

Evaluation of a 5% guanethidine and 0.5% adrenaline mixture (Ganda 5.05) and of a 3% guanethidine and 0.5% adrenaline mixture (Ganda 3.05) in the treatment of open-angle glaucoma

JOHN ROMANO AND GILLIAN PATTERSON

From the Glaucoma Clinics, Moorfields Eye Hospital, City Road, and High Holborn Branches, and Hillingdon Hospital, Uxbridge, London

SUMMARY A trial of a mixture of guanethidine 5% and adrenaline 0.5% (Ganda 5.05) and of guanethidine 3% and adrenaline 0.5% (Ganda 3.05) was conducted on 90 eyes in 53 patients with open-angle glaucoma or ocular hypertension. The cases fell into 5 groups: untreated cases, cases on pilocarpine 1%, on pilocarpine 2%, on pilocarpine 2 to 4% and adrenaline 1%, and on separate guanethidine 5% and adrenaline 1%. Baseline pressures and average pressures on the previous treatment were established. Substitution with Ganda 3.05 or 5.05 was started, and the patients attended 2 weeks, 1 month, 3 months, and 6 months from the start of the trial. Applanation tonometry was carried out at the same time of day. The pupil was measured, ptosis and superficial punctate corneal staining were looked for and evaluated, and the patients were questioned for symptoms of side effects and acceptability. All the eyes that had previously been treated with pilocarpine 1% or 2% presented significantly lower intraocular pressures on Ganda 3.05. The patients on pilocarpine 4% and adrenaline 1% also had lower intraocular pressures on Ganda 5.05, but the significance was less, and the patients on separate guanethidine and adrenaline had a small but not statistically significant drop in pressure. Ptosis and discomfort were evaluated on a subjective scale. Patient acceptability was good. The trial was interrupted in 5 cases for various reasons. Tachyphylaxis and tolerance to the mixtures were not observed in this series.

Interest in guanethidine and other beta-blocking agents for the possible lowering of intraocular pressure goes back to the early 1960s. Guanethidine eye drops were being successfully used to diminish the lid retraction produced by sympathetic overactivity associated with thyrotoxicosis. However, attempts by one of us (J.R.) to control the intraocular pressure in several cases with both thyrotoxicosis and open-angle glaucoma with topical guanethidine were not successful. Other workers (Stepanik, 1961; Castren and Pohjola, 1962; Anselmi *et al.*, 1968) reported a lowering of the intraocular pressure using guanethidine alone. The discrepancy between these results will be discussed later in this paper. The combination of adrenaline with guanethidine provided a breakthrough (Paterson and Paterson, 1972), and several studies attest to the efficacy of this combined therapy (Roth 1973; Gloster, 1974; Crombie, 1974; Paterson *et al.*, 1975; Etienne, 1975; Nagasubramanian *et al.*, 1976).

These trials were practically all concerned with new and untreated cases of glaucoma or cases in which all previous treatment had been discontinued. More recently a trial was carried out on severe cases of open-angle glaucoma most of which were already on maximal medical therapy. The addition of guanethidine and adrenaline eye drops to the previous treatment led to a satisfactory response in most cases (Romano, 1977). The guanethidine and adrenaline eye drops were used 10 minutes apart to enhance absorption (Phillips, 1971), and this was repeated twice a day. It was felt that a mixture of the 2 drugs would be more convenient for the patient. However, it was not known at the time whether it would be possible to mix the 2 drugs in a stable solution and whether the efficacy and absorption of the mixture would be adequate. The availability of such a mixture has made this study possible.

Material and methods

The study covers 90 eyes in 53 patients drawn from the Glaucoma Clinics of both branches of Moor-

Address for reprints: Mr J. H. Romano, FRCS, 96 Harley Street, London W1N 1AF

Evaluation of guanethidine and adrenaline mixtures

fields Eye Hospital, London, and that of Hillingdon Hospital. Its object is to study the effect of a guanethidine 5% and adrenaline 0.5% mixture (Ganda 5.05*) and of a guanethidine 3% and adrenaline 0.5% mixture (Ganda 3.05*) on patients with open-angle glaucoma and ocular hypertension. The patients fall into the following categories: (1) Untreated cases (15); (2) cases previously on pilocarpine 1% 2 to 4 times a day or pilocarpine 2% 3 to 4 times a day (19 cases); (3) patients on pilocarpine 2 or 4% 4 times a day with adrenaline 1% twice a day (16 cases); (4) patients previously on separate guanethidine 5% and adrenaline 1% twice a day (36 cases). The main object of the trial was to study, in the treated groups, the effect of substitution of Ganda 3.05 and Ganda 5.05 for the previous treatment.

