Timolol in operated closed-angle glaucoma

CALBERT I. PHILLIPS

*From the Department of Ophthalmology, University of Edinburgh, and
Princess Alexandra Eye Pavilion, Royal Infirmary, Edinburgh*

SUMMARY Tonometry in 9 eyes (7 patients) provides some evidence that timolol eye drops are useful in improving control of pressure in eyes operated for closed-angle glaucoma. In cases 1 and 2 (Figs. 1 and 2) this beta 1 and 2 blocker reduced pressure consistently. Case 3 (Fig. 3) showed that timolol 0.5% twice daily was as effective as pilocarpine 2% or 4% with adrenaline 1%. The effect of timolol 0.5% in case 4 (Fig. 4) and case 6 (Fig. 6) was additive to pilocarpine and adrenaline; in case 5 (Fig. 5) it probably improved the effect of adrenaline, but in cases 4 and 5 there may have been some loss of effect with time. Case 7 (Fig. 7) showed a good effect of timolol, reversed on withdrawal, but pressure fell again in spite of continued withholding of timolol. Timolol will be especially valuable in the control of pressure if an operation involving iridectomy has not been completely successful in open-angle glaucoma or more especially in closed-angle glaucoma because it has no effect on the pupil. Miotics will tend to produce posterior pupillary synechiae because aqueous humour will go through the iridectomy, not under the edge of the pupil. The danger will be greater in eyes with closed-angle glaucoma because the pupil is closely applied to the anterior lens surface, which will also tend to produce irritative iridocyclitis.

In published work on the efficacy of timolol^{1–7} or other beta-blockers^{8–19} in open-angle glaucoma it is curious that there seems to be no mention of its use for chronic closed-angle glaucoma which has not been controlled by operation involving an iridectomy or in which the patient has refused operation. Given (in the Bayesian sense) all the evidence of efficacy of timolol, especially that it very probably acts by reducing the rate of production of aqueous humour,^{20–22} it would be reasonable to conclude that the drug would be effective in chronic closed-angle glaucoma if iridectomy or drainage operation has failed to control pressure satisfactorily; a similar argument would apply to cases of open-angle glaucoma with a failed drainage operation, to 'aphakic' glaucoma with or without a closed angle, 'pigmentary' glaucoma, low-tension glaucoma, or any form of 'secondary' glaucoma.

The following 7 patients are described to provide some support for the use of timolol in the control of cases of operated chronic closed-angle glaucoma. Such patients are not common, and it is hoped that a larger series over a longer period will be assembled to provide more definite evidence.

Patients and methods

Patients attending the glaucoma clinic for 'routine' monitoring of chronic closed-angle glaucoma following iridectomy or drainage operation were chosen. Timolol eye drops 0.25% or 0.5% were prescribed twice daily, usually in addition to pilocarpine $\pm$ adrenaline already being given. They were then asked to attend more frequently so that tonometric response to timolol could be assessed—at the same time of day as the pretimolol visits and tonometry. Applanation tonometry was done throughout by the same 3 glaucoma technicians. (Fields of vision were charted, and visual acuities etc. were also recorded at 4–6 monthly intervals.)

Results

Case 1 (Fig. 1) is the most convincing because he had a high pressure and no drug was used along with timolol in his right eye. (His left eye was predisposed to CAG and had had a successful peripheral iridectomy with normal visual acuity, discs, and pressure.) His right eye had lost all vision, with deep pathological cupping when he presented in 1969. Pilocarpine 2% 4 times daily reduced the tension for about 4 years, but it rose

Correspondence to Professor Calbert I. Phillips, Eye Pavilion, Chalmers Street, Edinburgh EH3 9HA.

Figs. 1-7 Graphs of ocular tensions in cases of operated closed angle glaucoma in which additional medical treatment was judged advisable. Ordinates: mmHg (applanation). Abscissae (not to consistent scale) show month and year in which tonometry was done. See text for case histories. X = right eye, O = left eye.

again in 1973 when a sector iridectomy was done, in spite of the absence of vision, in order to delay degenerative changes. For about 5 years tension remained under or around 30 in a comfortable eye. Gonioscopy showed only 2/12 of the angle open. Timolol 0.5% reduced pressure to 20 or less for 3 months, but on withdrawal of treatment the pressure rose again; when the drug was recommenced a satisfactory response was again obtained. This patient will be continued on timolol indefinitely.

