A study of the effects of four concentrations of D-timolol, 0.25% L-timolol, and placebo on intraocular pressure on patients with raised intraocular pressure

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SUMMARY The intraocular pressure lowering effect in 30 patients with raised intraocular pressure and open angles following a single application in a randomised double-masked fashion of four concentrations of D-timolol (0.25%, 0.5%, 1.0%, and 2.0%), 0.25% L-timolol, and placebo are presented. The percentage reduction in intraocular pressure after four hours following single-drop instillation range from 20% to 25% in the D-timolol group, 32% in the L-timolol group, and only 8% in the placebo group of treated eyes.

The role of L-timolol (that is, the S-enantiomer of timolol) in the treatment of glaucoma is well established.¹⁻³ The success of L-timolol can be attributed to its relatively long duration of action, the minimal development of tolerance, and lack of membrane stabilising (local anaesthetic) activity. However, L-timolol, being a non-selective β -adrenergic blocking agent, must be used with caution in patients with known contraindications to the systemic use of β -adrenergic receptor blocking drugs. These include bronchial asthma, sinus bradycardia and greater than first degree heart block, and cardiogenic shock. Any systemically absorbed drug following topical administration may affect extraocular β -adrenergic receptor systems in the same patients.

The R-enantiomer of timolol (D-timolol) is also a non-specific β -adrenergic blocker, but its potency as a β -blocker is substantially less than that of L-timolol.⁴ D-Timolol has only 3% of the potency of L-timolol in blocking the isoproterenol-induced synthesis of adenosine 3–3', 5', monophosphate in iris-ciliary body preparations.⁵ In water loaded pigmented rabbits both stereoisomers blunt the peak increase in intraocular pressure and also reduce its down phase, though L-timolol is more effective.⁵ D-Timolol is about one-third as potent as timolol in displacing ³H-dihydro-alprenolol binding to iris-

ciliary body tissue, reducing aqueous humour formation, and lowering intraocular pressure of α chymotrypsin hypertensive eyes.⁶ In contrast the R-enantiomer is 50–90 times less potent than timolol in antagonising the effects of isoproterenol on pulmonary and atrial β -adrenergic receptors⁶ and may be effective in lowering intraocular pressure in man at concentrations which may reduce the systemic side effects associated with peripheral β -adrenergic blockade. D-Timolol has been shown to produce a significant lowering of intraocular pressure following single-drop application in patients with ocular hypertension.⁷

The present study was undertaken to compare the effects on raised intraocular pressure of a single application of four concentrations of D-timolol (0.2%, 0.5%, 1.0%, and 2.0%) with 0.25% L-timolol and placebo in patients with raised intraocular pressures and open angles.

Patients and methods

Patients with raised untreated, symmetrical (no more than 5 mmHg difference in intraocular pressure between eyes) intraocular pressures (of 22 mmHg in each eye or higher by Goldmann applanation tonometry) and open angles, between the ages of 18 and 75, were considered for inclusion in the study. Patients suffering from, or with a history of, cardio-

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vascular disease or constrictive airways disease, active corneal disease or corneal scarring, previous ocular surgery, or receiving concomitant systemic medication affecting intraocular pressure, including β -blocking drugs and clonidine, or taking adrenergic augmenting psychotropic drugs such as monoamine-oxidase inhibitors or tricyclic antidepressants were excluded from the study.

Thirty patients gave their informed written consent to take part in the trial (and were free to remove themselves from the trial without explanation at any time). Each of the 30 patients received two of the six possible treatments. The allocation of treatments was such that each was given to 10 different patients. Only one eye was treated, and the eye to be treated and the treatment to be received were determined by a random allocation schedule. Each treatment was delivered from identical 5 ml ocumeters containing one of the following six compounds; 0.25% D-timolol, 0.5% D-timolol, 1.0% D-timolol, 2.0% D-timolol, 0.25% L-timolol, and placebo to match (vehicle of D-timolol).

All intraocular pressure reducing medications were washed out for at least two weeks. Within this period all patients had, before treatment, history taken and examination made to ensure that they satisfied admission and exclusion criteria.

