

Drug therapy of glaucoma

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Of the groups of drugs used in the treatment of simple glaucoma, those acting at adrenergic sites constitute an important and interesting series. Adrenaline has proved its usefulness over the years, having been first introduced by Köllner in 1918, although it did not find its present established place until the last two decades, when the use of the gonioscope allowed the differentiation between open-angle and closed-angle glaucoma (Weekers, Prijot and Gustin, 1954; Becker and Ley, 1958; Garner, Johnstone, Ballintine, and Carroll, 1959; Becker, Pettit, and Gay, 1961). Its exact mode of action has posed many questions and stimulated much pharmacological research.

The present theory of adrenergic receptors was first proposed by Ahlquist (1948), who found that the effects of sympathomimetics could be classified in two groups, and suggested that the different effects could be explained on the basis of two forms of receptor, designated as α - and β -receptors. The α -receptors are on the whole responsible for the contractile or stimulant actions of adrenaline, *e.g.* the contraction of the dilator pupillae and other smooth muscle including that of the blood vessels. On the other hand, actions at the β -receptors cause relaxant effects as in the uterus and bronchioles. The stimulatory effect of adrenaline on the heart is one exception to this rule, since the activation of β -receptors causes an increase in cardiac activity.

It is generally agreed that adrenaline exerts its ocular hypotensive action by affecting both the aqueous inflow and outflow mechanisms. It has been shown to reduce the secretion of aqueous humour (Goldmann, 1951; Becker and Ley, 1958) and to increase the facility of outflow of aqueous humour from the anterior chamber (Garner and others, 1959; Becker and others, 1961) by a mechanism or mechanisms not yet completely understood.

Among the better known sympathomimetic drugs are NORADRENALINE (the mediator responsible for transmission at adrenergic nerve endings), PHENYLEPHRINE, ADRENALINE, and ISOPRENALINE.

Noradrenaline and phenylephrine are much more effective on α -receptors than on β -receptors, adrenaline has a dual action affecting both α - and β -receptors, whilst isoprenaline has an almost specific action on β -receptors.

The relative actions of noradrenaline, adrenaline, and isoprenaline on the intraocular pressure in normal eyes have been demonstrated by Weekers, Collignon-Brach, and Grieten (1966). They showed clearly that, in the concentrations used, the β -receptor agonist isoprenaline had the greatest ocular hypotensive action. This hypotensive action was confirmed by Ross and Drance (1970). Unfortunately, both groups of workers recorded a considerable tachycardia with topical application of isoprenaline, which precluded its use clinically as a therapeutic measure. In recent years it has been possible to achieve some degree of selectivity among β -receptor agonists (Lands and Brown, 1964; Lands, Arnold, McAuliff, Luduena, and Brown, 1967; Brittain, Farmer, Jack, Martin,

and Simpson, 1968; Cullum, Farmer, Jack, and Levy, 1969) such that some agonists can affect some structures with β -receptors without causing an associated tachycardia.

SALBUTAMOL

One such β -receptor agonist is salbutamol [(\pm) -2-t-butylamino-1-(4-hydroxy-3-hydroxy-methyl) phenylethanol; AH 3365; "Ventolin"], and after a pilot study with this drug in normal and glaucomatous subjects which demonstrated a significant ocular hypotensive effect, a further study was undertaken in patients with ocular hypertension (Paterson and Paterson, 1971) to compare its efficiency with that of adrenaline.

Method

The patients selected for trial were nine male and six female with an age range of 46 to 74. The patients were admitted to hospital for the trial. Intraocular pressures were measured with the Goldmann applanation tonometer, and each reading was repeated three times, or until three successive readings were consistent to within 1 mm.Hg of each other. Pressures were measured at 10 a.m. on the day of admission, at hourly intervals until 2 p.m. and then 2-hrly until 10 p.m. On subsequent days the hourly readings were begun at 8 a.m. Pulse rate and pupil diameter were recorded at the same times. After the 10 a.m. readings on the second day in hospital one drop of 4 per cent. salbutamol or of 1 per cent. (-)-adrenaline ("Eppy"; Smith and Nephew) was instilled into the conjunctival sac of one eye, the other eye serving as a control. A double-blind design was used throughout. In some instances, 48 hours after one drug had been instilled, a second instillation of the other drug under investigation was applied into the same eye.