Case 2 (Fig. 2) has a lower pressure, but the results are reasonably convincing. He presented with bilateral subacute closed-angle glaucoma. (His left eye has had a successful sector iris inclusion which has controlled its pressure, with normal vision.) When the pressure in the right eye rose to 25 mmHg a few weeks after sector iridectomy, timolol was given and reduced the tension impressively. Gonioscopy showed 4/12 of the angle open. Subsequently the slight tendency for the pressure to rise again may be the result of, say, closure of

the limbal wound (though no bleb was seen) or a loss of effectivity of the drug. The pressure, however, rose further to 24 mmHg when the drug was stopped, but fell again when it was restarted.

Case 3 (Fig. 3) shows that timolol 0.5% twice daily is as effective as pilocarpine 2% or 4% with adrenaline 1% in the left eye. (The right eye had a successful sector iris inclusion in 1974 which has controlled tension, fields, and visual acuity.) A left sector iridectomy in 1974 seemed to require the addition of pilocarpine and adrenaline to control the tension. The angle was 4/12 open on gonioscopy. On withdrawal of all treatment pressure rose to 24 mmHg on 28 May 1979 but it fell to 19 or less for at least 3 months thereafter on timolol 0.5% twice daily.

Case 4 (Fig. 4) in spite of rather low pressure shows reasonably good evidence of an additive effect of timolol 0.5% to pilocarpine and adrenaline. Both the right (subacute CAG superimposed on chronic CAG with field loss) and left (subacute CAG) eyes responded dramatically well to pilo-

Fig. 2 See Fig. 1 for explanation.

Fig. 3 See Fig. 1 for explanation.

Fig. 4 See Fig. 1 for explanation.

carpine at presentation, so that bilateral sector iridectomies were done with an interval of 1 week between. A month later, however, pilocarpine and adrenaline were judged necessary and reduced pressures to just over 20 mmHg. The open 7/12 of the right angle was heavily pigmented; 5/12 of the open 10/12 of the left angle was also heavily pigmented. Timolol 0.5% was added twice daily to both eyes when it became available and seemed to reduce the pressure further. Any or all of the 3 drugs may have lost some effect as the pressure tended to rise during the next few months—or a late postoperative change may have occurred. However, withdrawal of timolol raised the pressure from R.19 and L.20 to R.24 and L.25 which was reversed when the drug was restarted.

Case 5 had bilateral peripheral iridectomies in 1954, but in 1977 pressures rose, so that adrenaline twice daily was given with reasonable control of pressure, probably improved by timolol 0.5% twice daily. Gonioscopy showed the right angle to be 5/12 open, and the left 4/12 open. Some loss of effect of timolol seems more likely than of adrena-

line by August 1979. Pressure rose slightly more when timolol was withdrawn, and reintroduction of timolol again seemed effective.

In case 6 (Fig. 6) the right eye (X—X) is included for completeness, though after its sector iridectomy the angle was completely open. The left eye showed poor control after a drainage operation, although the angle was 7/12 open. Pilocarpine and adrenaline obtained some reduction in pressure, which was considerably improved by added timolol 0.5% twice daily, albeit with some fluctuations. Withdrawal of timolol resulted in a rise of left pressure (not right, that eye being hardly glaucomatous, if at all), which was reversed when timolol was restarted.

Case 7 (Fig. 7) may not be justifiably included because in 1979 angles appeared open all round on gonioscopy (but see discussion). However, the right eye presented with acute CAG in 1963 for which an iris inclusion was done, followed in 1964 by a left peripheral iridectomy. Pilocarpine and adrenaline were used from 1968 to 1979. Timolol 0.5% twice daily was added and caused an impressive fall in tension in February 1979; during the

Fig. 5 See Fig. 1 for explanation.

