

Ocular and cardiovascular effects of local and systemic pindolol

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SUMMARY Ocular and cardiovascular effects of topical and intravenous pindolol have been studied in a balanced cross-over double-blind trial in 6 healthy volunteers. When applied to 1 eye pindolol lowered intraocular pressure in both the treated and untreated eyes with only minimal reduction in resting pupil diameter and light reflex response. The concentration in plasma was much lower and inhibition of exercise tachycardia about half that when the same dose was administered intravenously. The findings suggest that β -adrenoceptor blocking drugs should not be used in the treatment of glaucoma in patients who also suffer from heart failure.

Pilocarpine has been the mainstay of glaucoma therapy for many years despite the impairment of vision caused by the accommodative spasm and pupillary constriction that accompany its use. The β -adrenoceptor blocking drugs offer a promising alternative to pilocarpine, since they have been reported to control intraocular pressure without impairing visual function (Phillips *et al.*, 1967; Bonomi and Steindler, 1975; Phillips *et al.*, 1977; Leading article, *British Medical Journal*, 1976; Editorial, *British Journal of Ophthalmology*, 1975).

There is, however, a danger that these drugs could exert a systemic effect following local application to the eye because β -blockers are highly lipid-soluble compounds that may pass directly into the circulation or be absorbed after passing down the nasolacrimal duct into the pharynx. The present study with pindolol, a particularly potent β -blocker (Harms, 1976), was designed to test this possibility and to record the pupillary, accommodative, and ocular hypotensive effects that follow its local and systemic administration.

Methods

SUBJECTS

Six healthy persons, 3 male and 3 female, aged 21 to 22 years, volunteered for this study. All had

normal visual acuity, light perception thresholds, and ocular tension.

TREATMENTS

Each person attended on 3 occasions, on each of which 4 eyedrops were applied to both eyes and an intravenous injection was given. The eyedrops, delivered with Pasteur pipettes, were of about half the volume given by most commercial droppers. On one occasion pindolol was incorporated to a concentration of 1% in the eyedrops applied to 1 eye; on a second occasion the same total dose of pindolol (1.13 mg) was incorporated in the intravenous injection; on a third occasion no pindolol was given. The solvents for the pindolol solutions were 0.15 M phosphate buffer pH 6.5 for the drops and 0.9% saline for the injection. Administration of both the drops and the injection was over a 3-minute period. The 3 treatments were given in a complete balanced cross-over design and were administered double-blind.

MEASUREMENTS

Before, and at 0.5-, 1-, and 2-hour intervals after treatment the following were measured in the order given. Intraocular pressure was measured by applanation tonometry under local anaesthesia with benoxinate 0.4%. Three readings were recorded from each eye on each occasion, the tonometer dial being read and reset by an independent observer. Venous blood samples were taken and subsequently analysed for plasma pindolol content by the spectro-

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fluorimetric method of Pacha (1969). The heart rate was measured at rest and during the last 15 seconds of a 4-minute period of exercise on a bicycle ergometer, using an electrocardiographic tracing. The level of exercise (workload 1.5 to 3.0 kiloponds) had been set in a preliminary study to be sufficient to produce an increase in rate of 70 to 120 beats/min, which amounted to a tachycardia of at least 150 beats/min in all but one subject. The near-point of visual accommodation was measured in quadruplicate with a sliding rule (Herxheimer, 1958). The resting pupil diameter and the reflex pupil responses to a train of 0.5-second light flashes at 0.125 Hz were recorded with a Whittaker Series 1800 infrared television pupillometer (Smith and Smith, 1978). The intensity of the light flashes was arranged to give reflex responses of approximately 1 mm, and the dim background illumination was constant for each experiment.

STATISTICAL ANALYSIS

Measurements obtained before drug administration were subjected to analysis of variance by standard techniques (Snedecor and Cochran, 1967) and found not to differ between experimental occasions. Treatments were therefore compared by analysis of variance of post-treatment measurements only, all treatment times being combined. Correlations between reductions in intraocular pressure or exercise tachycardia and log plasma pindolol concentrations were assessed by analysis of covariance (Snedecor and Cochran, 1967).

