

Comparison of ocular hypotensive effects of acetazolamide and atenolol

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SUMMARY The ocular hypotensive effect of single oral doses of (a) atenolol (50 mg), (b) acetazolamide (500 mg), (c) atenolol (50 mg) and acetazolamide (500 mg) in combination, and (d) vehicle (inert tablets) were compared in 8 patients with glaucoma. In this single-dose, double-masked trial the combination was observed as most effective in reducing ocular tension. Both the combination and atenolol performed markedly better than vehicle. That acetazolamide did not reduce ocular tension significantly more than vehicle is probably explained by relatively low initial ocular tensions. There was no evidence of interaction between atenolol and acetazolamide in this study. Acetazolamide probably remains the first-choice oral medication for glaucoma. It is cautiously suggested that beta-blocking drugs may have a future therapeutic role, but longer-term studies on larger numbers will be required to establish this.

The carbonic anhydrase inhibitors have been used in the therapy of the glaucomas for 20 years (Becker, 1954). It is accepted that their principal action is to reduce the production of aqueous humour, but their exact mode of action has not yet been established. Whatever their action, their effectivity has established them as the drugs most commonly given by mouth for glaucoma.

In recent years beta-adrenergic blocking drugs have been shown to reduce ocular tension in glaucoma patients both when administered systemically, as first reported by Phillips *et al.* (1967) and topically (Vale *et al.*, 1972; Bonomi and Steindler, 1975). Their ocular hypotensive effect is probably due to blockade of beta receptors and not to intrinsic sympathomimetic (beta) nor to a membrane-stabilising effect (Elliot *et al.*, 1975), though enhanced alpha activity is a possibility (Norton and Verstein, 1972). They may affect aqueous production and/or outflow, or conceivably have some other effector mechanism. In some other areas the beta-adrenergic receptor is thought to be linked to the enzyme adenylyl cyclase (Jenkinson, 1973).

Accordingly it would be interesting and useful to compare the ocular hypotensive effects of a carbonic

anhydrase inhibitor and a beta-blocking drug and also to ascertain whether there was any interaction between them. For this study we chose the new beta-adrenergic blocker atenolol (Tenormin, ICI), as it is free from sympathomimetic or local anaesthetic activity and has been used by us previously (Elliot *et al.*, 1975), and the carbonic anhydrase inhibitor acetazolamide (Diamox), as it is the most commonly used drug of the group.

Aims

(1) To compare the effects of single oral doses of acetazolamide (500 mg), atenolol (50 mg), and a vehicle preparation on the intraocular pressure of 8 glaucomatous patients. (2) To compare with the above the effect of a combination of atenolol 50 mg + acetazolamide 500 mg. (3) To assess whether there was any drug interaction.

Methods

1. Patients. Of the 8 patients selected, 6 had open-angle and 2 chronic closed-angle glaucoma. In all cases 1 eye only was examined; the right eye was selected unless clinically contraindicated (1 case). All had been attending the hospital for months or years and were selected because of their mobility

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and relative proximity to the hospital. Their informed consent was obtained for the investigations.

2. Measurements. The 8 subjects attended as out-patients for 4 test days, each separated by at least 1 week. Systemic carbonic anhydrase inhibitors (1 patient only) and local therapy to the test eye (all patients) were stopped 24 hours before each test day. These arrangements were made to diminish the influence on study results of non-test preparations.

On each day the ocular tension in the selected eye was measured at 09.00 hours. The tablets were then taken by mouth and the tension was measured hourly for 7 hours.

3. Design. It was recognised that the order in which patients received the 4 test drugs might influence drug response. The assumption was made that the residual effect of a previous test drug might act on the patient's response to the immediately following drug but would not influence response to later test preparations.

Patients entered the trial serially, but an attempt (not entirely successful) was made to study patients in blocks of 4, so that the 4 patients in a block received their first test preparation more or less at the same time. Within each block test drugs were assigned to patients according to a Latin square design. Besides ensuring that every patient received each test drug once and only once, this allowed residual treatment effects to be balanced and meant that on the patients' first study day exactly 1 patient from each block received each test drug, and similarly on study days 2, 3, 4. The design is illustrated in Table 1.

