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Sublingual timolol—an alternative to topical medication in glaucoma?

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Abstract

***Aims*—To assess whether timolol drops lower a raised intraocular pressure (IOP) when given sublingually. This route of administration would be useful for glaucoma patients who are unable to instil their own drops—for example, because of stroke, poor vision, arthritis, poor coordination, or blepharospasm.**

***Methods*—A placebo controlled randomised, double masked, crossover study was undertaken in the glaucoma clinic of a large teaching hospital. Twelve patients with ocular hypertension with IOPs over 21 mm Hg, normal optic discs, and full visual fields were examined by Humphrey perimetry. Single dose units of timolol maleate 0.5% drops and normal saline drops were given by instillation in one eye or sublingually. The IOP of both eyes, pulse rate, and blood pressure were all measured before and after each type of drop and route of administration.**

***Results*—Two hours after instillation of timolol in one eye, the IOP in the treated eye was reduced by a mean of 8.5 mm Hg (p=0.0000), and by 1.66 mm Hg in the fellow eye (p=0.03). Two hours after sublingual instillation of timolol, the IOP was reduced by 7.55 mm Hg in the study eye (p=0.0000) and by 7.7 mm Hg in the fellow eye (p=0.0000). There was an equal amount of reduction in pulse rate by either route, but there was no significant change in blood pressure.**

***Conclusions*—The results show that, at least after 2 hours, sublingual treatment is almost as effective as topical treatment in lowering a raised IOP.**

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Since the introduction of the first topical β blocker (timolol) for use in glaucoma in 1978, this form of therapy has become the commonest medical treatment for the condition. The majority of patients with glaucoma are over 70 years of age, but it is also this group who may have difficulty in inserting their eyedrops. In addition, many of these patients live alone and may have difficulty in obtaining help for their medication. A simple alternative route for delivering the therapeutic agent in the form of a sublingual application was therefore investigated.

Materials and methods

A placebo controlled, randomised double masked crossover study was designed to compare the effect on intraocular pressure (IOP) of timolol 0.5% drops given sublingually and topically. Ethics committee approval was obtained before commencement of the study. After appropriate explanation and informed consent, 12 patients with ocular hypertension (mean age 68.4 years, range 53–87 years) with IOPs over 21 mm Hg, normal optic discs, and full visual fields by Humphrey perimetry, were recruited. Patients were excluded if they were already using topical IOP lowering agents; were being treated with systemic β blockers or calcium channel blockers; were known to suffer from systemic hypertension, asthma, bronchitis, cardiac failure, sinus bradycardia or heart block; if they had undergone previous ocular surgery; or there was any corneal condition which prevented reliable applanation tonometry.

For each arm of the study, IOPs, seated blood pressure (Korotkov sounds I and V), and resting pulse rate were performed between 9.00 and 9.30 before instillation of the test drop. The four arms, each separated by a minimum of 7 days and performed in a random order, consisted of ocular instillation of timolol or placebo, and sublingual instillation of timolol or placebo. Ocular instillation was followed by punctal occlusion for 60 seconds. The sublingual drop was placed at the base of the tongue and the patient asked not to swallow for 30 seconds. Two hours after drug or placebo, all pretreatment tests were repeated. Two tailed analysis was performed using the Student's paired t test to test for any change in IOP, pulse, or blood pressure after each of the treatments. Significance was taken at values of $p \leq 0.05$.

One drop from single dose units of timolol maleate 0.5% (Glaucol, Baker Norton) and saline 0.5% (Minims, Chauvin) each measuring approximately 35 μl per drop, were used as the medication doses. Both of the solutions were contained in similar semiopaque droppers, although the shapes were slightly different. The patients were unaware of which solution they received.

Goldmann applanation tonometry was performed by an experienced tonometrist, with the tonometer being calibrated each morning. Three readings were obtained from each eye and the mean was used for the analysis. The tonometrist was masked to the tonometry readings which were noted by a clinic nurse who altered the tonometer dial after each reading. The tonometrist was also masked to the site and type of drop used which was inserted by another assistant who performed the

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randomisation process. Randomisation for the crossover was performed by the picking of folded labels on which were written the site of treatment and solution to be used.