Ethical approval for this study was given by the St Thomas's Hospital Research (Endowments) Committee.

Results

INTRAOCULAR PRESSURE

The effects of the 3 treatments are shown in Fig. 1. Topical pindolol lowered the pressure in both the treated ($P < 0.001$) and untreated ($P < 0.001$) eyes, the fall in the former being greater than in the latter ($P < 0.01$). Intravenous pindolol lowered the pressure equally in the 2 eyes. By comparison with local administration the pressure fall was less than that produced in the treated eye ($P < 0.001$) and equal to that in the untreated eye.

OTHER EYE SIGNS

Pupillography showed that topical pindolol reduced the resting pupil diameter and the amplitude of the light reflex of the treated eye only to a very small, though statistically significant (diameter $P < 0.001$; reflex $P < 0.01$), extent. The mean changes in diameter (< 0.6 mm) and reflex response (< 0.15

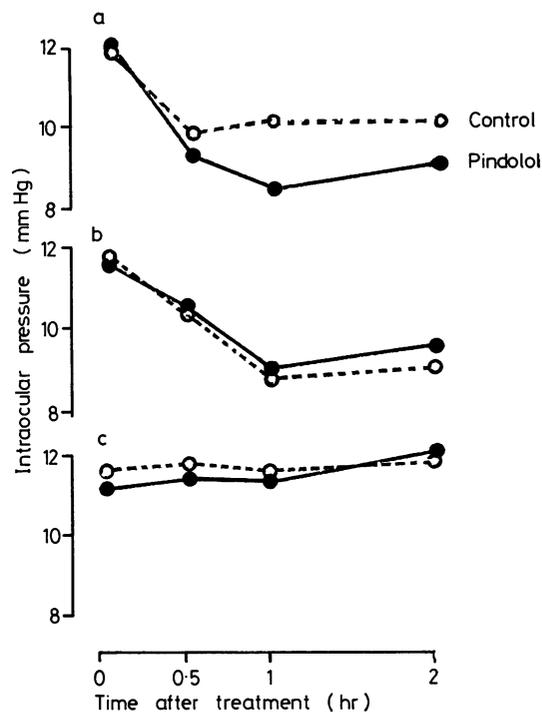


Fig. 1 Mean intraocular pressure (●—●, treated eye; ○—○, untreated eye) following: (a) pindolol 1% (total dose 1.13 mg) instillation into the eye; (b) pindolol 1.13 mg intravenously; (c) control vehicles

mm) were imperceptible to observers by simple inspection of the eye. No change followed intravenous pindolol. Visual accommodation was unaffected by any treatment.

HEART RATE

The effects of the 3 treatments on resting heart rate and on exercise tachycardia are shown in Fig. 2. Both ocular and systemic pindolol reduced resting heart rate and inhibited exercise tachycardia. The reduction in resting heart rate was small (mean change less than 7 beats/min) both with ocular ($P < 0.05$) and with intravenous ($P < 0.05$) administration. The exercise-induced increase in rate was inhibited 12.6% by ocular pindolol ($P < 0.05$), 25.6% by intravenous pindolol ($P < 0.001$).

PLASMA PINDOLOL CONCENTRATION

The findings are given in Table 1. After ocular instillation pindolol was detectable in plasma within 30 minutes, but the concentrations found were substantially lower than after intravenous injection at all times ($P < 0.001$). To investigate the dose response relationship for inhibition of exercise