The trial was double-masked. An envelope was prepared by the statistician for each patient; inside were sealed individually the patient's treatment assignments for study days 1 to 4. Each 'treatment' consisted of 3 tablets (since acetazolamide + atenolol was given as 2 acetazolamide tablets each of 250 mg + 1 atenolol tablet of 50 mg), and neither patient nor tonometrist was aware of which preparation was being taken. All tablets were white and of the same size, though not identically marked.

Table 1 *Latin square design*

Patient study day	Block 1				Block 2			
	1	2	3	4	5	6	7	8
1	d	a	V	ad	V	d	a	ad
2	ad	d	a	V	a	ad	d	V
3	a	V	ad	d	ad	a	V	d
4	V	ad	d	a	d	V	ad	a

V=vehicle; a=atenolol; d=acetazolamide; ad=atenolol+acetazolamide

Table 2

Average total fall in IOP		Comparison adjusted means	
V	0.58	a : d	NS
a	5.49	d : V	NS
d	2.73	a : a	NS
ad	8.82	a : V	0.01 < P < 0.05
		ad : V	P < 0.01

Table 3

Average fall in IOP during first 3 hours		Comparison adjusted means	
V	0.10	a : d	0.01 < P < 0.05
a	4.95	d : V	NS
d	1.79	ad : a	0.01 < P < 0.05
ad	8.31	a : V	P < 0.01
		ad : V	P < 0.01

Table 4

Average fall in IOP during last 4 hours		Comparison adjusted means	
V	1.08	a : d	NS
a	5.89	d : V	NS
d	3.43	ad : a	NS
ad	9.21	a : V	0.01 < P < 0.05
		ad : V	P < 0.01

Table 5

Average maximum expected fall		Comparison adjusted means	
V	1.46	a : d	NS
a	6.35	d : V	NS
d	3.78	a : a	NS
ad	9.40	a : V	0.01 < P < 0.05
		ad : V	P < 0.01

V=vehicle; a=atenolol; d=acetazolamide; ad=atenolol+acetazolamide. Measurements in mmHg. Figures adjusted for residual effects. NS=not significant. P values from multiple range test.

The statistical analysis was derived from the work of Williams (1949).

Results

Underlying the study were the prior assumptions that initial ocular tension would be in the range 20 to 30 mmHg and that a reduction of about 5 mmHg could be expected on treatment. The maximum fall in ocular tension was expected 4 to 5 hours after administration of the tablets (at 13.00 to 14.00 hours).

1. Comparison of atenolol, acetazolamide, and a combination of atenolol and acetazolamide

Although Tables 2 to 5 and Fig. 1 suggest that the order of potency as ocular hypotensive agents is 50 mg acetazolamide alone, then vehicle alone, the only significant comparisons are atenolol > vehicle (P < 0.05) and atenolol + acetazolamide > vehicle (P < 0.01).

Comparison of ocular hypotensive effects of acetazolamide and atenolol

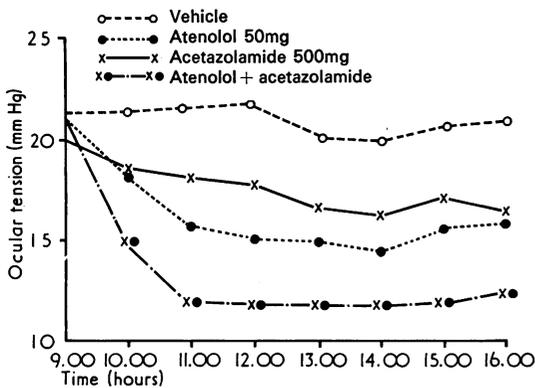


Fig. 1 Mean pressures (8 patients) in mmHg (applanation) for each treatment plotted against time in hours. Note: This graph is the clearest way of presenting the results visually, but differences were used for the statistical analysis

Only in the period of the first 3 hours after administration was atenolol alone more effective than acetazolamide ($P < 0.05$) and atenolol + acetazolamide more effective than atenolol alone ($P < 0.05$).

2. Evidence of interaction between atenolol and acetazolamide

Statistical analysis shows no evidence of any interaction. The combination of drugs is the most effective, but no extra or lesser effect is shown over the simple addition of the effects of the drugs singly.

3. Comparison between acetazolamide and vehicle

Although acetazolamide reduced ocular tension, surprisingly there was no statistically significant difference between its effect and that of the vehicle preparation.