One eye of each individual was selected as the treatment eye for the duration of the study from a randomised computer printout of right or left eyes, with the treatment eye being selected on the first visit. Each patient attended on four occasions.

Results

All 12 patients (four female and eight male) completed the four arms of the study. The right eye was the study eye in seven patients and the fellow eye in five patients.

PRETREATMENT INDICES

IOP

The mean IOPs in the study eyes were 23.47 (SD 3.2) mm Hg, 23.69 (2.48) mm Hg, 24.43 (2.62) mm Hg, and 24.22 (3.49) mm Hg, and were not significantly different for each phase of the study. The mean IOPs in the fellow eyes were 23.0 (2.30) mm Hg, 22.49 (2.0) mm Hg, 23.44 (3.01) mm Hg, and 24.04 (2.33) mm Hg. These were not significantly different except for one pretreatment comparison (fellow eye ocular timolol versus fellow eye sublingual timolol, p=0.03). There was also no significant difference in the mean IOPs between the study and fellow eyes for each phase of the study.

Pulse rate

The mean pulse rates were 79.3 (SD 12.16) beats per minute (bpm), 79.3 (10.49) bpm, 79.0 (16.01) bpm, and 77.0 (14.08) bpm, and were not significantly different from each other.

Blood pressure

The mean systolic pressures of 141.67 (18.99) mm Hg, 140.0 (24.06) mm Hg, 144.58 (18.40) mm Hg, and 144.83 (16.11) mm Hg were not significantly different from each other. The mean diastolic pressures of 89.42 (12.88) mm Hg, 89.5 (14.43) mm Hg, 90.04 (12.02) mm Hg, and 92.5 (12.88) mm Hg were also not significantly different.

POST TREATMENT INDICES—PLACEBO PHASES

IOP

Two hours after administration of placebo drops, the mean IOP in the study eye was 22.76 (3.69) mm Hg after ocular treatment, compared with 23.83 (2.83) mm Hg after sublingual treatment. These values do not show a significant change from the pretreatment IOPs in the study eye (p=0.3 for both), and were not significantly different from each other (p=0.2).

The mean IOP in the fellow eye was 22.28 (2.54) mm Hg after ocular treatment to the study eye, and 23.24 (2.48) mm Hg after sublingual treatment. There was no significant change from the pretreatment IOPs in the fellow eyes (p=0.2 and p=0.7 respectively), and they were not significantly different from each other (p=0.2).

Pulse

There was no change in mean pulse rates after sublingual placebo (79.0 (16.01) bpm and 76.33 (11.63) bpm; p=0.2) but the pulse did drop from a mean of 79.33 (12.16) bpm to 75.0 (11.7) bpm after ocular placebo (p=0.005).

Blood pressure

There was no change in systolic pressure after topical treatment with placebo drops (141.67 (18.99) mm Hg, p=1.0). Diastolic pressure changed from 89.42 (12.88) mm Hg to 86.92 (1.14), (p=0.3). After sublingual administration of placebo drops, systolic pressure changed from 144.58 (18.40) mm Hg to 143.75 (14.48) mm Hg (p=0.8), and diastolic pressure from 90.01 (12.02) mm Hg to 89.17 (15.20) mm Hg (p=0.7).

ACTIVE DRUG PHASES

IOPs (see Table 1)

Two hours after ocular administration of timolol drops followed by punctal occlusion for 60 seconds, there was a significant difference in the IOP decrease between the study and the fellow eye, p=0.0000. Two hours after sublingual administration of timolol drops, there was no significant difference in the IOP decrease between the study and fellow eye, p=0.7.

There was no significant difference in the post treatment IOP of the study eye after ocular or sublingual treatment (p=0.1), or between the study eye after ocular treatment and the fellow eye after sublingual timolol (p=0.2). There was a significant difference in the mean IOP fall in the fellow eye after topical treatment in the study eye when compared with the the IOP fall in the study eye (p=0.0005) and in the fellow eye (p=0.008) after sublingual treatment with timolol.

