PROPRANOLOL AS OCULAR HYPOTENSIVE AGENT*†

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AHLQUIST (1948) suggested that adrenergic activity is divisible into alpha and beta groups. The former is concerned mainly with contraction of smooth muscle, including vasoconstriction in some areas—noradrenaline is almost exclusively an alpha substance. The latter includes adrenergic effects on the heart and relaxation of bronchial muscles—isoprenalin restricts itself almost entirely to such actions. Adrenaline has both actions.

In recent years there has been increasing interest in the effect on intra-ocular pressure of adrenergic stimuli, cervical sympathectomy, and also alpha- and beta-blockade (Sears and Sherk, 1963; Sears and Bárány, 1960; Greaves and Perkins, 1952; Davson and Matchett, 1951; Linner and Prijot, 1955; Lieb, Guerry, and Ellis, 1958; Langham and Taylor, 1959) especially because topical adrenaline is clinically valuable in the treatment of glaucoma (Hamburger, 1923; Goldmann, 1951; Weekers, Delmarcelle, and Gustin, 1955; Aasved, 1964; Miller, 1962). From tonographic evidence it seems likely that an increase in the facility of outflow of aqueous humour is responsible for the fall in ocular tension in patients treated with adrenaline although a small reduction in secretion of aqueous may occur (Garner, Johnstone, Ballintine, and Carroll, 1959; Becker, Pettit, and Gay, 1961; Aasved, 1964). Experimental work with rabbits shows that α -stimulation increases the facility of outflow of aqueous humour (Sears and Sherk, 1963, 1964; Sears and Bárány, 1960; Eakins and Ryan, 1964; Eakins and Eakins, 1964; Bárány, 1962).

The advent of dichloroisoproterenol (Powell and Slater, 1958; Moran and Perkins, 1958), a β -blocker, provided an opportunity to assess the part played by β -activity, if any, on the facility of outflow. Unfortunately, this drug has some intrinsic sympathomimetic activity in addition to its β -blocking activity and this may account for some conflict in the published observations; most of the evidence, in rabbits, seems to suggest that β -stimulation will reduce the facility of outflow of aqueous humour (Sears and Sherk, 1963; Sears and Bárány, 1960; Gnädinger and Bárány, 1964), and a reduction in formation of aqueous humour has also been observed (Eakins, 1963). Beta receptors in the cat iris are thought to produce relaxation of the sphincter (Schaeppi and Koella, 1964).

As far as the writers are aware, no studies have been made of the effect of the specific β -sympathetic blockers pronethalol or propranolol on the ocular tension of the rabbits or of man. The preliminary study here described relates to observations made on seven patients who were given propranolol, at first intravenously.

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Method and Results

Group I.—Three patients had been admitted for a study of the effect of digoxin on ocular tension. All three had open-angle glaucoma as judged by field loss, tonometry, and gonioscopy; Case 3 was a Jamaican Negro. At the end of their fifth day of treatment it was decided to try the effect of 10 mg. intravenous propranolol, a specific blocker of β -sympathetic activity. Compared with the previous day, or indeed any of the previous days, at the same time, there was a very definite fall in ocular tension, especially in Case 2 (See Table I).

TABLE I
OCULAR TENSION IN GROUP I

Case No.	Ocular Tension (mm. Hg Applanation)							
	Intravenous Propranolol 10 mg. at 5.30 p.m.				On Day before Propranolol			
	4.30 p.m.		6.30 p.m.		4.30 p.m.		6.30 p.m.	
	R	L	R	L	R	L	R	L
1	23	15	9.5	9.5	25	15	21	14
2	42	41	27	23	40	38	40	33
3	24	24	15	15	21	22	20	20

Group II.—This interesting result prompted a study of a further four patients, uncomplicated by previous treatment with digoxin, all with open-angle glaucoma. After admission to hospital, they were allowed to "settle-in" for 2 days (one day only in Case 5); for a period of 3 days thereafter diurnal readings of ocular tension were made. Applanation tonometry was done, by the same observer each time, at approximately 9.0 a.m., 12.30 p.m., 2.30 p.m., 4.30 p.m., and 7.30 p.m. In order to avoid asking the patients to get up during the night, Schiötz tonometry was the method used at 11 p.m. and 6.0 a.m. The tensions at night were taken by the three house surgeons on duty. On the first "propranolol day" tensions were taken more frequently (Table II).