The salbutamol eye drops formulation used (prepared by Allen and Hanburys, Ltd.—Pharmaceutical Division) was as follows:

Salbutamol sulphate 4.8 per cent. w/v
Benzalkonium chloride B.P.C. 0.01 per cent. w/v
Distilled water, oxygen free to 100.

This solution of salbutamol sulphate was equivalent in concentration to 4 per cent. salbutamol base.

Results

One single instillation of one drop of 4 per cent. salbutamol lowered the intraocular pressure in all patients studied, but the extent of the fall varied with the height of the original pressure and from patient to patient. The fall was evident 2 hours after administration and reached a peak 8 to 10 hours later. It was maintained for 36 hours, but the pressure had returned to its original level 48 hours later. The initial rise in pressure, shown by Ross and Drance (1970) after instillation of isoprenaline in some subjects in their investigation, was not evident with salbutamol. During this time there was no statistically significant variation in pulse rate and no change in pupil diameter.

Fig. 1 (overleaf) shows the result with salbutamol in a male patient aged 67 years—a fairly typical result. The fall in intraocular pressure after one drop of 1 per cent. adrenaline in a female patient aged 60 years was similar in extent and duration to that seen with salbutamol as is shown in Fig. 2 (overleaf). A fleeting mydriasis of 1 to 2 mm. was seen 2 hours after instillation of the adrenaline, but there was no detectable alteration in heart rate.

Fig. 3 (overleaf) shows the results in a patient, a man aged 64, who received salbutamol on three successive days after initial control measurements. The results are represented as a range in the diurnal variations of intraocular pressure on the control day—C and the three days of treatment to both eyes. The range of pressure on the second day of treatment was at lower limits than on the first day, although on the third day there seemed to be some recovery in both eyes.

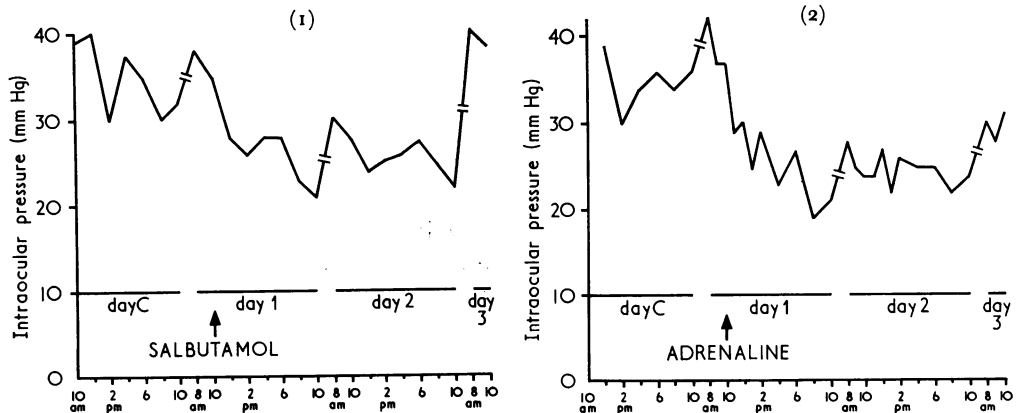


FIG. 1 Male aged 67 yrs. Effect of instillation of one drop of 4 per cent. salbutamol on diurnal variations in intraocular pressure. Day C represents control measurements in the absence of any drug. Days 1, 2, and 3 represent the day of instillation and subsequent days

FIG. 2 Female aged 60 yrs. Effect of instillation of one drop of 1 per cent. adrenaline (otherwise as in Fig. 1)

