Effect of pindolol on intraocular pressure

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It has been demonstrated that propranolol and practolol by both general and topical administration lower the intraocular pressure in glaucomatous patients (Phillips, Howitt, and Rowlands, 1967; Coté and Drance, 1968; Bietti, Bucci, Pecori Giraldi, Romani, and Virno, 1971).

Other beta-adrenergic blockers, such as dichloro-isoproterenol (DCI), N-isopropyl-paranitrophenylethanolamine (INPEA) and pronethalol, seem on the contrary to be devoid of any evident tension-lowering effect (Bonomi, 1964; Musini, Fabbri, Bergamaschi, Mandelli, and Shanks, 1971).

It is believed that beta-adrenergic blockade increases the outflow facility in animals, and the tonographic data so far obtained indicate that propranolol does so also in man (Perpignano, 1968; Bonomi and Carli, 1972; Bucci and Romani, 1972).

Nevertheless, considerations based on different grounds seem to indicate support for other modes of action (Virno, Marinosci, Pecori Giraldi, and Missiroli, 1969; Takáts, Szilvássy, and Kerek, 1972).

Furthermore, the ability of propranolol to reduce intraocular pressure has been ascribed to actions of the drug that are distinct from the beta-blocking effect, namely, to its surface anaesthetic or quinidine-like properties (Musini and others, 1971; Vale and Phillips, 1970).

The study of the ocular effects of other beta-receptor antagonists may offer more information on the action mechanism of this group of drugs which may become interesting both theoretically and practically.

The drug selected for the present study was pindolol (L.B. 46, Visken). The beta-blocking action of pindolol was first reported by Saameli (1967), see Fig. 1.

This compound has the following properties:

- (a) Beta-blocking activity on the guinea-pig heart 20 to 40 times stronger than propranolol (Clark and Saameli, 1970)
- (b) Slight anti-arrhythmic property (one-third of that of propranolol) (Lubawski and Wale, 1969)

FIG. 1 Chemical structure of three beta-adrenergic blockers: practolol, propranolol, and pindolol (LB 46)

- (c) No local anaesthetic action
- (d) Slight intrinsic adrenergic effect (Hill and Turner, 1969).

Method

The research was carried out on 37 patients of both sexes, aged 39 to 70 years.

- (a) A short-term experiment was performed on 26 normal eyes and 16 eyes suffering from previously untreated open-angle glaucoma, according to the following schedule. The first day readings of ocular tension by applanation tonometry were taken at 8 am, 9 am, 12 noon, 4 pm, and 8 pm in order to establish a base-line. The following day 2 drops of 1 per cent pindolol in buffered saline were instilled into the conjunctival sac and tonometric readings were taken at the same times of the day. On most eyes tonograms were also performed on both days at 12 noon. Pupil width and corneal sensitivity were also checked.

- (b) In a longer-term experiment 20 eyes with open-angle glaucoma were used. The drug was instilled 3 times a day for 30 days. Applanation tonometry was done and tonograms were made the day before starting treatment and on the seventh and thirtieth days of treatment, always at 12 noon. The readings obtained at corresponding times of the day were compared and the results tested for statistical significance by means of Student's method for paired data.

Results

The drug was always well tolerated, and no irritation or other unpleasant side-effects were observed in the treated eyes.

No change in pupil width or corneal sensitivity was observed.

All the eyes investigated responded to the single instillation of pindolol with an obvious decrease in tension lasting several hours.

The results are summarized in Fig. 2 and Tables I and II.

FIG. 2 Mean change in ocular tension after a single instillation of 1 per cent pindolol in normal and glaucomatous eyes

Table I Statistical evaluation of tonometric differences found in 26 eyes at corresponding times of day, after a single instillation of 1 per cent pindolol (Student's *t* for paired data)

Hour	1st	4th	8th	16th	24th
Difference of the means	-4.885	-3.615	-1.654	-0.500	+0.125
SD	±2.17	±2.49	±2.33	±1.102	±2.96
<i>t</i>	11.432	7.378	3.602	0.924	0.179
P	<0.001	<0.001	<0.005	>0.30	>0.80