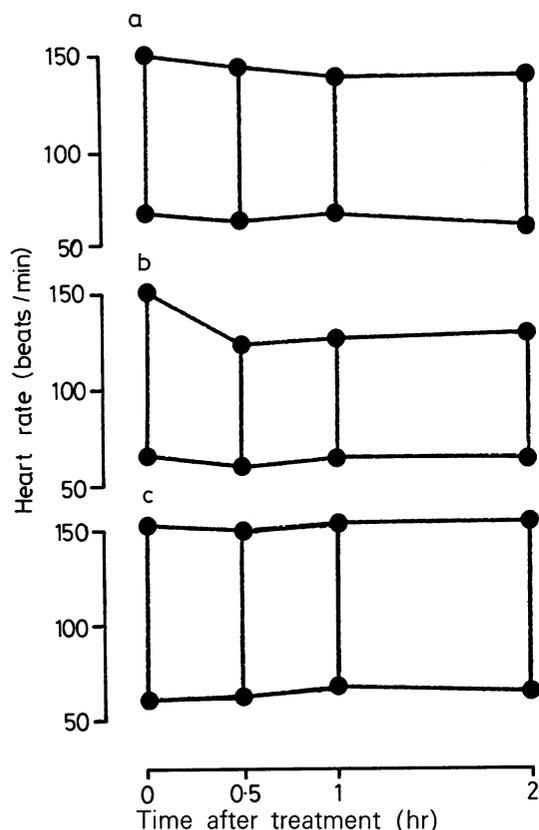


Fig. 2 Mean heart rate at rest (lower line) and after exercise (upper line) following: (a) pindolol 1% (total dose 1.13 mg) instillation into the eye; (b) pindolol 1.13 mg intravenously; (c) control vehicles

tachycardia and for reduction of pressure in the untreated eye, correlations were sought between the magnitude of these effects and log plasma concentration (intravenous and local administration). In this analysis 5 data points were excluded because the pindolol concentration was below the limit of detection. It was found that whereas the cardiac response correlated with log plasma concentration ($r = 0.752$, $P < 0.001$) the ocular response did not ($r = 0.179$, $P > 0.05$).

Table 1 Plasma pindolol concentration ($\mu\text{mol/l}$) (mean \pm SD)

Route of administration	Time (hr)		
	0.5	1	2
Ocular instillation	2.4 \pm 3.2	6.8 \pm 2.8	3.2 \pm 3.2
Intravenous	29.8 \pm 6.4	34.2 \pm 9.3	27.0 \pm 9.3

Discussion

Local and systemic pindolol caused ocular hypotension in these normal subjects without impairment of visual function. There was no effect on accommodation, and the small decrease in resting pupillary diameter and light reflex amplitude found after local administration was clinically insignificant. The direction of these small pupillary changes, which resemble those seen with low doses of cholinomimetic drugs (Smith and Smith, 1978), is consistent with the hypothesis that there is a small population of β -adrenoceptors on the human sphincter pupillae which mediates relaxation of this muscle during sympathetic dilatation of the pupil (Kern, 1971).

This study has revealed a potential drawback to the use of β -blockers in glaucoma in that there was sufficient absorption of pindolol from eyedrops to cause partial blockade of cardiac adrenoceptors. It is possible that lower doses might control pressure adequately with less chance of systemic side effects, but this finding does suggest that β -blockers should not be given to glaucomatous patients who also suffer from cardiac failure or, in the case of non-cardioselective blockers, from bronchial asthma.

In this study the cardiac β -blockade that followed local administration of pindolol resulted in a decrease in resting heart rate and a reduction of exercise tachycardia that was nearly half the size of the reduction obtained after intravenous injection of the same dose. This systemic effect was still present when the last reading was taken at 2 hours after application of the drops. The reduction of exercise tachycardia that followed intravenous pindolol and its correlation with plasma drug levels is in agreement with previous studies (Hicks *et al.*, 1972; Gugler *et al.*, 1975). However, the effect of pindolol on resting heart rate, though always small in magnitude, appears to be variable in direction, some authors reporting a decrease (Gugler *et al.*, 1975) as found in this study, whereas others (Hicks *et al.*, 1972) report an increase. These differences may be related to the partial agonist activity of this particular β -blocker acting on patients in variable basal conditions.

It was interesting to find that pindolol treatment of 1 eye resulted in a pressure fall in the contralateral untreated eye. Although it is possible that this resulted from systemic absorption of the drug, such an explanation seems unlikely, because the contralateral fall occurred in the presence of far lower plasma concentrations than were present after intravenous administration, which gave a comparable reduction in pressure. Other workers have reported a similar reduction in the contralateral eye after local timolol (Zimmerman and Kaufman, 1977)

and pilocarpine (Willets, 1969) treatment. Further, a pressure reduction produced simply by pressing on 1 eye to increase venous drainage of aqueous is also accompanied by a fall in the opposite eye (Prijot and Stone, 1956). Possibly there exists a regulatory mechanism whereby pressure in both eyes is maintained at a similar level.

