A comparison of the ocular hypotensive effect of 0.025% bromocriptine and 0.25% timolol eye drops in normal human volunteers

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- 1 The ocular hypotensive effect of 0.025% bromocriptine and 0.25% timolol eye drops was compared in nine healthy human volunteers, using non-contact tonometry.
- 2 Considering all post-dosing measurements compared with placebo and including the baseline values as continuous independent variables, using multiple linear regression analysis, both bromocriptine and timolol had a significant ocular hypotensive effect ($P < 0.0001$) in the treated eye with a significant but lesser effect in the contralateral eye.
- 3 In the concentrations used, timolol was more efficacious than bromocriptine in lowering intraocular pressure ($P < 0.025$).
- 4 Using other forms of vehicles for bromocriptine to improve efficacy and studying the ocular hypotensive effect of topical application of other dopamine-2-receptor agonists such as pergolide and lisuride was suggested.

Keywords bromocriptine dopaminergic agonists intraocular pressure non-contact tonometer timolol

Introduction

The relatively selective dopamine-2 receptor (D_2) agonists, bromocriptine, lergotril and pergolide (ergot derivatives), applied topically, have been shown to reduce intraocular pressure (IOP) in rabbits and monkeys (Potter & Burke, 1983). Domperidone (a relatively selective D_2 -receptor antagonist) and superior cervical sympathectomy inhibited this ocular hypotensive effect (Potter *et al.*, 1984). Cianergoline (Potter & Shumate, 1987) and LY141865 (Potter & Burke, 1988), other ergot derivatives which are relatively selective D_2 -receptor agonists, have been reported to produce ocular hypotension in monkeys and rabbits. Using fluorophotometry in monkeys, it has been shown that pergolide reduced IOP by inhibiting aqueous humour formation (Siegel *et al.*, 1987).

In normal human volunteers, a single oral dose of bromocriptine produced a significant

reduction in IOP (Al-Sereiti & Turner, 1989; Geyer *et al.*, 1987b; Mekki *et al.*, 1983). A single 0.1 mg oral dose of the relatively selective D_2 -receptor agonist, lisuride, has also been shown to reduce IOP in normal human eyes (Al-Sereiti & Turner, 1989). A similar ocular hypotensive effect was produced by 0.025% and 0.05% bromocriptine eye drops in normal human volunteers (Mekki *et al.*, 1984). Pre-dosing with intravenous metoclopramide (a relatively selective D_2 -receptor antagonist) blocked this effect and metoclopramide itself had no effect (Mekki & Turner, 1985). Recently it has been shown that a single 25 µg oral dose of pergolide, a D_2 - and D_1 -receptor agonist, reduced IOP significantly in normal volunteers (Al-Sereiti *et al.*, 1989).

In patients with Parkinson's disease and glaucoma who received timolol eye drops,

bromocriptine given orally had an additive effect to timolol's ocular hypotensive action (Lustig, 1983). It has also been shown that oral bromocriptine decreased IOP in glaucomatous human eyes (Geyer *et al.*, 1987a).

Timolol is a non-selective β -adrenoceptor antagonist which has been shown to reduce IOP in normotensive (Katz *et al.*, 1976) and glaucomatous (Zimmerman & Kaufman, 1977) human eyes. It is the most widely used drug for treatment of chronic simple glaucoma.

We conducted this work to study the ocular hypotensive effect of a topical 0.025% aqueous solution of lyophilised bromocriptine mesylate (Sandoz Pharmaceuticals), the concentration which had been shown to produce a maximum effect (Mekki *et al.*, 1984), over longer time than had been studied before (Mekki *et al.*, 1984; Mekki & Turner, 1985), and to compare it with that of 0.25% timolol, the most widely used concentration clinically, in normal human volunteers.

This work was presented as a poster communication in the British Pharmacological Society meeting in January, 1988 (Al-Sereiti *et al.*, 1988).

Methods

Nine healthy volunteers (four males and five females, aged 21–54, mean age 32 years) took part in the study on three occasions, at least 1 week apart, starting at 13.00–13.30 h. The study was approved by the local ethics committee and a consent form was signed by the volunteers. On each occasion two drops of bromocriptine 0.025%, timolol 0.25% or placebo were instilled

(5 min apart) in the left eye in a randomised, double-blind, cross-over and balanced design based on three three-by-three latin squares with no treatment in the contralateral eye. IOP was measured by non-contact tonometry (Grolman, 1972; Shields, 1980) just before and at 1, 2, 3, 4, 5 and 6 h after drug instillation. Pupil diameter was measured just before and at 1.5, 3 and 4.5 h after dosing, by a photographic method (Czarnecki *et al.*, 1979) after modification.

