Control of glaucoma by reduced dosage guanethidine-adrenaline formulation

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SUMMARY The effect of formulations of guanethidine and adrenaline of different composition has been tested in rabbits and in patients with glaucoma. The concentrations of guanethidine and adrenaline used for the rabbits were 5.0% and 1.0%; 2.5% and 0.5%; 1.0% and 0.2%; 0.5% and 0.1%. All except the lowest combination were equally effective in the magnitude of the decrease in intraocular pressure brought about and in their duration of activity. Two formulations containing guanethidine and adrenaline at concentrations of 3.0% and 0.5% and 1.0% and 0.2% respectively (formulated as Ganda drops by Smith and Nephew Pharmaceuticals Ltd) were tested in a blind, cross-over, short-term clinical trial on 20 patients. The drops containing the lower concentration of drugs were as effective as those of higher concentration. These results lead us to believe that most patients who respond to this treatment could be put on a reduced dosage regimen, which should result in a decreased incidence and severity of side effects.

Guanethidine and adrenaline are now well established in the treatment of glaucoma, and we have previously shown (Jones *et al.*, 1977) that it was possible to manage glaucoma in some patients with this combination of drugs over a 5-year period. The drugs were instilled separately, guanethidine 5% first followed by adrenaline 1% 30 minutes afterwards. Although it was possible to avoid the routine use of miotics by this method, the treatment led to the development of a number of side effects, in particular conjunctival hyperaemia, pupillary dilatation, catarrh, and sinusitis. Moreover a number of patients developed resistance to these drugs over a 3-year period and had to have their therapy changed.

We showed in an acute clinical trial (Jones *et al.*, 1977) that guanethidine 3% and adrenaline 0.5% was as effective clinically as guanethidine 5% and adrenaline 1%. This trial also showed that the drops were equally effective when given as a single formulation as when instilled separately, which confirmed an earlier study with rabbits (Jones *et al.*, 1975). Several clinical studies have indicated that they may be more effective in combination

than alone (Patterson and Patterson, 1972; Roth, 1973; Gloster, 1974). A formulation of guanethidine 3% and adrenaline 0.5% is now available as Ganda 305 and there have been favourable reports on its use in glaucoma (Mills and Ridgway, 1978; Hoyng and Dake, 1979; Romano and Patterson, 1979). The latter workers did not encounter any instances of tachyphylaxis or resistance in their trials over 6 months. Side effects are reduced but are still present, and our clinical experience shows that conjunctival hyperaemia and pupillary dilatation in particular cause inconvenience to a significant proportion of patients.

We have therefore investigated the possibility of reducing the concentration of the drugs further to see whether the incidence of side effects might be reduced while leaving the therapeutic efficiency unchanged. This paper reports the results of experiments performed with rabbits on guanethidine/adrenaline drops of different concentrations and also on a short-term clinical trial on 20 glaucoma patients comparing the efficacy of guanethidine/adrenaline in concentrations of 1.0 and 0.2% w/v respectively with 3.0 and 0.5% w/v.

Rabbit experiments

The experimental animals were 12 male New Zea-

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land white rabbits aged between 5 and 8 months. They were conditioned to having eye drops instilled into their eyes and having their intraocular pressure (IOP) measured at intervals throughout each working day for 1 month before the experiment began.

IOP measurements were taken with the rabbits in a holding box, a Perkins hand-held applanation tonometer being used. Benoxinate 0.4% w/v was instilled into each eye as a local anaesthetic before the measurements were taken.

For the assessment of activity of the different dosage forms the rabbits were divided into 4 groups of 3. Each member of each group was given 1 drop of the test formulation in one eye and 1 drop of sterile saline in the other. IOP measurements were then performed on both eyes at regular intervals over 48 hours. The rabbits were allowed 5 clear days between treatments, and then the groups were rotated. In this way over 4 weeks each group of 3 rabbits received each of the 4 experimental formulations. The results were calculated as a reduction in IOP using the untreated eye as a control and then expressed as an average response for the 12 rabbits. The experimental justification for this protocol and treatment of results has been given previously (Jones *et al.*, 1975).

Four different formulations were used, differing only in the amounts of guanethidine sulphate and adrenaline hydrogen tartrate. The drops were prepared in Kolthoff's borate-phosphate buffer at pH 7.4 and contained 0.01% w/v benzalkonium chloride and 0.1% w/v sodium metabisulphite. The drops were sterilised by filtration through a 0.22 μ m membrane filter and packed aseptically into sterile 10 ml glass bottles. The different formulations contained the amounts of guanethidine and adrenaline shown in Table 1.

The results obtained for the 4 treatments are given in Fig. 1 as a mean reduction in IOP for the 12 rabbits with readings taken at 0, 2, 5, 10, 25, 30, and 35 hours. The IOP of all rabbits had returned to normal after 48 hours.

