Ganda	Simplene	Ganda	Sno-Pilo
Headache/browache	7	8	6	6
Hyperaemia	9	9	6	2
Burning/smarting	8	10	10	10
Ptosis	1	—	6	2

trial and 29 eyes in the Ganda/Sno-Pilo trial). In the Simplene trial 6 eyes had a visual acuity corresponding to 1 line better on the Snellen chart with Ganda, and 2 cases had 2 lines better, while 5 cases had 1 line more while on Simplene. In the Ganda/Sno-Pilo trial 4 eyes saw 1 line better on Ganda and 5 eyes 1 line better on Sno-Pilo. These changes can be correlated with the pupillary diameter in the absence of lens opacities.

SIDE EFFECTS

Systemic. There was no significant difference in the pulse rate or blood pressure of the patients receiving any of the 3 drugs. This is in contrast with the bradycardia and lowered blood pressure occasionally observed in patients treated with beta-blocking preparations.

Topical. See Table 3. It can be seen that these were relatively rare. The intensity of the hyperaemia and the severity of burning/smarting were substantially lower with Ganda 1.02 than with Simplene. The greater incidence of ptosis (which was mild in all cases in which it was present) with Ganda is to be expected.

Conclusion

The results of both the double-masked cross-over trials suggest that a mixture of guanethidine 1% with adrenaline 0.2% provides an effective topical therapy for the control of open-angle glaucoma, with minimal side effects. Experience with higher concentrations of these 2 drugs, now long established, suggests that the effect is likely to be long-lasting.

We thank Smith and Nephew Pharmaceuticals Ltd. for the supply of eye drops.

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doi: 10.1136/bjo.65.1.50

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