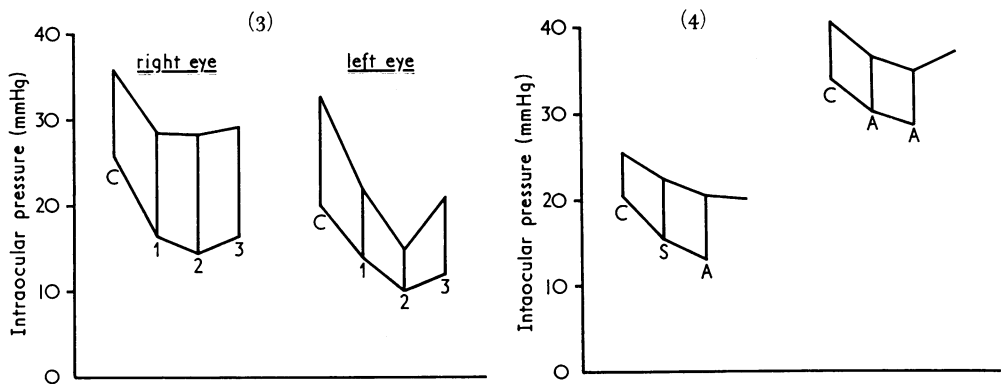


FIG. 3 Male patient aged 64 yrs. Range in diurnal variations in intraocular pressure measurements before and during 3 days' treatment with salbutamol. C represents range in pressure measurements taken between 12 noon and 10 p.m. on control day. 1, 2, and 3 represent the ranges between the same times on days 1, 2, and 3 of treatment with one drop of 4 per cent. salbutamol, instilled at 10 a.m. each day

FIG. 4 Range in diurnal variations in intraocular pressure measurements. C represents the range in pressure measurements taken between 12 noon and 10 p.m. on control day; S represents range during these times on the day on which 1 drop of 1 per cent. salbutamol had been instilled into the conjunctival sac at 10 a.m.; A represents the range in intraocular pressure between 12 noon and 10 p.m. on the day on which 1 drop of 1 per cent. adrenaline had been instilled into the conjunctival sac at 10 a.m. Each range is the mean of measurements in four patients

Fig. 4 shows a comparison of the range of diurnal variations between 4 per cent. salbutamol and adrenaline, each range being the mean of measurements on four patients. Again C is the control day, S is salbutamol, and A is adrenaline. On the basis of the concentrations used in this study, the fall in intraocular pressure induced by 4 per cent. salbutamol was equivalent to 1 per cent. (-)-adrenaline. So that, on the basis of this short-term experiment, salbutamol seemed a promising alternative to adrenaline in the treatment of simple glaucoma, and these four patients, together with fifteen other out-patients, were instructed to instill the drug twice daily. Unfortunately, however, over half of them developed an intolerable hyperaemia with associated irritation which led to rejection of treatment. Outflow studies were made on seven patients at the end of 1 and 2 weeks'

treatment, but little or no change was demonstrated in the value of the coefficient of facility. In addition, about one patient in five developed tachyphylaxis to salbutamol therapy after as short a period as 2 weeks. A further trial with the drug, possibly in a different formulation and at several concentrations, will be necessary to investigate this tachyphylaxis and the side-effects.

Little or no effect on the outflow mechanism was demonstrated by Ross and Drance investigating the action of isoprenaline. Certainly there is no evidence for an increase in outflow; in fact the reverse has been reported in some cases, and it is generally believed that the adrenergic β -receptor agonists exert their action on intraocular dynamics by inhibiting the inflow of aqueous humour (Bonomi, 1964; Eakins, 1963; Ross and Drance, 1970). This concept conflicts somewhat with the findings of Vale and Phillips (1970), who demonstrated a hypotensive action of the adrenergic β -receptor blocking agent propranolol administered systemically, although they suggested that this drug may yet have a direct ionic action on the ciliary body inhibiting the secretion of aqueous humour.

THYMOXAMINE

Marmion (1969) reported that thymoxamine, a selective α -receptor blocking agent, reduced the intraocular pressure of normal subjects; it was thought worthwhile investigating its action in simple glaucoma.

