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Ocular hypotensive effect of atenolol (Tenormin, I.C.I.)
A new beta-adrenergic blocker

MARGARET J. ELLIOT, PATRICIA M. CULLEN, AND CALBERT I. PHILLIPS
From the Department of Ophthalmology, University of Edinburgh, and the Princess Alexandra Eye Pavilion, Royal Infirmary, Edinburgh

Ahlquist (1948) classified adrenergic activity into alpha and beta groups. The former group is concerned mainly with contraction of smooth muscle, including vasoconstriction in some areas. Recently beta-adrenergic effects have been further subdivided into β_1 and β_2 (Lands, Arnold, McAuliff, Luduena, and Brown, 1967), for example

β_1: increased cardiac contractility and lipolysis

β_2: increased bronchodilation and vasodilation in skeletal muscles.

Alpha-adrenergic receptors can be selectively blocked, for example, by phentolamine. Beta receptors can also be blocked by several compounds, for example, propranolol, practolol, and oxprenolol (which have different degrees of selectivity for β_1 and β_2 receptors).

It is now well documented that beta-adrenergic blocking drugs reduce ocular tension after systemic (intravenous and oral) and topical administration in humans (Phillips, Howitt, and Rowlands, 1967; Coté and Drance, 1968; Bucci, Missiroli, Pecori Giraldi, and Virno, 1968; Weinstein, 1969; Vale and Phillips, 1970; Bietti, 1972; Vale, Gibbs, and Phillips, 1972; Öhrström, 1973; Pandolfi and Öhrström, 1974). The mode of action is unknown; possibly the effect is mediated by a membrane-stabilizing effect (local anaesthetic or quinidine-like effect) or intrinsic sympathomimetic activity rather than, or in addition to, the drugs' beta-adrenergic blocking properties.

Atenolol (Tenormin, I.C.I. 66082) is a new beta-adrenergic blocker which is unique in lacking both sympathomimetic and membrane activity and in being cardio-selective (Barrett, Carter, Fitzgerald, Hull, and le Count, 1973; Imperial Chemical Industries, 'Data for Clinical Investigators', 1974) so that a study of its effects is of considerable theoretical as well as practical interest.

These properties may be summarized as follows:

Drug	*Beta adrenergic blockade*	*Membrane-stabilizing activity*	*Intrinsic sympathomimetic activity*
Propranolol	+	+	−
Practolol	+	−	+
Atenolol	+	−	−

The structural formulae are shown below.

Address for reprints: Dr Margaret J. Elliot, The Eye Pavilion, Chalmers Street, Edinburgh EH3 9HA

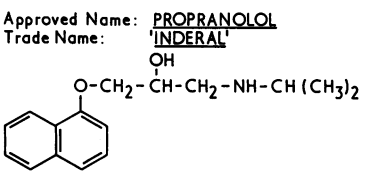
Aims of present study

An assessment of the effect of a single oral 50 mg tablet of atenolol on ocular tension was undertaken on five patients, and compared with the effect of an identical-seeming tablet in a carefully controlled standardized double-blind trial on the same five patients.

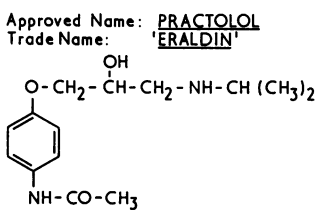
Patients

The five patients were selected as shown in the Table (opposite).

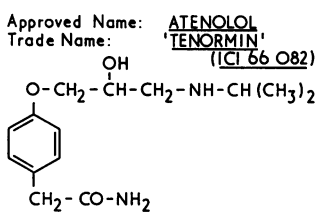
Only Patient 3 had ever had adrenaline drops (eppy) and this had been withdrawn 6 weeks before the investigation.



1-isopropylamino-3-(1-naphthyloxy) propan-2-ol hydrochloride



4 (2-hydroxy-3-isopropylamino-propoxy) acetanilide



4-(2'hydroxy-3-isopropylamino-propoxy) phenyl acetamide

Table *Details of five patients studied*

Case no.	*Sex and age (yrs)*	*Diagnosis*	*Treatment in tested eye*
1	Female (69)	Open-angle glaucoma	Pilocarpine drops 1 per cent four times daily
2	Female (60)	Cupped discs (no field loss or raised pressure)	Nil
3	Male (66)	Open-angle glaucoma	Pilocarpine drops 4 per cent four times daily
4	Male (63)	Chronic closed-angle glaucoma	Nil (Bilateral sector iridectomies three months before series)
5	Male (64)	Open-angle glaucoma	Pilocarpine drops 0·5 per cent three times daily and 1 per cent at night

All patients were less than 70 years and had:

no signs or symptoms of cardiovascular disease (including no undue exertional dyspnoea, no orthopnoea, no evidence of congestive heart failure, no cardiac irregularity or bradycardia <60 per minute, no hypertension >200/110)

no evidence of bronchospasm (no history of wheeze and no expiratory rhonchi)

no evidence of renal failure, that is, blood urea <40 mg per cent.