Pulse

There was a significant fall in the mean pulse rate by 11.16 bpm (14%), both after ocular treatment with timolol (despite punctal occlu-

Table 1 Intraocular pressure (IOP) changes (SD) after timolol

	Ocular timolol		*Sublingual timolol*	
	Study eye	*Fellow eye*	*Study eye*	*Fellow eye*
Pretreatment IOP (mm Hg)	23.69 (2.48)	22.49 (2.0)	24.22 (3.49)	24.04 (2.33)
IOP (mm Hg) 2 h after treatment	15.19 (1.74)	20.83 (2.32)	16.67 (2.99)	16.34 (3.74)
IOP decrease (mm Hg)	8.5	1.66	7.55	7.7
Percentage decrease	35.9	7.4	31.2	32.0
Significance level	p=0.0000	p=0.03	p=0.0000	p=0.0002

sion) (from 79.33 (10.49) bpm to 68.17 (8.96) bpm; p=0.0000), and after sublingual treatment with timolol by 13.33 bpm (17.3%) (from 77.0 (14.08) bpm to 63.67 (12.62) bpm; p=0.0006). The reduction was similar by both routes of administration (p=0.2).

Blood pressure

There was no significant change in the mean systolic pressure after ocular treatment and sublingual treatment (from 140 (24.06) mm Hg to 141.25 (19.79) mm Hg, p=0.6; and from 144.83 (16.11) mm Hg to 142.08 (23.98) mm Hg, p=0.6 respectively), nor in the diastolic pressure after ocular treatment and sublingual treatment (from 89.50 (14.43) mm Hg to 93.33 (12.85) mm Hg, p=0.07; and from 92.5 (12.88) mm Hg to 87.75 (16.29) mm Hg, p=0.3 respectively).

Discussion

An effective oral medication with minimal side effects would be a welcome addition to our present repertoire of glaucoma treatments, especially as it may be expected to improve compliance in some problem patients.

Following the demonstration of the ocular hypotensive effect of propranolol by Phillips *et al* in 1967,[1] many β blockers have been investigated for their effectiveness in reducing IOP, the most notable being timolol. Williamson *et al* found once daily oral nadolol therapy at doses of 20 mg and 40 mg comparable in efficacy to twice daily topical timolol at 0.25% and 0.5%, over both the short and the long term in normal volunteers.[2] Unfortunately, Dowd *et al* only achieved temporary control in newly diagnosed patients using nadolol at 20 mg and at 40 mg.[3] This suggests that the response of normal patients and those with abnormalities of aqueous humour dynamics may be different.

Atenolol has been used at a dose of 50 mg daily and was found to cause a significant and sustained fall in IOP (25.5% on the first day) in both normal and raised IOP patients,[4] but both systemic blood pressure and pulse rate were lowered significantly, which is undesirable in glaucoma therapy as optic nerve perfusion may be reduced.

Maren *et al* treated patients with 10 mg of timolol orally and observed a decrease in IOP of 3.35 mm Hg (20.1%); however when topical timolol was added to the regimen, a further significant reduction in IOP of 1.05 mm Hg occurred.[5] They suggested that receptor binding in the eye is incomplete after oral administration of timolol, whereas high local levels of timolol from topical administration are much more effective. They concluded that topical treatment alone seemed to give the maximum IOP reducing effect, although those patients receiving oral β blockers for systemic diseases could benefit from additive topical timolol treatment to get a further reduction in IOP.

For the purpose of our study, a separation period of 7 days between each visit was felt to be adequate as we were only using a single rather than a cumulative dose of timolol. Also, the peak plasma levels of timolol occur between 0.5 and 1.5 hours after ocular instillation,[6] and it is not detectable in the evening following an ocular dose of timolol in the morning.[7]

We also observed strict occlusion of the lacrimal punctum after both of the ocular doses, as it has previously been shown that there is reduced systemic drug absorption after instillation of topical timolol 0.5% if the eyes are closed or the lacrimal punctum is occluded.[8] Punctal occlusion for 60 seconds was chosen because scintillography has shown that the major portion of an eyedrop is pumped through the lacrimal drainage system into the nasolacrimal duct within the first 30 seconds if the lacrimal punctum is not occluded.[9] It is possible that longer occlusion of the lacrimal punctum might reduce nasal mucosal absorption even further.

