

# Guanethidine and adrenaline used in combination in chronic simple glaucoma

J. A. ROTH

*Department of Experimental Ophthalmology, Institute of Ophthalmology, University of London*

Guanethidine is effective in the control of intraocular pressure (IOP) in some patients with chronic simple glaucoma. Stepanik (1961) and Kutschera (1961) found it better than pilocarpine, whilst Kùchle (1961) found it equally effective. Guanethidine reduces aqueous formation (Oosterhuis, 1962; Bonomi and di Comite, 1967; Anselmi, Bron, and Maurice, 1968; Quintana, Menezo, and Menezo, 1969) and improves aqueous outflow (Kutschera, 1961; Stepanik, 1961).

Adrenaline has been used for many years in the control of IOP in chronic simple glaucoma. It produces a significant fall in IOP by reducing aqueous production and improving aqueous outflow (Weekers, Prijot, and Gustin, 1954; Sears and Bárány, 1960; Becker, Pettit, and Gay, 1961; Eakins, 1963; Langham, 1965; Criswick and Drance, 1966; Kronfeld, 1967).

Guanethidine is a postganglionic blocking agent. It has been shown to produce supersensitization of tissues to catecholamines (Boura and Green, 1962; Green and Robson, 1965; Hendley and Eakins, 1965; Sneddon and Turner, 1967). Eventually it causes depletion of catecholamines from tissues and prevents their uptake into sympathetic nerve endings. The action of adrenaline in reducing aqueous production and improving outflow is enhanced by the supersensitizing action of guanethidine. Bron (1969) postulated that the ciliary body responds to the  $\beta$  action of catecholamines by decreasing aqueous production. The drugs therefore act as synergists, so that it is reasonable to expect an enhanced action when both are used together.

In the following work both drugs were used in combination in an attempt to control IOP in a group of patients who were not responding adequately to other forms of treatment.

A report by Paterson and Paterson (1972) on unpublished work by Crombie, who used guanethidine 5 per cent. in combination with adrenaline 1 per cent. (Eppy), suggested that the combination was more effective in controlling tensions than adrenaline alone.

## Methods

Patients were selected from the Glaucoma Clinic at the Institute of Ophthalmology. The group consisted entirely of patients who were referred to this clinic because their IOP was difficult to control.

Guanethidine was used as the commercially prepared Ismelin 5 per cent. drops. Adrenaline was used as neutral adrenaline in strengths of either 0.25 per cent. or 0.5 per cent. instead of the more usual Eppy 1 per cent. solution. Neutral adrenaline was formulated by the Pharmacy Department, Moorfields Eye Hospital. The solution is buffered to pH 7.2 and differs from Eppy in several constituents (Baker, 1972).

The patient was initially phased for a whole morning from 9.30 a.m. on the treatment used on referral. Phasing involved hourly measurements of IOP using the Goldmann applanation tonometer. At a subsequent visit one drop of guanethidine was instilled into one eye in addition to the original

treatment after the tension had been measured on arrival. If no rise in tension occurred, guanethidine 5 per cent. was added to the original treatment for use by the patient himself.

The patient was then phased on full treatment at a later date. Other treatments were subsequently reduced in strength or frequency or eliminated at later visits.

Some patients were already receiving either adrenaline or guanethidine before the trial. In these cases the protocol was altered appropriately. Thus at the end of the trial all patients were receiving guanethidine drops 5 per cent. twice daily and neutral adrenaline drops 0.25 per cent. as a minimum treatment.

The number of patients in the trial was 29, and the number of eyes involved was 49. Where only one eye from one patient was included in the trial the other presented no clinical problem.

The diagnostic classification of the eyes included are shown in the Table.

**Table** *Diagnostic classification of eyes in the trial*

<i>Diagnosis</i>	<i>No. of eyes</i>
Chronic simple glaucoma	33 of which one had had a drainage operation
Closed-angle glaucoma with drainage operations	5
Mixed glaucoma	2
Other (including secondary, glaucoma capsulare, and low tension glaucoma)	9

## Results

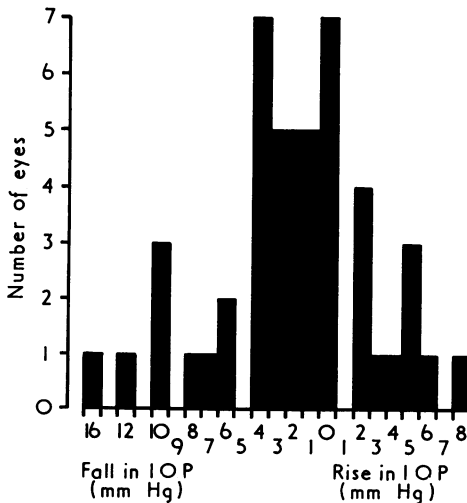
The 9.30 a.m. tension at the first visit (*i.e.* on the treatment used at the time of referral) was compared with the 9.30 a.m. tension at the next visit when both guanethidine and adrenaline drops had been added to the treatment.

