British Journal of Ophthalmology, 1988, **72**, 598–600

Dopamine-2 receptor blockade does not affect the ocular hypotensive action of timolol

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SUMMARY We have shown that metoclopramide, a dopamine-2 antagonist, failed to antagonise the ocular hypotensive action of timolol. The practical implication of combining dopamine agonists with β-adrenoceptor antagonists in the treatment of glaucoma is discussed.

Mechanisms other than β-adrenoceptor antagonism were suggested by some workers involved in the mechanism of hypotensive action of timolol in the eye. The D-isomer of timolol (D-timolol) was shown to have potent ocular hypotensive action in animals associated with minimal classical β-adrenoceptor antagonistic action.[1,2] Watanabe and Chiou[3] showed that incubation of the rabbit iris root ciliary body preparation with timolol resulted in a decrease in dopamine content when compared with control preparations. Alcondon *et al.*[4] showed that pretreatment of rabbit eyes with atropine significantly antagonised the ocular hypotensive action of timolol and propranolol.

Mekki *et al.*[5–7] showed that stimulation of dopamine-2 receptors can reduce intraocular pressure (IOP) in man. Mekki and Turner[7] and Lavin and Andrews[8] have also shown that the two dopamine receptor blockers, metoclopramide and haloperidol, have no ocular hypotensive action in man, though metoclopramide antagonises the ocular hypotensive action of bromocriptine.[7]

We have investigated whether stimulation of dopamine-2 receptors is involved in the mechanism of the ocular hypotensive action of timolol by observing the effect of blocking these receptors with metoclopromide prior to the administration of timolol.

Subjects and methods

Six healthy volunteers, three males and three females, aged 22–35 years participated in this study. None had a history of asthma or wore contact lenses.

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Each volunteer attended on three occasions one week apart at the same time of day. In each session baseline measurements of intraocular pressure (IOP) were taken by non-contact tonometry[9] and followed by one of three treatments: placebo, timolol alone, or metoclopramide followed by timolol. Three IOP measurements were taken at each time point and the mean was recorded. The treatment administration was arranged as follows: an intravenous injection of either metoclopramide 10 mg or matching placebo was given, folowed 15 minutes later by one drop of timolol 0·5% or placebo into the conjunctival sac of the left eye only, resulting in the three combinations. The treatments were given double-blind balanced design based on two Latin squares. IOP was then measured at one and at two hours after instillation of timolol eye drops. The study has been approved by the local Ethics Committee.

The baseline readings were compared by 2-way analysis of variance, and within-subject comparison revealed no statistical difference between the three trial sessions. The areas under the post-treatment response versus time curves for each subject on each treatment were calculated and compared by analysis of variance. The areas under the curves are presented in Table 1.

Results

A graphical representation of the IOP responses is shown in Fig. 1. Timolol resulted in a significant fall of IOP when compared with placebo on both occasions, that is, alone ($p<0·05$) and after metoclopramide ($p<0·01$). There was also a small decrease of IOP in the right (untreated) eye, but this did not reach statistical significance.

Table 1 *Areas under the post-treatment intraocular pressure response versus time curves*

Subject	*Placebo*	*Timolol*	*Metoclopramide and timolol*
Left eye			
1	8·5	6·7	6·3
2	5·9	3·9	3·5
3	9·9	9·5	9·5
4	10·9	7·2	5·5
5	9·7	9·7	9·5
6	8·0	7·7	6·4
Right (untreated) eye			
1	8·3	7·4	8·7
2	8·9	5·7	5·7
3	15·7	12·5	15·5
4	10·5	8·7	8·2
5	11·5	9·7	12·2
6	9·2	9·5	8·4

There was no difference between the two responses to timolol: $F(1,10)=0{\cdot}09$, $p>0{\cdot}35$.

Discussion

We have investigated the effect of pretreatment with metoclopramide on the ocular hypotensive action of timolol. As the aim of this experiment was not to confirm the absence of an ocular hypotensive action of metoclopramide[7] or to study other interactions, we did not include an additional treatment with metoclopramide alone.

These results show that pretreatment with metoclopramide, a selective dopamine-2 receptor antagonist, did not affect the ocular hypotensive action of timolol. We therefore conclude that stimulation of dopamine-2 receptors does not have an important role in the mechanism of action of timolol in lowering IOP. In high concentrations metoclopramide can also block dopamine-1 receptors,[10] but even if this occurred in our study it did not affect the ocular hypotensive action of timolol. The dose of metoclopramide used was the same as that which blocked the action of bromocriptine in our earlier study.[7]

Although results from animal experiments show that dopaminergic blockade can be associated with an ocular hypotensive action,[11,12] and that the action of timolol may be related to the dopaminergic system,[3] it seems that this is unlikely in man.

Bromocriptine and timolol, therefore, lower IOP by different mechanisms. This finding is not merely of academic interest. One or more dopamine agonists may be introduced for the treatment of glaucoma. If so, a combination with a β-adrenoceptor antagonist may result in potentiation of the ocular hypotensive action.