Immediately prior to treatment the resting heart rate and blood pressure were measured in all 30 patients after they had been sitting for four minutes. The visual acuity, pupillary size, and results of an external ocular examination followed by an initial applanation intraocular pressure were recorded for both eyes. The first of the randomly assigned drops was instilled into the conjunctival sac of one randomly selected eye. All examinations were repeated at one, two, and four hours after treatment.

Each patient returned two weeks later to receive the second treatment in the same eye as the first treatment. No ocular treatment was allowed during the period between the first and second treatment days. Examinations for the second treatment day followed the same schedule as for the first day. Any subjective side effects following topical instillation of any of the treatments were noted.

Results

All 30 patients completed the study. The mean IOP in the treated eyes at the studied time points are shown in Fig. 1. The results were compared by single classification analysis of variance. The mean starting intraocular pressures (as shown in Table 1) were statistically similar in each treatment group ($p>0.05$) and ranged from 25.4–30.5 mmHg. Four hours following the administration of the eye drops the

Fig. 1 Mean IOP: treated eyes. P=placebo. 0.25= D-timolol 0.25%. T=L-timolol 0.25%. 1.0=D-timolol 1%. 0.5=D-timolol 0.5%. 2.0=D-timolol 2%.

intraocular pressure had fallen by varying amounts according to the treatment used (Table 1). Placebo and 0.25% D-timolol did not produce a significant reduction in intraocular pressure. However, 0.5, 1%, and 2% D-timolol and 0.25% L-timolol did all produce a significant reduction in intraocular pressure four hours after treatment in comparison with placebo (variance ratio 2.6; $p<0.05$). These reductions in intraocular pressure did not differ significantly from one another. Fig. 2 and Table 2 show the mean change in intraocular pressure in the treated eyes over time following single-drop instillation of each treatment.

The initial intraocular pressures in untreated eyes were similar in each group (variance ratio 1.5%;

Table 1 Initial and four-hour mean IOPs and percentage IOP reduction over four hours—treated eyes

Treatment	n	Starting mean IOP	SD	Final mean IOP (4 hours)	SD	IOP Reduction % over 4 hours
R-timolol (0.25%)	10	29.00	6.8	22.8	6.2	19.42
R-timolol (0.5%)	10	25.4	3.44	20.0	4.4	20.92
R-timolol (1.0%)	10	27.0	4.2	20.6	5.1	23.97
R-timolol (2.0%)	10	27.0	5.4	19.9	4.8	25.34
L-timolol (0.25%)	10	30.5	5.5	20.7	6.7	32.89
Placebo	10	30.2	7.1	27.1	5.7	8.98

Fig. 2 Mean fall in IOP: treated eyes. P=placebo. 0.25=D-timolol 0.25%. T=L-timolol 1.0%. 1.0=D-timolol 1%. 0.5=D-timolol 0.5%. 2.0=D-timolol 2%.

$p > 0.05$) ranging from 27.20 to 31.90 mmHg (Table 3). The pretreatment mean intraocular pressures for each group of 10 untreated eyes were the same or slightly higher (NS) than the treated fellow eyes. The mean intraocular pressures in the untreated eyes for each treatment group were all lowered four hours after treatment (Table 3). No significant difference could be detected in the untreated eyes between treatments or between treatment and placebo. Any

Table 3 Initial and four hour mean IOPs and percentage IOP reduction over four hours—untreated eyes

Treatment	n	Starting mean IOP (mmHg)	SD	Final (4 hours) IOP mmHg	SD	IOP Reduction %
R-timolol (0.25%)	10	29.00	5.4	25.9	5.93	8.51
R-timolol (0.5%)	10	27.2	4.2	22.9	3.75	15.53
R-timolol (1.0%)	10	28.5	4.93	25.2	4.69	11.05
R-timolol (2.0%)	10	28.1	4.7	26.1	3.7	6.49
L-timolol (0.25%)	10	31.9	4.04	26.1	3.87	18.08
Placebo	10	31.8	6.68	27.3	5.77	13.79

difference in percentage reduction of intraocular pressure between groups in the untreated eyes appeared to be random.