No patients were being treated for diabetes mellitus.

Methods

STANDARDIZATION

All subjects attended as outpatients from 9.0 am to 4.30 pm, on two days separated by one week (except for Patient 5 for whom the two days were separated by one month). Pilocarpine drops were withdrawn 48 hours before each test day. Food and fluid intake were standardized as far as practicable. All patients were asked to have not more than a half slice of toast and half a cup of tea for breakfast; during each test day, each patient had 20 ml water to take with the tablet, 100 ml coffee at 10.30 am, 100 ml milk or water with lunch (no soup), and 100 ml tea at 3.0 pm. After arrival, physical activity was minimal; reading and television viewing were allowed *ad lib*.

All tensions were measured hourly by the same observer using the same standardized applanation tonometer; a mixture of fluorescein 0.5 per cent (one part) with benoxinate 0·4 per cent (three parts) with phenylmercuric nitrate 0·002 per cent was used.

Immediately after the 9.0 am tonometry, each patient was given a tablet containing either (*a*) 50 mg atenolol or (*b*) only vehicle; the appearance and taste were identical and neither patients nor observers knew by whom the drug was being taken. After tonometry, blood pressure and pulse rate were measured. All except Patient 2 then had 3 ml venous blood withdrawn for estimation of blood levels of atenolol.

RANDOMIZATION

(*a*) *Tablets* Patients 2 and 4 had drug on day 1 and vehicle on day 2, while Patients 1, 3, and 5 had vehicle on day 1 and drug on day 2; this allotment was chosen at random.

(*b*) *Eye* Tension was measured in one eye only, the side being randomly selected by the toss of a coin in four patients (one right; three left); in Patient 3 the right eye was chosen because the left had had a drainage operation.

Results

In all five patients, there was a fall in tension on the atenolol-day. See Fig. 1(*i*) to (*v*). The maximum

FIG. 1 (*Patients 1 to 5*) *Applanation tonometry. In all patients, atenolol has produced a fall in ocular tension; the higher the initial tension, the greater the fall*

observed falls in tension during the 7 hours expressed as percentages of initial tension, were:

Patient	*Atenolol per cent*	*Vehicle per cent*
1	66	9
2	26	6
3	59	35
4	42	0
5	33	4

In all cases, the tension after administration of atenolol began to fall by 1 hour, and maximum response occurred at 2 to 5 hours. Although in all, except no. 2, tension was rising at 7 hours, in none had it attained its initial value.

After atenolol, whatever the initial tension or percentage fall, without exception a fall to <20 mm Hg for a minimum of 4 hours occurred and in no case was it greater than 20 mm Hg at 7 hours. After administration of vehicle, in all patients except no. 2, pressure was >20 mm Hg at 7 hours.

Whole blood samples were analysed for atenolol in four of the five patients. The peak blood levels occurred 3 to 4 hours after oral administration, that is, 1 to 2 hours before the time of the maximum fall in ocular tension.

Patient 1 (Fig. 1(*i*)). The most dramatic response of all.

Patient 2 (Fig. 1(*ii*)). The minimum response, presumably because the ocular tension is not raised. However, the fall was 26 per cent on atenolol day compared with the initial tension; on vehicle day the fall was 6 per cent.

Patient 3 (Fig. 1(*iii*)). Unfortunately the initial tensions were very different on the two days, which shows the value of randomization. Despite the lower initial pressure on drug-day the absolute fall in pressure was greater than on vehicle-day.

Patient 4 (Fig. 1(*iv*)). Even in chronic closed-angle glaucoma, an obvious fall in pressure has occurred.

Patient 5 (Fig. 1 (*v*)). A good response, the initial pressure not being very high.

The average general effect of atenolol expressed as a mean percentage change in pressure is convincingly demonstrated in Fig. 2.

It is unlikely that pure chance is an explanation for the qualitative effect of atenolol; the odds against that are 32 to 1, that is, $0{\cdot}01 < P < 0{\cdot}05$ (sign test).

SIDE-EFFECTS

Blood pressure remained essentially the same throughout both days in all patients. Pulse rate fell by a few beats per minute early on both days in all patients. None of the patients noticed any subjective effects. However, it should be noted that patients who might be at risk from untoward reactions were excluded (see 'Patients' above).