The baseline intraocular pressure was noted, and the average intraocular pressure on the previous treatment was established by recording all previous tensions and averaging the results. All pressures were estimated with the Goldmann applanation tonometer at approximately the same time each day to offset the possible effect of diurnal variations. The patients were started on the mixture, and attended 2 weeks, 1 month, 3 months, and 6 months from the onset of the trial. A pressure of 20 to 22 mmHg or lower was accepted as evidence of control. If this was not achieved after 2 weeks the treatment was continued for another 2 weeks, as it has been suggested (Paterson and Paterson, 1972) that the guanethidine-adrenaline combination may not reach its full effect until after a month or so of treatment. If still uncontrolled after a month a case would be considered to be a failure and additional or alternative treatment prescribed. At each visit the pupils were measured, either on the Goldmann perimeter with a background illumination setting of 31.50 apostilb, or on the Haag-Streit slit lamp with a graticule eyepiece and the slit beam narrowed

*Supplied by Smith & Nephew Pharmaceuticals, Welwyn Garden City, Herts. Ganda is short for Guanethidine AND Adrenaline.

to the 1.0 setting and directed at an angle of 30° from the temporal side.

At each visit the following were searched for and estimated: Ptosis (measured in millimetres); hyperaemia of the bulbar conjunctiva and of the eyelids, and lid-sensitivity reaction; punctate epitheliopathy, by fluorescein staining of the cornea.

The patients were closely questioned for symptoms such as discomfort, browache, burning, and blurring of vision. The fields of vision, charted before the trial, were compared with those at the end of the trial.

At the end of the trial, the average intraocular pressures, average pupil diameter, and degree of ptosis were noted. The symptoms were assessed on a subjective scale: Discomfort was described as nil, minimal (m), moderate (M), or severe (S). Ptosis was described as nil, minimal (1 to 2 mm), moderate (2 to 3 mm), or severe (more than 3 mm). Punctate epitheliopathy was described as present (+) or absent (-).

Results

See Tables 1 and 2 for analysis of results.

In 9 out of 9 cases previously on pilocarpine 1% 2 to 4 times a day compared with Ganda 3.05 the average pressure was lower on the guanethidine-adrenaline mixture. The average intraocular pressure on pilocarpine 1% was 24 mm (SD 2.1), and on Ganda 3.05 18.20 mm (SD 2.7) ($t=10.9$, $P\leq 0.001$).

All 10 cases previously on pilocarpine 2% 3 to 4 times a day compared with Ganda 3.05 had

Table 1 Analysis of all cases on Ganda 3.05

Average fall of intraocular pressure			
At 2 weeks	At 1 month	At 3 months	At 6 months
10.14 mm	10.88 mm	10.57 mm	9.84 mm
(SD, 0.72)	(SD, 0.62)	(SD, 0.64)	(SD, 0.66)
Percentage fall of intraocular pressure			
37% (SD, 2.1)	39% (SD, 1.6)	38% (SD, 1.8)	36% (SD, 1.9)

Table 2 Study of the different groups of cases for accommodation to Ganda

Previous treatment:	IOP at 2 weeks (mmHg)	IOP at 4 weeks (mmHg)	IOP at 3 months (mmHg)	IOP at 6 months (mmHg)
<i>Cases previously on:</i>				
pilocarpine 1%	18.3 (SD, 2.9)	18.3 (SD, 1.3)	17.7 (SD, 4.0)	19.2 (SD, 4.5)
pilocarpine 2%	15.5 (SD, 2.3)	15.9 (SD, 2.7)	16.1 (SD, 3.8)	16.4 (SD, 4.3)
pilocarpine 2 to 4% and adrenaline 1%	19.2 (SD, 4.0)	17.3 (SD, 4.3)	17.2 (SD, 5.7)	19.3 (SD, 4.1)
separate guanethidine 5% and adrenaline 1%	18.1 (SD, 3.2)	18.4 (SD, 3.0)	17.8 (SD, 3.1)	17.4 (SD, 3.7)
Untreated cases	20.6 (SD, 1.73)	18.4 (SD, 1.62)	19.0 (SD, 1.0)	19.9 (SD, 1.5)

lower average intraocular pressure on Ganda. The average intraocular pressure on pilocarpine 2% was 21.8 mm (SD 2.7), and on Ganda 3.05 16.0 mm (SD 2.9) ($t=5.68$, $P<0.002$).

In the 6 cases previously on pilocarpine 2–4% 3 to 4 times a day and adrenaline 1% twice a day compared with Ganda 5.05: 10 eyes had lower pressure on Ganda 5.05, 3 eyes had the same pressure on Ganda 5.05, and 3 eyes had a higher pressure on Ganda 5.05. The average intraocular pressure on pilocarpine 2 to 4% and adrenaline was 20.1 mm (SD 2.7), and on Ganda 5.05 18.7 mm (SD 3.1) ($t=2.45$, $P\leq 0.05$).