There were no significant differences in blood pressure, pulse, or pupil size between the different treatment groups and placebo at four hours in comparison with the pretreatment state. No subjective side effects were reported.

Discussion

Even allowing for the fact that the mean pretreatment IOPs were slightly though not significantly lower for D-timolol 0.5%, and less so for the D-timolol 1% and 2%, our results confirm that D-timolol concentrations of 0.5%–2% were effective in lowering an elevated intraocular pressure following single-drop application. These reductions were comparable to the reduction produced by 0.25% L-timolol following single-drop application. The percentage fall in IOP for the 0.25% L-timolol was greater than the D-timolol concentrations tested, though not significantly so. The slightly higher initial IOP for the 0.25% L-timolol group makes it difficult to make a completely reliable comparison on these data. The ocular hypotensive effect lasted throughout the period of the study (four hours).

The results of the studies by Share *et al.*⁶ indicate that D-timolol lowers intraocular pressure by the same mechanism of action as timolol. However, in extraocular tissues D-timolol is considerably less potent than L-timolol in blocking β -adrenergic receptors.^{6,8} This implies that the R-enantiomer may represent an ocular-selective antiglaucoma effect.

Table 2 Mean differences in IOP (mmHg) (SD)—treated eyes

Time from instillation	D-Timolol 0.25%	D-Timolol 0.5%	D-Timolol 1%	D-Timolol 2%	L-Timolol 0.25%	Placebo
1 hour	4.1 (1.74)	3.3 (1.68)	5.1 (1.78)	6.4 (1.92)	7.7 (1.99)	2.4 (1.4)
2 hours	5.4 (2.29)	4.9 (1.76)	5.4 (1.97)	6.9 (2.1)	8.9 (2.29)	3.0 (1.47)
4 hours	6.6 (2.54)	5.4 (2.04)	6.4 (1.84)	7.1 (2.25)	9.8 (2.09)	4.5 (1.65)

D-Timolol may act on a population of ocular β -adrenergic receptors which show relatively poor stereo selectivity. If studies on respiratory and cardiac function effects of R-timolol confirm the animal and tissue study data, there will be clear clinical advantages to be gained from the use of this more ocular-selective enantiomer.

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References

- 1 Katz IM, Hubbard WA, Getson AJ, Gould AL. Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. *Invest Ophthalmol Vis Sci* 1976; **15**: 489–92.
- 2 Zimmerman TJ, Kaufman HE. Timolol—beta-adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977; **95**: 601–4.
- 3 Mills KB. Blind randomised non-crossover long-term trial comparing topical timolol 0.25% with timolol 0.5% in the treatment of simple chronic glaucoma. *Br J Ophthalmol* 1981; **67**: 216–9.
- 4 Wasson BK, Gibson WK, Stuart RS, Williams HWR, Yates CH. Beta-adrenergic blocking agents 3-(3-substituted-amino-2-hydroxy-propoxy)-4-substituted-1,2,5-thiadiazoles. *J Med Chem* 1972; **15**: 651.
- 5 Liu JH, Bartels SP, Neufeld AH. Effects of L- and D-timolol on cyclic AMP synthesis and intraocular pressure in water-loaded, albino and pigmented rabbits. *Invest Ophthalmol Vis Sci* 1983; **24**: 1276–82.
- 6 Share NN, Lott VJ, Gautheron P, *et al.* R-enantiomer of timolol—a potential selective ocular antihypertensive agent. *Graefes Arch Clin Exp Ophthalmol* 1984; **221**: 234–8.
- 7 Keates EU, Stone R. The affect of D-timolol on intraocular pressure in patients with ocular hypertension. *Am J Ophthalmol* 1984; **98**: 73–8.
- 8 Chiou GCY. Effects of D-timolol on intraocular pressure, heart rate, cardiac contractibility and tracheal muscle function. *Curr Eye Res* 1983; **2**: 507–10.

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