Fig. 6 See Fig. 1 for explanation.

Fig. 7 See Fig. 1 for explanation.

next few months pressure rose again. Withdrawal of timolol, however, caused the pressure to rise further. It was decided to continue to withhold timolol, and, very surprisingly, pressure has fallen progressively: no satisfactory explanation seems available.

Discussion

It would be consistent with the known properties of timolol that it should be effective in cases of closed-angle glaucoma in which drainage operation or iridectomy had failed to control the pressure satisfactorily. That theoretical conclusion is supported by the evidence presented in the series of cases described in this paper. However, a double-blind controlled trial on a larger series would be preferable—but suitable patients are not common. Patients with chronic CAG or predisposed to CAG, who have refused operation, or patients for whom operation is not advisable for some reason, would also benefit from timolol (along with pilocarpine, of course) since reduced production of aqueous humour would reduce the ballooning of the iris and therefore open the angle.

Timolol is valuable for the medical treatment of open-angle glaucoma but is even more suitable for eyes which have had iridectomy ($\pm$ drainage operation) yet require medical treatment, especially in the case of CAG. After an iridectomy, peripheral or sector, presumably aqueous humour takes the path of least resistance, that is, does not pass under the pupil margin. Posterior synechiae are therefore

very likely to develop, especially of course if there is postoperative iridocyclitis. In eyes with CAG the pupil is more closely applied to the anterior lens surface than in eyes with OAG, so that posterior synechiae are more likely to develop in the former. *Miotics will aggravate this tendency* and may well in addition elicit some iritic response to mechanical trauma at the pupil, which would be an additional factor in production of synechiae. Pupillary synechiae will tend to produce occlusio pupillae and also cataract, especially when the pupil is small and its margin intact (as in case 7). (Adrenaline would not carry this risk, but significant pupil dilation even after iridectomy could compromise the narrow angle, as well as impose the optical disadvantages of mydriasis.) Accordingly, timolol is pre-eminently suited for control of pressure after an operation involving an iridectomy, both in OAG and especially in CAG.

No patient in this series suffered any untoward side effects from timolol eye drops.

Some graphs (Figs. 1–7) suggest that in some cases timolol may lose some of its effect—also a characteristic of many drugs, including pilocarpine and adrenaline. In studies on open-angle glaucoma only a slight loss of effect in the first few weeks of treatment has been observed.^{5 7 19 23 24}

Gonioscopic findings were not always consistent with tonometry. Sometimes it was difficult to be sure that posterior trabecular synechiae were absent in parts of the angle apparently open. Sometimes it was suspected that, although areas of angle were open, the meshwork was in fact occluded by im-

pacted peripheral iris (especially when pigmented) which had been left behind when iris bombé had collapsed, or when mechanical traction at (sector) iridectomy had failed to pull all layers of iris clear of the meshwork.

ADDENDUM. In a publication²⁵ received since this paper was written, namely, 'Timolol: its effectiveness in different types of glaucoma', Wilson *et al.* provide evidence in support of its title (including cases of chronic closed-angle glaucoma). Lass and Pavan-Langston²⁶ have also demonstrated its efficacy in closed-angle glaucoma following penetrating keratoplasty.