Post-dosing IOP data were analysed using multiple linear regression with the baseline values included as continuous independent variables and those of treatment, time of measurement and subjects as discrete independent variables using the dummy variable technique.

Results

Means and s.e. means of the nine subjects' IOP and pupil diameter experimental data at different time points and different treatments, in the right and left eyes, are represented graphically in Figures 1, 2, 3 and 4. Means and s.d. of IOP and pupil diameter are presented in Tables 1 and 2 respectively.

Considering all post-dosing measurements, compared with placebo, IOP was reduced significantly by both timolol 0.25% eye drops, regression coefficient (B) = -2.5 mm Hg, F -ratio (F) (1,145) = 70.7, $P < 0.0001$, in the treated left eye and $B = -0.8$ mm Hg, $F = 8.6$, $P < 0.005$, in the untreated right eye, and bromocriptine 0.025% eye drops, $B = -1.7$ mm Hg, $F = 30$, $P < 0.0001$ in the left eye and $B = -0.6$ mm Hg, $F = 4$, $P < 0.05$ in the right eye.

Figure 1 Changes in intraocular pressure in the right eye (untreated) after placebo (●), timolol (○) and bromocriptine (□). Each point is the mean of intraocular pressure readings obtained from nine healthy volunteers. Vertical bar represents s.e. mean.

Figure 2 Changes in intraocular pressure in the left eye (treated) after placebo (●), timolol (○) and bromocriptine (□). Each point is the mean of intraocular pressure readings obtained from nine healthy volunteers. Vertical bar represents s.e. mean.

Figure 3 Changes in pupil diameter in the right eye after placebo (●), timolol (○) and bromocriptine (□). Each point is the mean of pupil diameter readings obtained from nine healthy volunteers. Vertical bar represents s.e. mean.

Figure 4 Changes in pupil diameter in the left eye after placebo (●), timolol (○) and bromocriptine (□). Each point is the mean of pupil diameter readings obtained from nine healthy volunteers. Vertical bar represents s.e. mean.

Table 1 Means and s.d. of intraocular pressure readings obtained from nine healthy volunteers, using non-contact tonometry

Treatment		Time (h)						
		0	1	2	3	4	5	6
<i>Right eye</i>								
Placebo	Mean	12.6	12.9	12.9	13.3	13.1	13.1	12.4
	s.d.	2.5	3.2	3.6	3.0	3.1	4.3	3.1
Timolol	Mean	12.3	12.7	12.2	11.6	11.9	11.6	12.1
	s.d.	2.6	2.5	3.6	3.4	3.0	2.8	2.6
Bromocriptine	Mean	13.4	13.0	13.3	12.2	12.7	11.9	12.3
	s.d.	3.2	2.9	3.7	3.3	3.2	2.2	2.4
<i>Left eye</i>								
Placebo	Mean	13.2	13.4	13.3	12.9	13.2	13.6	13.6
	s.d.	2.8	2.8	3.9	3.8	3.0	3.6	3.4
Timolol	Mean	13.0	11.7	10.2	10.6	10.5	11.1	11.0
	s.d.	2.7	3.1	2.8	2.2	2.0	2.5	2.8
Bromocriptine	Mean	14.4	12.2	11.8	11.4	12.0	11.7	11.6
	s.d.	4.1	3.3	3.7	2.7	3.4	3.5	2.7

In these concentrations, timolol was more efficacious than bromocriptine in reducing IOP in the treated eye ($P < 0.025$) with no significant difference in the contralateral untreated eye. Neither of the drugs had a significant effect on pupil diameter. A summary of the statistical analysis results of the experimental data is shown in Tables 3 and 4.

Discussion

Bromocriptine has been shown to reduce IOP in normotensive, orally administered (Geyer *et al.*, 1987b; Mekki *et al.*, 1983) and topically

applied (Mekki *et al.*, 1984), and glaucomatous (Geyer *et al.*, 1987a; Lustig, 1983) eyes. Other D_2 -receptor agonists, given orally, such as lisuride (Al-Sereiti & Turner, 1989) and pergolide (Al-Sereiti *et al.*, 1989) also have an ocular hypotensive effect in normal human volunteers. The ocular hypotensive effect of pergolide was inhibited by pre-dosing with domperidone (Al-Sereiti *et al.*, unpublished observation). The ocular hypotensive effect of topical 0.025% bromocriptine was also blocked by metoclopramide (Mekki & Turner, 1985). This collective evidence suggests that D_2 -receptor agonists are possible future drugs for glaucoma treatment whether alone or in combination with other drugs.