In the cases previously on separate guanethidine 5% and adrenaline 1% compared with Ganda 5.05 16 eyes had lower pressure on Ganda 5.05, 19 eyes higher pressure on Ganda 5.05, and 1 eye the same pressure. The average intraocular pressure on separate guanethidine 5% and adrenaline 1% was 18.29 mm (SD 2.2), and on Ganda 5.05 17.92 mm (SD 2.7) ($t=0.75$, $P\geq 0.05$).

All 15 untreated cases had their average intraocular pressures lowered by Ganda 3.05. The average untreated intraocular pressure was 26.36 mm, and on Ganda 3.05 it was 18.45 mm.

As to side effects in 86 eyes: discomfort was absent in 28 cases, minimal in 45, moderate in 13, and severe in none. Ptosis was absent in 12 cases, minimal in 44 (16 on Ganda 3.05, 24 on Ganda 5.05), moderate in 26 (6 on Ganda 3.05, 17 on Ganda 5.05), and severe in 4 (all on Ganda 3.05). Hyperaemia of variable degree noted in 30 cases.

Discussion

It is now fairly widely accepted that topical guanethidine induces a state of 'chemical sympathectomy' in the autonomic nervous system of the anterior segment of the eye, rendering the postganglionic receptors hypersensitive to the action of the chemical transmitter adrenaline. In a recent communication (Romano, 1977) two possibilities regarding the mode of action of guanethidine were envisaged: (1) The hypersensitisation effect is created anew, or at least 'topped up' with each instillation of guanethidine; (2) it gradually builds up over several days with repeated instillations.

If the first view is the correct one, separate administration of guanethidine followed by adrenaline after a suitable interval would be the logical way to use the drugs. However, in some cases the effect of these drugs has been observed (Paterson and Paterson, 1972) to be delayed for some weeks, which supports the second view. Furthermore, the use of a mixture of the 2 substances has proved to be at least as effective—and in the present series it

has been marginally more successful—than that of separate administration. If this is so, the added convenience to the patient of a single instillation must make the mixture the treatment of choice.

In this context the difference in the success-rate reported by various workers with topical guanethidine *alone* is interesting.

SIDE EFFECTS

Ganda has been well tolerated by the patients in this trial, the intolerance rate being around 5.5%. This improved tolerance can be attributed to the use of 0.5% adrenaline instead of the more traditional 1% solution. Discomfort, when present, was usually an initial sensation of grittiness and brow-ache, passing off with continued use of the drops. It was often transient, lasting a minute or two only. As regards ptosis, in 1 case vision was impaired by a 'severe' ptosis of 3 to 4 mm. Although minimal ptosis was a frequent finding, the patients were usually unaware of it. Moderate or severe ptosis could cause some cosmetic disability. Hyperaemia was severe in a dozen or so cases; it was certainly not so marked as has been observed with 1% adrenaline. Punctate epitheliopathy, a rare finding, was associated, when present, with discomfort in about half the cases.

Five cases were rejected from the trial for intolerance to the drops, probably to adrenaline; 1 case for poor control of pressures with small visual fields; and 2 cases for mistakenly using pilocarpine along with Ganda for one or more visits.

Where little or no hypertensive effect is achieved, it may be speculated that local or circulating catecholamines are not sufficient in some individuals, in spite of the hypersensitisation of the adrenergic receptors, to produce a significant lowering of the intraocular pressure, the reverse being true in other individuals.

VISUAL FIELDS

There was no evidence of field loss or of any increase in pre-existing field loss in any patient during the 6-month period of the trial. As mentioned above, 1 case with previously very constricted fields was withdrawn from the trial as his intraocular pressures were considered to be insufficiently controlled.

TACHYPHYLAXIS AND ACCOMMODATION TO GANDA

Tachyphylaxis, defined as the loss of effectivity of a drug occurring early (i.e., in the first few days of treatment), was not specifically studied. It is, however, unlikely to occur, as guanethidine and adrenaline mixtures appear gradually to build up to their maximum effectivity, often over the first few

weeks. *Accommodation*, defined as a gradual loss of effectivity over a longer period, did not seem to occur in this series (Tables 1 and 2).

Conclusion

In our series the ocular hypotensive action of Ganda 3·05 was significantly greater than that of pilocarpine 1% 2 to 3 times a day, pilocarpine 2% 3 to 4 times a day, and of pilocarpine 2 to 4% 4 times a day, with adrenaline 1% twice daily. Most patients were grateful to be relieved partly of the miosis produced by pilocarpine. Compared with separate instillation of guanethidine 5% and adrenaline 1% twice daily, the average intraocular pressure was lower on Ganda 5·05 twice daily, but the difference was small (one must remember, however, that 1% adrenaline was being compared with 0·5% adrenaline). The absence of a significant difference between the separate use of the drugs and that of a mixture argues in favour of using the mixture. Our elderly glaucoma patients certainly found it easier to manage. Well over half—32 out of 53 patients—were happy with the drops, and many wished to continue with Ganda when the trial was over.

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