

Stimulation of dopamine receptors (type 2) lowers human intraocular pressure

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SUMMARY The interaction between bromocriptine and metoclopramide on intraocular pressure (IOP), pupil diameter, and other parameters were studied in healthy volunteers. Pupil diameter was not affected by both treatments and only bromocriptine lowered IOP. Prior treatment with metoclopramide blocked the IOP-lowering effect of bromocriptine. It is concluded that bromocriptine lowers IOP by stimulation of dopamine-2 receptors.

Oral bromocriptine (1.25 mg single dose) lowers intraocular pressure (IOP) in healthy volunteers without affecting blood pressure or pupil diameter.¹ Topical bromocriptine lowers IOP without affecting pupil diameter or prolactin levels.² Bromocriptine has dopamine 2 (DA₂) receptor agonist and dopamine 1 (DA₁) and alpha adrenoceptor blocking actions.^{3,4} Metoclopramide (a substituted benzamide) is a specific DA₂ receptor antagonist.^{5,6} We planned to study the effects of these two compounds alone and in combination in healthy volunteers on IOP, serum prolactin, pupil diameter, heart rate, and blood pressure to evaluate the interaction between them and to try to find which property of bromocriptine lowers IOP.

Materials and methods

Eight healthy male volunteers participated in this study. None wore contact lenses. They attended on four occasions, at least seven days apart, at the same time of the day (10.30-11.00 am) to receive either metoclopramide (10 mg) or matched placebo intravenously followed (15 minutes later-time zero) by either bromocriptine (1.25 mg) or a matched placebo tablet orally in a randomised double blind balanced design on the basis of two four-by-four Latin squares. They arrived fasting, and nothing except water to quench thirst was allowed until two hours after dosing, when a light meal was provided.

Pupil diameter, radial pulse rate, blood pressure (sitting), intraocular pressure, and prolactin level were measured in that order, before and at 1, 2, 3, and 4 hours after the subject took the tablet. Pupil

diameter was measured by a pupil gauge,⁷ blood pressure by a Hawksley random zero sphygmo manometer, intraocular pressure by non-contact tonometry,^{8,9} and serum prolactin levels by radioimmunoassay.

Volunteers were asked to report any subjective adverse effects. Diazepam and procyclidine were available to treat dystonic reactions if they occurred.

The IOP, pupil diameter, heart rate, and blood pressure readings were analysed by calculating the area under the response versus time curve for each subject and on each treatment. These were then analysed by multiple regression analysis after log_e transformation to normalise the distribution of the residuals. The areas under the curves for serum prolactin calculated as above were not normally distributed and were therefore analysed by Friedman's two-way analysis of variance. Paired comparisons were then done by the Mann-Whitney test.

Results

Significant effects were observed on the IOP (Fig. 1). In comparison with the placebo the IOP was significantly reduced in both eyes (right eye $p < 0.04$, left eye $p < 0.01$) only when bromocriptine alone was given. This effect was abolished by pretreatment with metoclopramide, which alone had no effect on the IOP. There were no significant changes in pupil diameter, blood pressure, or heart rate.

Analysis of serum prolactin showed a significant effect of treatment ($p < 0.01$) (Fig. 2). The effect of all treatments was significantly different from that of placebo. Bromocriptine inhibited the secretion of prolactin ($p < 0.05$), and this response was again

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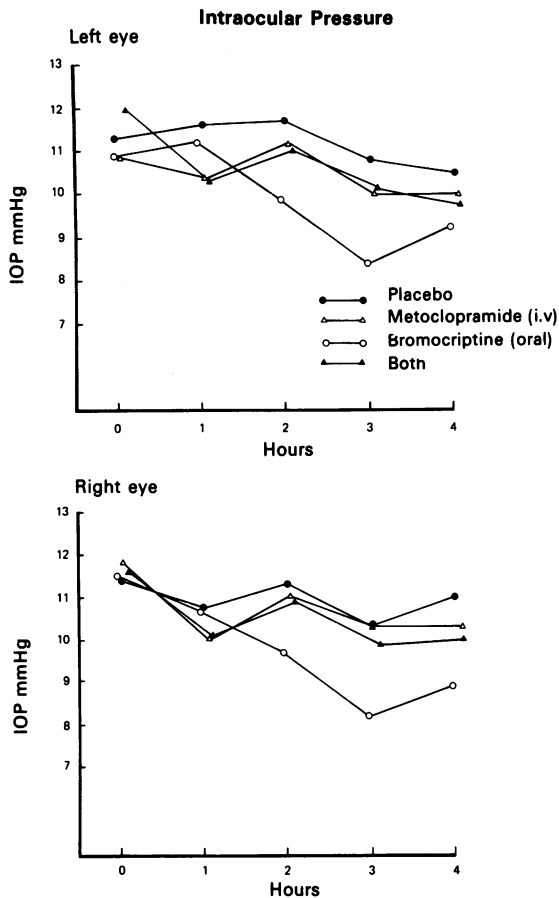


Fig. 1 Mean values of IOP (mmHg).

abolished by pretreatment with metoclopramide, which caused a significant increase in prolactin levels both when given alone and in combination with bromocriptine ($p < 0.01$); the difference between these two responses was not significant.

Discussion

The absence of changes in pupil diameter in this study makes unlikely the possibility that the IOP was reduced through alpha adrenoceptor blockade by bromocriptine or the cholinergic effect¹⁰ of metoclopramide.

The changes in prolactin levels show that the dose of metoclopramide used was enough to block the effect of bromocriptine totally; in fact the difference between the responses to metoclopramide with and without bromocriptine was not significant. This was accompanied by a total abolition of the ocular hypotensive effect of bromocriptine. If the IOP-lowering effect of bromocriptine was, totally or

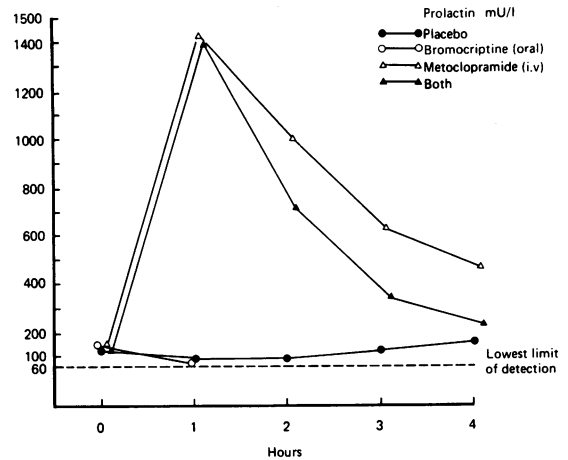


Fig. 2 Mean values of serum prolactin (mU/l).

partially, due to inhibition of DA1 receptors, we should expect a lowered IOP after treatment with the combination of bromocriptine and metoclopramide, which did not occur. We therefore conclude that stimulation of DA2 receptors in man lowers IOP.

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