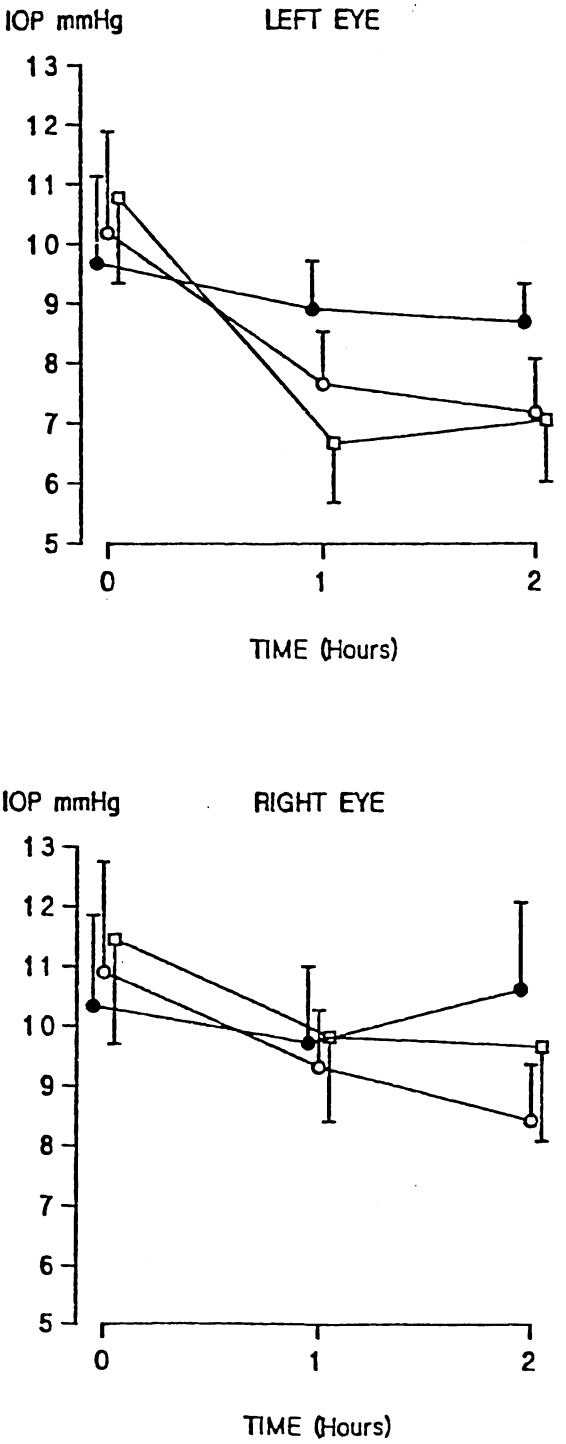

Fig. 1 *IOP changes (mean±SEM) after (□) metoclopramide and timolol, (○) timolol alone, and (●) placebo.*

We thank Dr M A Rhandawa for assistance in the study.

References

1 Chiou GCY. Effects of D-timolol on intraocular pressure, heart rate, cardiac contractility and tracheal muscle function. *Curr Eye Res* 1983; **2:** 507–10.
2 Share NN, Lotti VJ, Gatheron P, *et al.* R-enantiomer of timolol: a potential selective ocular antihypertensive agent. *Graefs Arch Clin Exp Ophthalmol* 1984; **221:** 234–8.
3 Watanabe K, Chiou GCY. Action mechanism of timolol to lower the intraocular pressure in rabbits. *Ophthalmol Res* 1983; **15:** 160–7.
4 Alkondon M, Ray A, Sen P. Autonomic regulation involved in the ocular hypotensive action of beta adrenergic blocking agents. *J Pharm Pharmacol* 1986; **38:** 319–22.
5 Mekki QA, Hassan SM, Turner P. Bromocriptine lowers intraocular pressure without affecting blood pressure. *Lancet* 1983; i: 1250–1.
6 Mekki QA, Warrington SJ, Turner P. Bromocriptine eyedrops lower intraocular pressure without affecting prolactin levels. *Lancet* 1984; i: 287–8.
7 Mekki QA, Turner P. Stimulation of dopamine receptors (type 2) lowers human intraocular pressure. *Br J Ophthalmol* 1985; **69:** 909–10.
8 Lavin MJ, Andrews V. Is haloperidol a useful glaucoma treatment? *Br J Ophthalmol* 1986; **70:** 448–50.
9 Grolman B. A new tonometer system. *Am J Optom Physiol Opt* 1972; **49:** 646–60.
10 Cavero I, Mesingham R, Lefevre-Borg F. Peripheral dopamine receptors, potential targets for a new class of antihypertensive agents. Part I: Subclassification and functional description. *Life Sci* 1982; **31:** 939–48.
11 Chiou GCY. Ocular hypotensive actions of haloperidol, a dopaminergic antagonist. *Arch Ophthalmol* 1984; **102:** 143–5.
12 Chiou GCY, Chiou FY. Dopaminergic involvement in intraocular pressure in the rabbit eye. *Ophthalmic Res* 1983; **15:** 131–5.

Accepted for publication 18 May 1987.