As seen regularly in clinical practice, topical application of timolol caused a reduction in IOP in the treated (study) eye, as well as the untreated fellow eye. The latter, although significant, was only 19.53% of the drop of the former, and is a much smaller contralateral effect than that found previously.[10] The reason for this could be the strict punctal occlusion we performed after instillation of topical treatment which reduces (but does not seem to abolish) systemic absorption of the drug.

During the course of our study, Dunham *et al* published the results of a study comparing the IOP lowering properties of lingual and ocular timolol in normal volunteers.[11] The IOP reduction was a mean of 3.1 mm Hg (23.9%) from an average pretreatment IOP of 13 mm Hg after ocular treatment, and 3.9 mm Hg (30%) after lingual timolol. However, in their study, punctal occlusion was not performed after topical instillation of drops, and systemic instillation involved placing the drops on the subjects' tongues, rather than sublingually. The sublingual route may be preferable as instillation in this site is less likely to result in swallowing the agent before its transmucosal absorption, as we believe that this absorption through the buccal mucosa is responsible for the high IOP reductions we obtained.

Sublingual timolol caused an IOP drop which was very similar to that seen after topical treatment, which indicates that sublingual treatment may be as effective as topical treatment in lowering the IOP of the target eye. As expected, this effect was seen in both the study and the fellow eye. Lowering the IOP in a fellow eye with normal pressure (for example, in unilateral glaucoma or in an eye having undergone previous trabeculectomy), may be considered undesirable by some. In such cases, we would expect a smaller and clinically insignificant effect on IOP in the fellow eye because the pretreatment IOP is lower. However, there may be an effect on optic nerve head perfusion which we are unable to measure.

First pass metabolism of timolol by the liver accounts for at least 25% of the administered oral dose,[6] and the IOP reductions we have seen in both the study and the fellow eyes after sublingual administration are probably because maximum plasma levels are obtained

rapidly, leading to early receptor blockade before drug metabolism can occur. This may also account for the fact that these significant reductions were obtained with a relatively small dose of timolol (35 µl of a 0.5% solution) compared with the larger oral doses used in previous studies.

There was a similar and significant fall in pulse rate after both topical and sublingual routes of administration (despite punctal occlusion after the topical treatment). The reduction which would cause greatest concern (to < 50 bpm) occurred in those patients who had a pretreatment pulse rate of 60 bpm in the sublingual arm of the study. If sublingual treatment is considered, it would clearly be advisable to perform an ECG both before and after treatment in those patients with a resting pulse rate of 65 bpm or less.

The one significant pretreatment IOP comparison (fellow eye ocular timolol versus fellow eye sublingual timolol, p=0.03) may have been a chance finding as the same pretreatment comparison for the study eye was not significant (p=0.1). We are unable to explain adequately why there was a significant fall in pulse rate 2 hours after topical treatment with the placebo. It may have occurred because the patients were more relaxed after a wait of 2 hours between pre- and post treatment pulse measurements. There was a small rise in systolic and diastolic blood pressure after topical timolol, and a small fall after sublingual timolol. However, neither was significant and therefore the benefits of IOP lowering on optic nerve head blood flow would not be counteracted by a reduction in perfusion pressure from lower blood pressure.

Our results show that, at least after 2 hours, timolol used sublingually may be a useful ocular hypotensive agent, particularly for those patients who are unable to insert their own drops reliably, and for those patients with an ocular sensitivity to the agent or its preservative. It is encouraging that none of our patients remarked on any unpleasant taste sensation caused by the sublingual administration of drops.

The results of this study also indicate that sublingual β blocker administration in glaucoma should be researched further. If a rapidly absorbing single dose vehicle can be developed, the potential for 'overdosing' the patient with additional drops will be reduced. This hazard was avoided in our study thanks to the insertion of drops from single dose units by a professional rather than by the patients themselves. In addition, the longer term efficacy of this route of medication requires investigation, as does the effect on respiratory function.

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