Table II Statistical evaluation of tonometric differences found in 16 eyes suffering from open-angle glaucoma, at corresponding times of day, after a single instillation of 1 per cent pindolol (Student's *t* for paired data)

Hour	1st	4th	8th	16th	24th
Difference of the means	-7.187	-6.375	-3.438	-2.500	-2.312
SD	±4.047	±3.515	±2.920	±2.031	±2.308
<i>t</i>	7.102	7.254	4.708	4.923	4.006
P	<0.001	<0.001	<0.001	<0.001	<0.005

Table III Variations in intraocular pressure and in outflow facility in 10 normal eyes and in 10 eyes suffering from open-angle glaucoma, after a single instillation of 1 per cent pindolol

Eyes	Normal		Glaucoma	
	Po	C	Po	C
Difference of the means	-2.9	-0.08	-7.9	+0.005
SD	±1.20	±0.022	±2.133	±0.0114
<i>t</i>	7.63	1.114	11.703	1.385
P	<0.001	>0.20	<0.001	>0.10

Table IV Variations in intraocular pressure and in outflow facility during treatment with 1 per cent pindolol in 20 eyes suffering from open-angle glaucoma

Time	After 1 week		After 1 month	
	Po	C	Po	C*
Difference of the means	-7.9	+0.0085	-6.65	+0.027
SD	±3.605	±0.0173	±4.123	±0.0223
<i>t</i>	9.795	1.837	7.209	4.770
P	<0.001	>0.05	<0.001	<0.001

* Determination obtained on 14 eyes only

All the differences are highly significant, except those found at 18 and 24 hours in the groups of normal eyes.

Table III shows the tonographic results obtained in the single instillation experiment. In both normal and glaucomatous eyes the treatment produced a clear and highly significant lowering of the intraocular pressure, while no effect on the outflow was seen.

In Table IV the results of the long-term experiment are summarized.

After one week of treatment the pressure-lowering effect was clear and the outflow facility unaffected. After one month, however, although the reduction of pressure was of the same order of magnitude, a slight but significant increase in outflow appeared.

Discussion

The results of our study clearly demonstrate that pindolol lowers the intraocular pressure in normal eyes and, to a greater extent, in eyes suffering from open-angle glaucoma.

This effect is not at first accompanied by any significant variation in the outflow facility. It is, therefore, most probably to be ascribed to inhibition of aqueous humour production. Only after one month of treatment does an increase in outflow facility appear.

It is noteworthy that also at that time the variation of facility is too small to explain the lowering of pressure, and that no more than one-third of the effect on intraocular pressure can be ascribed to it.

Thus, pindolol seems to act in a different way from propranolol, the action of which has been found to

consist of an increase of outflow facility. This may be explained by the different properties of the two drugs. Pindolol indeed has a higher beta-blocking effect, a higher intrinsic beta-mimetic action, less quinidine-like effect, and no surface activity.

Recently Bucci and Romani (1972) explained the action mechanism of propranolol as being due to an alteration in balance between the alpha- and beta-adrenergic receptors in the eye, with prevalence of the alpha effects and consequently an increase of outflow facility.

The observation of the lack of effect on facility in the first phase of the action of pindolol makes this explanation unsatisfactory for a general interpretation of the effect of beta-blockers on intraocular pressure. The problem seems to be more complex and needs further investigation. Nevertheless, on practical grounds, pindolol seems to be potentially useful in the treatment of glaucomas. Its strong tension-lowering effect, its lack of action on the pupil and on the corneal sensitivity, and its easy tolerance make it, in our opinion, a very good drug for topical use, deserving a larger trial.

We have no evidence of any toxic effect of pindolol on the eye. However, since practolol, another beta-blocking agent, has shown a damaging effect on the eye when given systemically (Wright, 1974), the possibility of a similar danger cannot yet be ruled out.

Summary

Pindolol, a strong beta-adrenergic blocking agent, instilled into the conjunctival sac of normal and glaucomatous eyes, produced a significant drop in intraocular pressure.

This was not, at first, accompanied by any variation in outflow facility; only after prolonged treatment did an increase in facility appear, which accounted only for one-third of the tension-lowering effect.

The drug was well tolerated, and did not affect either pupil motility or corneal sensitivity. It seems suitable for a trial use in the treatment of glaucoma.

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