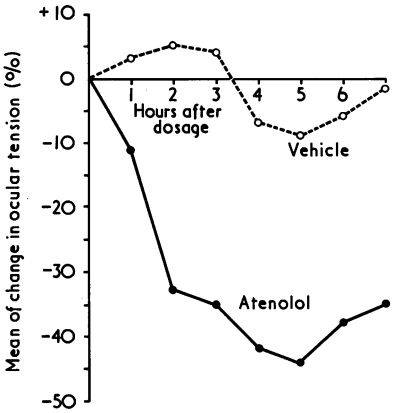


FIG. 2 *Average fall in ocular tension expressed as percentage of initial pressure*

Discussion

Since atenolol lacks any membrane (local anaesthetic) effect and any intrinsic sympathomimetic activity, (Musini, Fabbri, Bergamaschi, Mandelli, and Shanks, 1971) the tension lowering property which we have described must be due to its beta-adrenergic blocking-characteristic—probably β_1 blocking effect, because atenolol is cardio-selective (except in high dosage). We also observed no evidence in our patients of β_2 blocking effects, that is, no bronchospasm, but they were selected to minimize that risk.

The mechanism by which a systemic β_1 *blocker* reduces ocular tension is speculative. The problem is discussed by Vale and Phillips (1973). The β_2 *stimulator*, salbutamol, also reduces tension (Paterson and Paterson, 1971, 1972), probably initially by reduced aqueous production but also later by improved facility of outflow (Langham and Diggs, 1974). However, Sears and Bárány (1960) presented evidence which they interpreted as suggesting that β-tone keeps up resistance to outflow of aqueous in albino rabbits. Isoproterenol, which stimulates both β_1 and β_2 receptors (also α receptors in high concentration) reduces ocular tension when applied topically in man (Weekers, Delmarcelle, and Gustin, 1955; Prijot, 1961; Ross and Drance, 1970; Langham, Kitazawa, and Hart, 1971) but systemic absorption causes tachycardia so that it cannot be used therapeutically; surprisingly, the effect is prevented by intravenous propranolol in rabbits (Langham, 1965; see also Langham, Simjee, and Josephs, 1973). It would be interesting to know if systemic atenolol *enhanced* the ocular hypotensive effect of isoproterenol (as well as eliminating the tachycardia).

In any attempt to produce a consistent explanation for these drugs' effect on ocular tension, it would be very important to know whether they act on production or drainage of aqueous humour or both; the possibility that there is some other mechanism such as an effect on the corneo-scleral envelope, on

non-adrenergic tension affectors or even on the central nervous system is worth considering.

Some of the apparently contradictory observations recorded about adrenergic effects on ocular tension may be explained on a basis of species differences, variations in background adrenergic activity, whether local or general anaesthetics have been used (and their particular pharmacological attributes), and whether normal or glaucomatous eyes have been studied. It is difficult however to explain why Langham and others (1973) found no effect on tension in six conscious rabbits of 5 mg/kg propranolol, whereas Vale and Phillips (1970) reported a significant fall in pressure with the same dose (smaller doses produced smaller but also significant effects), and also on conscious rabbits (male, Flemish and Dutch). Langham (1965) observed no effect on ocular tension of albino rabbits under local anaesthesia of either propranolol alone or phenoxybenzamine alone. Bill (1970) studied adrenergic effects in vervet monkeys under methohexital sodium anaesthesia but did not mention any significant effect on intraocular pressure of propranolol used incidentally in the experiments.

Stimulation of α receptors, for example, by noradrenaline is generally held to produce a fall in ocular tension (see, for example, Eakins and Ryan, 1964), but it is interesting that the α adrenergic antagonist phenoxybenzamine intravenously seems to cause a marked fall in tension (and in arterial blood pressure) for several hours (Langham and others, 1973)—although Langham (1965) observed no effect on intraocular pressure after administration of phenoxybenzamine in albino rabbits.

To explain why β_1 *blockade* and β_2 *stimulation* both seem to reduce ocular tension, we tentatively suggest that the net β_1 and β_2 effects on aqueous dynamics are opposite.

Systemic atenolol may have a place in the treatment of glaucoma. However it would be useful to have further information about its mode of action, its total duration of action, whether the tension maintains its satisfactory response to repeated dosage over a period of several weeks or months, whether it is more effective than propranolol or practolol, and whether its effect is additive to other tension-reducing agents. Appropriate investigations are planned.

In general, β blocking agents do not appear to have serious toxic effects, except for practolol which has recently been shown in a small proportion of cases to cause muco-cutaneous reactions and dry eyes, sometimes with corneal ulcers (Wright, 1974; Felix, Ive, and Dahl, 1974).

Summary

Atenolol (Tenormin or I.C.I. 66082) is a new beta-adrenergic blocking drug, unique in being cardioselective and in having no intrinsic sympathomimetic or membrane activity. In a controlled double-blind study, a single 50 mg oral dose produced a significant fall in ocular tension for about 7 hours in five patients with definite or suspected glaucoma. The average maximum fall was 35 per cent of the initial pressure; it occurred at 5 hours after oral ingestion.

Accordingly neither intrinsic sympathomimetic nor membrane activity can account for all the ocular hypotensive effect of beta blockers in humans.

The practical implications for treatment of glaucoma require longer-term investigations some of which are in progress.

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