A double-blind pilot study was initiated on seven subjects, four females and five males suffering from the disease, with ages ranging from 48 to 68 years, and the method used was similar to that described for the salbutamol study. The patients were admitted for phasing, base-line pressures were recorded on the first day and either drug or placebo on the following two days. A 1 per cent. solution of thymoxamine and a similar placebo without the drug were prepared by William Warner and Co., Ltd. The result showed no significant change in pressure on the day the patients

Table *Effect of thymoxamine on the coefficient of outflow facility (average values for twelve eyes)*

Base-line	0.16 ± 0.01 (S.E.)
After drug	0.10 ± 0.01 (S.E.)
After placebo	0.14 ± 0.01 (S.E.)

received thymoxamine as compared with the base-line pressures on the control day. In case a chronic effect had been missed, the patients were discharged and instructed to return at 3.30 p.m. in one week's time for tonography on either the drug or placebo, and then after a further week for final measurements at the same time. No significant pressure changes occurred. There was, however, a reduction in the outflow facility, as is shown in the Table.

It is generally accepted that outflow facility is under adrenergic receptor control by a mechanism or mechanisms not yet clearly defined. A slight miosis occurred, but no useful hypotensive action was demonstrated.

GUANETHIDINE

The drug guanethidine is a sympathetic post-ganglionic blocking agent acting by preventing the release of noradrenaline from the nerve stores in response to nervous stimulation. It causes an initial depletion of noradrenaline from the nerve fibre, blocks the neuronal release of the transmitter, and prevents re-uptake of catechol amines into neuronal stores. Keates, Krishna, and Leopold (1960) first reported its potential use in the treatment of simple glaucoma. It may be regarded as a pharmacological sympathetic denervator of the eye, and it produces a ptosis and miosis similar to that seen in Horner's syndrome.

The effects of 1, 2, 3, 4, and 5 per cent. solutions of guanethidine were examined in nine patients (eighteen eyes) with simple glaucoma. After base-line measurements the subjects were phased for 24 hours after an instillation of the drug at 10 a.m. They were

then discharged with instructions to use the drug twice daily. The average maximum fall in intraocular pressure within 8 hours was 9.7 ± 1.1 mm.Hg with the 3 per cent. solution and 7.3 ± 1.3 mm.Hg with the 5 per cent. solution. This was reduced to $+1.0 \pm 1.0$ mm.Hg and -3.2 ± 1.4 mm.Hg with the 3 and 5 per cent. solutions respectively at the end of one month (Fig. 5). The increase in facility of outflow 4 hours after instillation was confirmed. Fig. 6 shows this effect in increasing concentrations of the drug in one patient in this group.

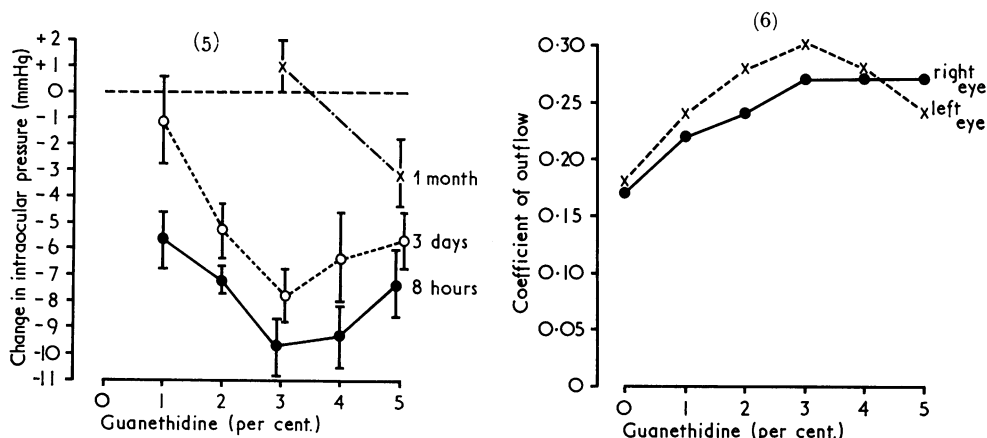


FIG. 5 Change in intraocular pressure caused by administration twice daily of different concentrations of guanethidine in nine patients (eighteen eyes) with simple glaucoma. Bars show standard errors of the means