TABLE II
OCULAR TENSION IN GROUP II (CASES 4, 5, AND 7)

Case No.	Ocular Tension (mm. Hg Applanation)							
	Intravenous Propranolol 10 mg. approx. 9.50 a.m.				Previous Day			
	9.0 a.m.		12.30 p.m.		9.0 a.m.		12.30 p.m.	
	R	L	R	L	R	L	R	L
4	10	10	9	7	10	10	11.5	11.0
5	41	41	34	29	41	41	43	40
7	19	22	16	15	19	20	19	20

Previous Treatment and Ophthalmic History

Case 4 had gross glaucomatous field loss and pathological cupping of optic discs when seen for the first time about 3 weeks before admission. As an out-patient, he had used guttae adrenaline 1 per cent. at night and guttae demecarium bromide 0.06 per cent. (0.12 per cent. having produced

too much discomfort) in the mornings; on admission guttae adrenaline 2 per cent. were prescribed to replace the 1 per cent. solution. It is rather surprising that this patient, admittedly on treatment, never showed an ocular tension of more than 16 mm. Hg in the right eye and 13 mm. Hg in the left during the day, or of more than 19 and 15 mm. Hg respectively at night, especially as he had gross glaucomatous field loss in both eyes.

Case 5 had no treatment for glaucoma before admission: "advanced" open-angle glaucoma was diagnosed a few days previously.

Case 6 was also admitted, untreated, a few days after the diagnosis had been made. He was myopic (-7 D sph. and -6.5 D sph. in the right and left eyes). Although pathological cupping of the discs was definitely present along with very high ocular tensions (see Figure), the central visual fields were almost normal, a small nasal defect being present on the left side; the peripheral fields, recorded with glasses, showed a moderate left and slight right nasal loss. He had a very low ocular rigidity, 0.013 in each eye, estimated by the graphic method of Friedenwald (1957) from readings of applanation followed immediately by Schiötz tonometry with a 10 g. weight. The Schiötz readings (*i.e.* at night) have been corrected for this unusually low ocular rigidity, but seem to "fit" well with the applanation readings during the day.

FIGURE.—Case 6. Ocular tensions in mm. Hg (applanation during the day and Schiötz at approximately 11 p.m. and 6.0 a.m.) corrected for ocular rigidity. Note the effect of intravenous propranolol 10 mg. on Day 4, the fall in pressure being maintained by oral treatment; withdrawal on Day 6 caused return of pressure to pre-treatment levels, which was again controlled by oral propranolol on Day 7.

Case 7 had had corneo-scleral trephine operations 6 years previously but about 5 weeks before admission was found to have increasing visual field loss and the trephine areas looked "blocked"; from that time until 6 days before admission, when all treatment was stopped, he was treated with guttae demecarium bromide 0.06 per cent. at night (the 0.12 per cent. used at first being too uncomfortable) and guttae adrenaline 1 per cent. each morning. The highest tensions recorded in this patient in either eye was 21 mm. Hg during the day and 24 and 23 mm. Hg at night, in the right

and left eyes respectively. The angle of the right anterior chamber was open all round and the left had two small sectors of goniosynechia.

Effect of 10 mg. Propranolol Intravenously.—Compared with the previous day—or any of the previous days—at the same times, there was a definite fall in ocular tension (see Table II for Cases 4, 5, and 7, and the Figure for Case 6).