Table 2 Means and s.d. of pupil diameter readings (mm) obtained from nine healthy volunteers, using Polaroid CU-5 Close-Up Land camera

Treatment		Right eye Time (h)				Left eye Time (h)			
		0	1.5	3	4.5	0	1.5	3	4.5
Placebo	Mean	4.7	4.5	4.6	4.4	4.6	4.6	4.4	4.5
	s.d.	0.8	0.9	0.9	1.0	0.8	0.9	0.8	0.8
Timolol	Mean	4.7	4.6	4.6	4.5	4.4	4.6	4.3	4.3
	s.d.	1.1	0.9	1.1	1.0	0.9	0.8	0.9	0.7
Bromocriptine	Mean	4.6	4.6	4.6	4.4	4.4	4.3	4.5	4.6
	s.d.	1.1	0.9	1.1	1.0	1.0	0.8	0.9	0.9

Table 3 Multiple linear regression analysis of intraocular pressure (IOP) and pupil diameter (dependent variables) post-dosing measurements obtained from nine volunteers at 1, 2, 3, 4, 5 and 6 h after two drops instilled in the left eye, 5 min apart, of 0.025% bromocriptine and 0.25% timolol, compared with placebo for IOP and at 1.5, 3, and 4.5 h for pupil diameter. The baseline IOP values were included as continuous independent variables and those of treatment, time of measurement and subjects as discrete independent variables using the dummy variable technique

Treatment (independent variable)	Regression coefficient	F ratio	P value	Multiple r ²
1. IOP (mm Hg)		(1,145)		
a. Left eye				
Timolol	-2.5	70.7	< 0.0001	78.7%
Bromocriptine	-1.7	30.0	< 0.0001	
b. Right eye				
Timolol	-0.8	8.6	< 0.005	79.1%
Bromocriptine	-0.6	4.0	< 0.05	
2. Pupil diameter (mm)		(1,67)		
a. Left eye				
Timolol	0.0	0.1	NS	72.5%
Bromocriptine	0.0	0.2	NS	
b. Right eye				
Timolol	0.1	0.8	NS	93.4%
Bromocriptine	0.1	1.4	NS	

Table 4 Multiple regression analysis of intraocular pressure (IOP) (dependent variable) post-dosing measurements obtained from nine volunteers at 1, 2, 3, 4, 5 and 6 h after two drops instilled in the left eye, 5 min apart, of placebo and 0.025% bromocriptine, compared with 0.25% timolol. The baseline values were included as continuous independent variables and those of treatment, time of measurement and subjects as discrete independent variables using the dummy variable technique

Treatment (independent variable)	Regression coefficient (mm Hg)	F ratio (1,145)	P value	Multiple r ²
a. Left eye				
Placebo	2.5	70.7	< 0.0001	78.7%
Bromocriptine	0.8	5.8	< 0.025	
b. Right eye				
Placebo	0.8	8.6	< 0.005	79.1%
Bromocriptine	0.6	0.6	NS	

In this study bromocriptine had a significant ($P < 0.0001$) and persistent ocular hypotensive effect throughout the time studied (Figures 1 and 2) although it was less efficacious than 0.25% timolol ($P < 0.025$). Topical bromocriptine penetration of the cornea and hence its bio-availability have not been studied. The accessibility of other drugs such as pilocarpine has been shown to be increased when applied in an oil vehicle (Smith *et al.*, 1978). Topical application of bromocriptine in this form or another might increase its efficacy and duration of action. The ocular hypotensive effects of bromocriptine and timolol in the untreated eye are probably due to a systemic absorption of these drugs.

In conclusion, topical bromocriptine is an

effective ocular hypotensive drug in normal human eyes and further studies in glaucoma patients with this aqueous preparation or in other forms, as well as studying its additive action with other drugs such as timolol, are justifiable. Work is also needed to study the ocular hypotensive effect of topical lisuride and pergolide, and to determine if one of these, or another D_2 -receptor agonist, is as, or more effective than, timolol.

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