FIG. 6 Changes in intraocular pressure caused by increasing concentrations of guanethidine in one patient out of the group shown in Fig. 5

These results show that the application of guanethidine to the conjunctival sac produces an initial effective fall in intraocular pressure which is poorly maintained, so that at the end of 1 month little hypotensive effect remains. The initial fall has been shown to be due to an increase in facility of outflow (Stepanik, 1961; Kutschera, 1961; Hendley and Eakins, 1965), followed after approximately 12 hours by an inhibition of secretion of aqueous from the ciliary body (Bonomi and Comite, 1967). It is probable that this initial fall in pressure results from the action of the sympathetic mediator which is released when the drug is applied.

A similar initial hypotensive effect, again not maintained, was shown by us (unpublished) with bethanidine, an adrenergic neurone blocking drug like guanethidine, in both normal and glaucomatous eyes.

Tissues treated with guanethidine become sensitized to the natural mediator and similar pharmacological substances so the idea of combining guanethidine with adrenaline was conceived. This idea was discussed at the Gilston Glaucoma Symposium when Drance (1966) reported an initial lack of success. However, Langham (1971) using protryptiline as the potentiating agent, and Crombie (unpublished) using guanethidine, reported more promising results, so that a trial of this combination was started in our department, and to date thirteen patients (a total of 23 eyes) are being treated. They include eleven males and two females with ages ranging from 40 to 72 years. They are each instilling both guanethidine 5 per cent. ("Ismelin": CIBA) and adrenaline 1 per cent. ("Eppy": Smith and Nephew) twice daily, on rising and before retiring. The longest duration of this

treatment in any one patient has been 17 months and the average reductions in pressure after 1, 3, 6, 9, and 12 months are shown in Fig. 7.

These results compare very favourably with the long-term results obtained with adrenaline alone. Becker and Ley (1958) reported, with 1 per cent. adrenaline alone, a fall in intraocular pressure of -4.8 mm.Hg after 3 months and of -4.7 mm.Hg after 6 months in their series. The results compare even more favourably with the effect of guanethidine alone. At the end of 1 month's treatment, the fall in pressure was 10 mm. more when the drugs were combined than with guanethidine alone, as is shown in Fig. 8.

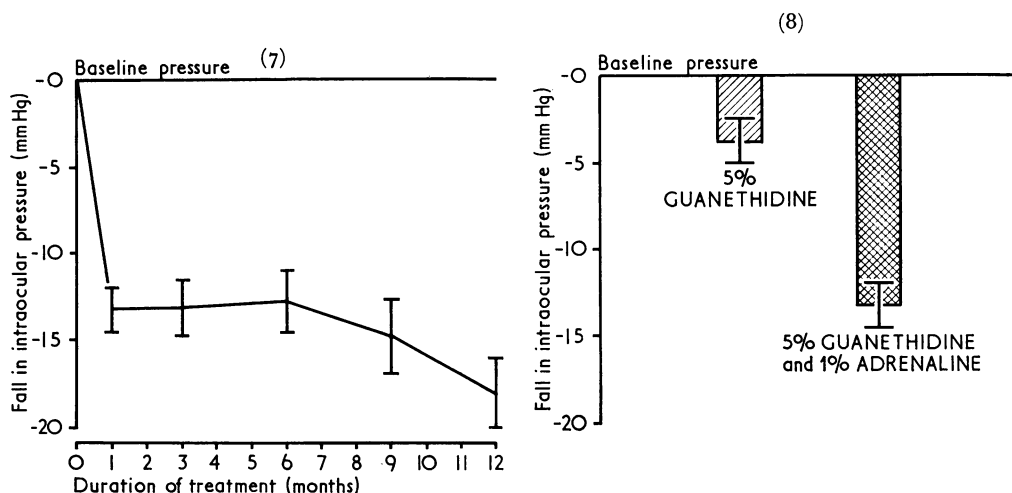


FIG. 7 Fall in intraocular pressure (from initial base-line pressure reading) caused by combined treatment with 5 per cent. guanethidine and 1 per cent. (-) adrenaline in thirteen patients with simple glaucoma. Bars indicate standard errors of the means