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Notes

Elderly persons

A multidisciplinary seminar on the 'Elderly person with failing vision—the problems and how best they can be met' will be held on 6 November 1979 at New Addenbrooke's Hospital, Hills Road, Cambridge, by the Department of Geriatric Medicine, Cambridge, jointly with the Disabled Living Foundation. Details from Miss Margaret Dowden, Conference Secretary, Disabled Living Foundation, 346 Kensington High Street, London W14 8NS (tel. 01-602 2491).

Contact lens technology

The annual course in contact lens technology will be held at the Cullen Eye Institute, Baylor College of Medicine, Houston, Texas, on 29 November–1 December 1979. Further details from David Paton MD, Cullen Eye Institute, Baylor College of Medicine, 6501 Fannin (NC 200), Houston, Texas 77030, USA.

Glaucoma

The 29th annual symposium on glaucoma will be held at the New Orleans Academy of Ophthalmology on 22–26 March 1980. Details from Paula Di Leo, Executive Secretary, New Orleans Academy of Ophthalmology, 931 Canal Street, Suite 517, New Orleans, LA 70112, USA.

Afro-Asian Congress

The VIIth Afro-Asian Congress of Ophthalmology will take place in Tunis on 26–29 October 1980. The provisional programme has for its main subjects 'Virus eye diseases' and 'Trauma of the eye'; for its symposia 'Ocular microsurgery', 'Fundus in metabolic diseases'; 'Onchocercosis', 'History of ophthalmology', and 'Educational trends in ophthalmology'; and for round table discussions 'Paramedicals and prevention of blindness', and 'Traditional medicine'. Further details from the Secretariat, Institut d'Ophthalmologie, Bab Saadoun, Tunis, Tunisia.

Road safety

The 2nd International Congress on Vision and Road Safety, sponsored by the International Road Safety Council, will be held at the International Conference

Centre in Paris (Porte Maillot) on 20–22 November 1980. Subjects under discussion will be night vision, road lighting, vehicle lighting, traffic signals, and reflecting signals. Registration fee is Fr750. Further information from R. Pansard, General Secretary, Linas 91310, Montlhery, France.

Correction

In the paper entitled 'Ocular and cardiovascular effects of local and systemic pindolol' (*BJO*, 1979, 63, 63–66) by Smith, S. E., Smith, S. A., Reynolds, R., and Whitmarsh, V. B., the caption to Table 1 contained an error. The concentration of plasma pindolol should have been given in nmol/l instead of $\mu\text{mol/l}$.

Change in style of references

In accordance with the Vancouver agreement many medical journals are to standardise the instructions they issue to authors on the preparation of articles. References will be cited by the numerical system already familiar in many journals, including the *British Medical Journal*.

A paper (or book) cited in the text is referred to there by a superscript number. In the list of references the papers (or books) appear in the numerical order in which they are first cited in the text, not in alphabetical order by authors' names. For convenience in preparing the typescript the reference number may be typed between parentheses on the line, not superscript. The titles of journals will be abbreviated in accordance with the style of *Index Medicus*. In the typescript they should either be abbreviated in that style or given in full. This journal will change to the numerical system from the first issue of 1980. *Authors submitting papers are asked to adopt it now in order to facilitate editing.* Three examples follow:

- 1 Green A B, Brown C D, Grey E F. A new method of measuring the blood glucose. *Br J Ophthalmol* 1980; 64:27–32.
- 2 Green A B, Brown C D. *Textbook of Medicine*. London: Silver Books, 1980.
- 3 Grey E F. Diseases of the pancreas. In: Green A B, Brown C D, eds. *Textbook of Medicine*. London: Silver Books, 1980; 349–362.

Copies of the Vancouver agreement (50p, post free) are obtainable from the Publishing Manager, British