Mean tension at 9.30 on original treatment: 22.22 mm. Hg  $\pm$  4.08

Mean tension on guanethidine and adrenaline ( $\pm$  other treatment): 20.18 mm. Hg  $\pm$  4.71

$t = 2.273$      $0.05 > P > 0$

See Figure for distribution of individual tensions.



**FIGURE** *Distribution of responses of tension in individual eyes*

Two patients (4 eyes) were unable to continue the treatment because of side-effects. One of them developed ptosis and conjunctival hyperaemia which recovered when guanethidine was stopped, and one developed headache and gross reactive hyperaemia which ceased when adrenaline was withdrawn.

Seven patients (9 eyes) can be regarded as failures because it was decided after the trial that operation was necessary, medical treatment having failed to provide consistent satisfactorily low IOPs.

### Follow-up

Patients involved in the trial were followed up in the Glaucoma Clinic for a minimum 6 months. The mean follow-up period was 11 months.

Of the 36 eyes in 20 patients, which remained in the trial, two patients (2 eyes) proved unable to cope with self-administration of drops and one patient (2 eyes) no longer required treatment because a few months after an unintentional lapse in medication no further high tensions were recorded.

Of the remaining 32 eyes (17 patients), seven were taken off guanethidine and adrenaline after a few weeks because tensions recorded at midday were high.

Thus, over a mean period of 11 months, the total number of failures due to any cause was 24 eyes, and the final number of eyes still on treatment was 25.

### Discussion

These patients were selected for the trial because their tensions were poorly controlled or because they were losing visual field in spite of apparently satisfactory tensions. They do not represent a typical group of patients with glaucoma.

It is difficult to decide what constitutes control of IOP, but comparing IOP levels at a certain time of day is one way in which the results of the trial can be subjected to statistical analysis; on this basis a significance level of 5 per cent. is an indication at least that the drug combination was effective. The criteria of improvement in this experiment relate only to 9.30 a.m. IOPs and not to other factors such as control of field loss. It is evident that 9.30 a.m. tensions do not give an indication of the degree of control over a 24-hour period. In some of these patients it was midday tension that was high while the early readings were satisfactory.

Altogether thirteen of 49 eyes were definitely not benefited by guanethidine and adrenaline, four because of side-effects and nine because the intraocular pressure was not considered to be adequately controlled by the surgeons in charge of the patients. This represents an initial failure rate of 26.5 per cent. and an improvement rate of 73.5 per cent.

Over the follow-up period a further 11 eyes were withdrawn from the trial for the reasons stated earlier. Thus the total number of failures was 24 eyes which represents a success rate of 50 per cent.

Ptosis is not a frequent side-effect of guanethidine. Castrén and Pohjola (1962) and Trzcńska-Dabrowska and Majewska (1970) found no ptosis. Kutschera (1961), however, reported its occurrence. Merté and Toppel (1960) reported conjunctival irritation as a side-effect but did not notice any ptosis. Brow ache was mentioned as a side-effect of adrenaline by Drance (1962).

If it is considered that, as a result of adding guanethidine and adrenaline to the treatment (or substituting it for other treatment), 50 per cent. of these eyes did not require operation, then the result of the trial was satisfactory. It should be remembered that all eyes involved

in the trial had already proved difficult to control and would probably have required surgery had they not received guanethidine and adrenaline.

Although no detailed clinical studies have been done on this subject it may be possible to use weaker solutions of adrenaline than 0.25 per cent. in combination with guanethidine to obtain an adequate level of control of IOP.

### Summary

Guanethidine 5 per cent. and adrenaline 0.25 per cent. or 0.5 per cent. drops were used together in an attempt to provide adequate control of intraocular pressure in eyes which had proved difficult to manage on other medical treatment.

The results of the trial suggest that the combination was effective by virtue of the synergistic actions of guanethidine and adrenaline.

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