FIG. 8 Comparison of treatment of glaucomatous eyes with 5 per cent. guanethidine alone and in combination with 1 per cent. adrenaline after 1 month's treatment. Bars indicate standard errors of the means

Certain of the sympathomimetic drugs are therefore extremely useful in the treatment of simple glaucoma. The miotic action of parasympathomimetic drugs, together with their effect on accommodation, especially in the younger age group, enhances the popularity of adrenaline either alone or in combination with a potentiating agent.

However, adrenaline is not without its side-effects, which include redness, brow ache, occasional blurring of vision from the mydriasis, a maculopathy in aphakic subjects (Kolker and Becker, 1968), and the deposition of pigment in the conjunctivae. It has been suggested (Weekers and others, 1966) that it may cause a deterioration in the field of vision from vasoconstriction of the deeper choroidal vessels, but this is difficult to prove. One must therefore be wary of these drawbacks when treating patients with these agents.

The importance of the β -receptor sites in the eye has been confirmed with salbutamol. The presence of a physiological α -adrenergic drive on the outflow mechanism is suggested by the reduction in the coefficient of outflow after thymoxamine.

These observations, together with the knowledge that guanethidine causes an inhibition of aqueous secretion which can be restored to normal by the addition of the α -agonist noradrenaline, are leading to the emergence of a picture of the part played by adrenergic receptors in the control of intraocular dynamics. The ciliary body is probably under dual control, with α -receptors stimulating the formation of aqueous, and β -receptors inhibiting

it, and the outflow mechanism is under α -adrenergic influence. Further studies will be needed to confirm these ideas. From the clinical point of view, adrenaline, either alone or in combination with an adrenergic potentiating agent, is still the most useful drug in the group.

We should like to acknowledge assistance by members of the Glaucoma Unit, Moorfields Eye Hospital, High Holborn, and the Frost Trust for a grant in support of the work.

COMMENTARY

ADRENALINE AND GUANETHIDINE COMBINATIONS IN GLAUCOMA

Professor Drance commented that the use of a combination of adrenaline and guanethidine might be of great importance in reducing the side-effects due to adrenaline alone. He noted that the results from his own series were different from those reported by Dr. Paterson and Mr. Miller. In Professor Drance's study the patients had been pretreated with guanethidine only for 3 days and were then studied with the instillation of a single drop of adrenaline. This was a single-dose response study, whereas in Dr. Paterson's study the guanethidine was used for prolonged periods so that the sympathetic denervation had occurred which was obviously not complete in his own shorter studies.

Punctate epitheliopathy did occur on occasion with guanethidine therapy but was much more common when the 10 per cent. solution was used rather than the 5 per cent. or even 2 per cent. solution now in common use. The epitheliopathy always disappears if the drugs are discontinued.

Management of infantile glaucoma

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The objectives in the continuing management of children with congenital glaucoma are twofold: namely, evaluation of control of the glaucoma and prevention of amblyopia; they are of equal importance.

EVALUATION OF CONTROL OF GLAUCOMA

Anaesthesia

To obtain the data needed to evaluate the control of glaucoma in infants it is necessary to make regular examinations under general anaesthesia. It had been our practice to use ether anaesthesia for this purpose, the advantages being that it appears to have a reasonably consistent effect on the intraocular pressure and that it is safe in infants. However, repeated inhalation anaesthesia in children does have important disadvantages, not the least of which are the psychological effects. Recently we have been using ketamine hydrochloride (Ketalar: Parke-Davies) for the routine examination of children with congenital glaucoma, and we have found it to have a number of advantages over ether anaesthesia. Ketamine hydrochloride is a potent analgesic agent. When given by intra-