References

- ¹Katz IM, Hubbard WA, Getson AJ, Gould AL. Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. *Invest Ophthalmol* 1976; **15**: 489-92.
- ²Zimmerman TJ, Kaufman HE. Timolol A β -adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977; **95**: 601-4.
- ³Zimmerman TJ, Kaufman HE. Timolol dose response and duration of action. *Arch Ophthalmol* 1977; **95**: 605-7.
- ⁴Saari KM, Airaksinen PJ, Jaanio EAT. Hypotensive effect of timolol on secondary glaucoma in chronic uveitis. *Lancet* 1978; **442**.
- ⁵Demaillly P, Lehner MA, Pigot C. Le maléate de timolol—résultat de son action à long terme dans le traitement du glaucome chronique primitif à angle ouvert. *J Fr Ophthalmol* 1978; **1**: 743-4.
- ⁶Johnson SH, Brubaker RF, Trautman JC. Absence of an effect of timolol on the pupil. *Invest Ophthalmol* 1978; **17**: 924-6.
- ⁷Boger WP, Puliafito CA, Steinert RF, Langston DB. Timolol ophthalmic solution in open angle glaucoma. *Ophthalmology* 1978; **85**: 259-67.
- ⁸Phillips CI, Howitt G, Rowlands DJ. Propranolol as ocular hypotensive agent. *Br J Ophthalmol* 1967; **51**: 222-6.
- ⁹Coté G, Drance SM. The effect of propranolol on human intraocular pressure. *Can J Ophthalmol* 1968; **3**: 207-12.
- ¹⁰Bucci MG, Missiroli A, Giraldi JP, Virno M. Local propranolol in the treatment of glaucoma. *Boll Oculist* 1978; **47**: 51-60.
- ¹¹Vale J, Phillips CI. Practolol (Eraldin) as an ocular hypotensive agent. *Br J Ophthalmol* 1973; **57**: 210-5.
- ¹²Hagedoorn A, Tjoa ST. Practolol in the control of intraocular tension. *Lancet* 1974; **1**: 733.
- ¹³Bucci M. Topical administration of oxprenolol (β -blocking agent) in the treatment of glaucoma. *Boll Oculist* 1976; **54**: 235-42.
- ¹⁴Sharaf EED, Aaroun EA, Ishaac A, El Shewy TM, Nassef AEH. The effect of some β adrenergic blockers on human intraocular pressure. *Exp Eye Res* 1974; **19**: 223-5.
- ¹⁵Phillips CI, Macdonald MJ, Gore SM, Cullen PM. Atenolol (Tenormin ICI) eye drops in glaucoma. *Br J Ophthalmol* 1977; **61**: 349-53.
- ¹⁶Kriegelstein GK, Sold-Darseff J, Leydhecker W. The intraocular pressure response of glaucomatous eyes to topically applied bupranolol. A pilot study. *Albrecht von Graefes Arch Klin Ophthalmol* 1977; **202**: 81-6.
- ¹⁷Takase M, Komuro S, Nanbu H, Araie M. Effects of topical bupranolol hydrochloride on the intraocular pressure. *Jpn J Ophthalmol* 1978; **22**: 142-54.
- ¹⁸Pandolfi M, Öhrström A. Treatment of Ocular Hypertension with oral beta-adrenergic blocking agents. *Acta Ophthalmol (Kbh)* 1974; **52**: 464-7.
- ¹⁹Nielsen NV. Timolol hypotensive effect: used alone and in combination for treatment of increased intraocular pressure. *Acta Ophthalmol (Kbh)* 1978; **56**: 504-9.
- ²⁰Zimmerman TJ, Harbin R, Pett M, Kaufman HE. Timolol and facility of outflow. *Invest Ophthalmol* 1977; **16**: 623-4.
- ²¹Yablonski ME, Zimmerman TJ, Waltman SR, Becker B. A fluorophotometric study of the effect of topical timolol on aqueous humour dynamics. *Exp Eye Res* 1978; **27**: 135-42.
- ²²Sonntag JR, Brindley GO, Shields MB. Effect of timolol therapy on outflow facility. *Invest Ophthalmol* 1978; **17**: 293-6.
- ²³Dausch D, Honegger H. Timolol maleate ophthalmic solution in the treatment of glaucoma. Selected papers from XXIII Int Congr Ophthalmol, Kyoto. Rahway, NJ: Merck, Sharpe and Dohme, 1978; 5.
- ²⁴Ritch R, Hargett NA, Podos SM. The effect of 1.5% timolol maleate on intraocular pressure. *Acta Ophthalmol (Kbh)* 1978; **56**: 6-10.
- ²⁵Wilson RP, Kanal N, Spaeth GL. Timolol: its effectiveness in different types of glaucoma. *Ophthalmology* 1979; **86**: 43-50.
- ²⁶Lass JH, Pavan-Langston D. Timolol therapy in secondary angle closure glaucoma post penetrating keratoplasty. *Ophthalmology* 1979; **86**: 51-9.