Analysis

Four response variables were defined, and the results of analyses are shown in Tables 2 to 5: (1) Average fall in ocular tension throughout the day, referred to as average total fall; (2) average fall in ocular tension during first 3 hours; (3) average fall in ocular tension during last 4 hours; (4) average expected maximum fall in ocular tension—that is, difference between ocular tension at 09.00 hours and mean ocular tension at 13.00 and 14.00 hours (see Fig. 1).

Allowance was made in the analysis for patient effects and in-block study day factors. Tables 2 to 5 show mean fall under treatment after adjustment to compensate for residual treatment effect (the adjustments are in all cases minor). The standard deviation for the comparison between two adjusted treatment means is 1.56, 1.38, 1.78, 1.67 for response variables 1 to 4 respectively. The

statistical significance for several comparisons between pairs of treatment means, based on the multiple range test of Duncan (1955), is noted in Tables 2 to 5.

It should be pointed out that responses by the same patient to 4 drugs are almost surely positively correlated, so that the analysis of variance described above, relying as it does on uncorrelated error terms, is likely to be conservative and may fail to detect a significant difference between treatments. As a check, therefore, a paired comparison has been made within patients of response to vehicle and acetazolamide. There is still no statistically significant difference between response to vehicle and acetazolamide. The 3 patients who responded well to acetazolamide were those with the highest initial ocular tension. The average total falls for these 3 patients were 6.0, 5.7, and 5.3 mmHg.

Interaction (+ or -) between atenolol and acetazolamide was assessed by comparison between the observed effect of the combination on ocular tension and that predicted from the sum of the observed falls in pressure produced by each drug separately.

Discussion

In this study a single oral dose of atenolol (50 mg) was more effective than acetazolamide (500 mg) in reducing ocular tension in the first 3 hours after administration of the drug by mouth. The use of the 2 drugs together in these doses produced an additive effect but no interaction—i.e., the combination neither enhances nor diminishes the individual drug effect.

It is surprising that in this single-dose study acetazolamide, although reducing ocular tension, did not do so to a significantly greater extent than a vehicle preparation. The explanation probably lies in the fact that initial ocular tensions were not very high in this series (median 20, range 16 to 30).

We think that, even if both drugs reduce production of aqueous humour, they act by a different mechanism, since there was no evidence of interaction between the two. Although in this single-dose study a beta blocker was more effective than a carbonic anhydrase inhibitor, longer trials would be required to establish whether this relative effectiveness was maintained. There is some evidence that the beta-blocking drugs *can* maintain their ocular hypotensive action (Coté and Drance, 1968; Pandolfi, 1974; Bonomi and Steindler, 1975).

Toxicity

The side-effects of carbonic anhydrase inhibitors are well known and include gastrointestinal intolerance, paraesthesiae, ureteric colic, and drug eruptions. The beta-blocking drugs have 2 main groups of side-effects. The first are due to their generalised beta-adrenergic blocking activity and include bronchospasm, precipitation of heart

failure and, in treated diabetics, slight hypoglycaemia; they lower systemic blood pressure, which is a potential disadvantage if they are used for systemic treatment of glaucoma.

Some of these reactions can be minimised by utilising drugs which are more selective in their action and by avoiding their use in 'at-risk' patients—e.g., those with a history of bronchospasm. A more serious group of toxic reactions, however, have in the past few years been described in association with the beta₁-blocker practolol. These have been fully discussed recently (leading article, 1975; editorial, 1976).

The non-selective beta-blocker propranolol, which has been in use for over a decade, has not been reported as being associated with the oculo-mucocutaneous syndrome (though it can, of course, cause the other generalised effects of beta-blockade indicated above). Propranolol is almost equipotent with atenolol in its ocular hypotensive effect when given orally (Macdonald *et al.*, 1976), and despite the disadvantage of having some local-anaesthetic-like activity is also effective on topical administration (Vale *et al.*, 1972).

Although the beta-blocking drugs given orally are now being used in the clinical management of the glaucomas in some centres (Pandolfi and Öhrström, 1974), acetazolamide probably remains the oral treatment of choice. In difficult selected cases supplementing treatment with a beta-blocking drug systemically would not at present appear to reduce the effectiveness of a carbonic anhydrase inhibitor; indeed, their effects are additive in this single-dose study.

Topical treatment, of course, remains the initial treatment of choice (pilocarpine, adrenaline, etc.). Preliminary trials with atenolol eye drops have given some encouraging results (Phillips *et al.*, 1976) and the need for systemic administration may be superseded.

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