Although the period of activity in rabbits is much longer than that reported for man, we nevertheless believe that the rabbit is a reasonable model for comparing the efficiency of different formulations. It is clear that there is little difference in therapeutic

Fig. 1 Effect of formulations containing different concentrations of guanethidine and adrenaline on the intraocular pressure of rabbits

efficiency between any of these formulations, the weaker solutions having an entirely satisfactory onset, intensity, and duration of activity in comparison with the stronger solutions. There is, however, some indication that the intensity of effect elicited by the weakest formulation containing 0.5% guanethidine and 0.1% adrenaline is less than the others. It was decided therefore to test the efficiency of guanethidine 1.0% and adrenaline 0.2% in patients and compare it to that of one of the commonly used combination strengths.

Clinical trials

Two different formulations were used, differing in their concentrations of active drugs. One contained 1.0% guanethidine and 0.2% adrenaline, the other 3.0% and 0.5%. Both formulations were prepared at our request by Smith and Nephew Pharmaceuticals Ltd as experimental solutions packed in plain 10 ml plastic bottles with an integral dropper. In each case the vehicle was the ordinary vehicle used for their marketed drops under the trade name Ganda.

The trial was carried out on 2 successive Saturdays on a group of 20 patients who had been under treatment for simple open-angle glaucoma for at least 2 years. Ten of the patients were male, 10 female, and their ages ranged from 55 to 81. Their normal treatment varied but all were placed on pilocarpine alone for 1 week before the trial and for the week between the 2 experimental Saturdays. They continued to use the appropriate strength of

Table 1 Drug composition in the experimental formulation

Formulation	A	B	C	D
% w/v Guanethidine sulphate	5.0	2.5	1.0	0.5
% w/v Adrenaline hydrogen tartrate	1.0	0.5	0.2	0.1

Fig. 2 Response of patients to 2 formulations of guanethidine and adrenaline

pilocarpine eye drops until 6 pm on the Friday evenings before the 2 days of the trial, when all therapy was suspended. Their uncontrolled IOP, as measured on the days of the trial with a Goldmann applanation tonometer, ranged from 16 to 48 mmHg, with the majority being in the upper 20s. They were divided randomly into 2 groups of 10.

On the days of the trial the IOP of each patient was taken by one of us (DEPJ), and each patient then received in both eyes drops of one or other of the experimental formulations. Neither the patients nor DEPJ knew which patients received which drops, and the order in which the patients were treated was randomised. Their IOPs were measured after 1, 2, 3, 4½, 6, and 8 hours and the results recorded. At the time of each reading the state of the patient's eyes was noted and his subjective opinion on any effect was also recorded. The formulations received by the patients were different on each of the 2 days of the trial so that a normal, blind, cross-over trial was performed.

The results were expressed for each eye as a percentage reduction of the initial reading; each eye therefore acted as its own control. A full description of the rationale behind this treatment has been given previously (Jones *et al.*, 1977). Inspection of the data for each week indicated no difference in the response of the 2 groups, so that the results from both days were pooled. Each experimental period therefore is the mean of 40 readings. These results are shown in Fig. 2.

The data show clearly that with these patients

the low-concentration drops are as effective in terms of onset of activity and intensity of action as the high-concentration drops. It may be that the duration of activity is slightly less, though this is not yet clear, and the clinical significance of any small difference in duration is likely to be negligible. The side effects noted were hyperaemia and pupil dilatation. In the first week 1 patient on the low-dosage drops had pupil dilatation while 5 on the high-dosage drops experienced these effects. Of these 5, 4 also had pupil dilatation during the second week, and these were joined by 4 others now receiving the high dosage, including the patient who responded to the low dosage in week 1. The incidence of hyperaemia was low in week 1, only 5 patients having a noticeable response. However, in week 2, 10 patients had a significant hyperaemia, the response being apparently unconnected with the dosage received.

It should be remembered that all these patients were being subjected to the trauma of IOP readings on seven occasions during the day, which might also have played a part in this observed response. No significant subjective changes were volunteered by the patients except that, in week 1, two patients on the low dosage complained of a transient headache. As they did not complain in week 2 when receiving the high dose these side effects can probably be ignored.

As we have found in all our trials using adrenaline the response is in two stages, there being an initial fall followed by a rise and then a second fall in IOP. These 2 effects are probably due to the 2 reported actions of adrenaline, namely, in reducing production of aqueous humour and in stimulating outflow, having different time responses. The transient increase in pressure after 2 hours may be the consequence of pupillary dilatation in some persons. A similar effect has been reported by Hoyng and Dake (1979).

The significant findings from these experiments is that, as measured by the response of this group of patients, the drops containing the low concentration of both guanethidine and adrenaline are as effective in reducing IOP as the high-concentration drops. It should be possible, therefore, to put patients who respond to this treatment on to a reduced dosage regimen, which should be beneficial to them in terms of their ability over a long period to tolerate the treatment.

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