Effect of Continued Oral Propranolol.—Cases 4, 5, and 7 failed to maintain on oral treatment the fall in tension produced initially by intravenous propranolol; this is hardly surprising in Case 4 who had low ocular tensions. The explanation in Case 5 may be that he had very advanced glaucoma with a “tube-field” in the right eye, and loss of the whole upper nasal quadrant on perimetry in the left (central fields were unsatisfactory, mainly because of his deafness). In all three, the gentle fall in diurnal tension readings of their three pre-propranolol days merely seemed to be maintained, although dosage by mouth, given thrice daily in all patients, was increased to 30 mg. in Cases 4 and 7, and to 40 mg. in Case 5. Higher dosage would probably have been worth using, at least in Case 5 who had quite high tensions.

Patient 5 died just before the withdrawal of propranolol by mouth. He had bronchogenic carcinoma, and an acute myocardial infarction was the precipitating cause of death as found at autopsy. It is considered that propranolol did not contribute to his death, though the drug should be used with caution in patients who have evidence of cardiac failure or obstructive airway disease.

Case 6, however, maintained on oral treatment most of the fall in ocular tension produced by intravenous propranolol (Figure). By, at most, 36 minutes after the intravenous injection, the tension began to fall from the initial high levels of 50 mm. Hg right and 55 mm. Hg left; they had reached 30 and 28 mm. Hg 2 hours and 40 minutes later, and 17 and 19 mm. Hg after 10 hours. A partial rebound occurred on the following day, but on that and the subsequent day the tensions remained substantially below the levels of the first 3 days. To confirm the effect of propranolol, the drug was temporarily stopped after the morning dose on the sixth day; 24 hours later the tensions had shot up to levels at least as high as before treatment, but again showed a dramatic response to an oral dose of 15 mg. propranolol. A further fall seems to have occurred with guttae adrenaline 1 per cent., then 2 per cent., presumably because of α -stimulation, but these low pressures showed no rebound on withdrawal of propranolol—an observation worth further investigation.

Discussion

Further studies are being started to “analyse” the mode of action of this drug in producing a fall in ocular tension; an increase in facility of outflow of aqueous humour is expected, but any explanation for this in chemical terms is just as unknown as the effect of adrenaline. An effect on the rate of secretion of aqueous humour, on the intra-ocular blood vessels, on the ciliary muscle and pupils, on “ocular rigidity”, and on blood pressure are possibilities. Of great interest is the fact that one of the four patients treated by mouth (Case 6: see Figure) maintained a lower ocular tension than before for at least 3 days. This suggests that the mode of action, in his case, is not a once-for-all effect on the intra-ocular blood vessels, or an effect of the small amount—10 ml.—of vehicle injected (it is hypotonic). Even if only a small proportion of patients with glaucoma respond—perhaps a sub-type of open-angle glaucoma may exist?—in them a valuable drug may be applicable. The effects on normal eyes and on other forms of glaucoma will form an interesting study.

Most important, the possibility of the production of eye-drops is being explored. The low pH of the 0.1 per cent. solution used for intravenous use creates difficulties; a compound analogous to that formed by adrenaline and borate (Trautner and

Messer, 1952), which is in common use clinically at the present time as "Eppy" (Miller, 1962), might well provide the answer to this problem. A careful watch will be maintained for ocular toxic effects, especially on the crystalline lens.

Summary

Alpha- and beta-adrenergic effects on the eye, especially on the intra-ocular pressure, have been the subject of increasing interest and investigation in recent years. Intravenous injection of 10 mg. propranolol, a specific blocker of β -adrenergic activity, has produced a fall in ocular tension, marked about 1–2½ hours later, in seven patients with glaucoma, some of whom had also had other anti-glaucoma drugs.

After the injection, four of the seven patients were also given oral treatment three times daily, the dosage varying from 5 to 40 mg. Three probably failed to maintain any of the fall produced by the intravenous injection, but one showed a very good response (Figure) which was reversed on withdrawal of the drug 2 days later; when the drug was given again by mouth, however, the good response was repeated.

Further investigations are planned, including a trial of eye-drops.

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