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Effects of 2% Ibopamine on Pupil, Refraction, Anterior Segment Anatomy and Intraocular Pressure

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ABSTRACT

The aim of the study was to determine the effects of a dopaminergic drug, 2% ibopamine, on the pupil, intraocular pressure and other ocular and ultrasound biometric variables.

Thirty healthy subjects and 15 patients with primary open-angle glaucoma, aged from 40 to 78 years (mean age: 59.2 ± 11), were included in two prospective open controlled trials. In the first, the mydriatic effect of 2% ibopamine and its inhibition and reversibility were evaluated in 15 healthy subjects using the alpha$_1$-adrenergic drug, 0.5% dapiprazole. In the second, refraction, visual acuity, pupil diameter, intraocular pressure and 5 A-scan ultrasound biometric variables were evaluated in 15 healthy subjects and in 15 glaucoma patients.

As early as forty min after administration of 2% ibopamine, a marked mydriatic effect (7.3 vs 3.9 mm; $P < 0.0001$), which was completely inhibited or reversed by 0.5% dapiprazole, was detected. The drug induced no changes in refraction, visual acuity or A-scan ultrasound biometric variables in any of the subjects examined. In healthy subjects, the intraocular pressure values were not changed to a statistically significant extent (13.8 vs 14.8 mm Hg; $P = 0.668$), whereas a slight, though significant, hypertensive effect (24 vs 22.2 mm Hg; $P = 0.002$) was observed in the glaucoma patients.

The study confirms the intense mydriatic effect of 2% ibopamine with no changes in refraction, visual acuity or A-scan ultrasound biometric variables. The drug has no effect on intraocular pressure in healthy subjects, but induces a significant hypertensive effect in patients with initial glaucoma. This characteristic could be used for early diagnosis of primary open-angle glaucoma.

INTRODUCTION

Dopaminergic drugs have generated interest in the ophthalmological field over the past decade, among other things because a number of them have been shown to induce a reduction of intraocular pressure (IOP) (1,2).

Ibopamine is a nonselective dopaminergic prodrug which, when absorbed in tissues, is rapidly transformed to deoxyepinephrine, a catecholamine which is active on DA 1, DA 2, alpha 1, alpha 2, beta 1 and beta 2 receptors (3,4). This drug has no IOP-lowering effects and, on the contrary, would appear to be capable of increasing IOP in eyes predisposed to glaucoma (5,6). This action, which is thought to be due to increased production of aqueous humor (7), has led to the drug being proposed as a test substance for the detection of initial glaucoma. By virtue of its potent alpha 1 effect, ibopamine induces a marked mydriasis unaccompanied by accommodative paralysis and may be very useful for diagnostic purposes (8,9). Moreover, its use has also been advocated in the therapy of postoperative ocular hypotony (10). An ultrasound biomicroscopy study revealed no evidence of changes in the anterior segment other than pronounced mydriasis (11).

In view of the effects of this substance, which has already come onto the market in a number of countries, we thought it would be useful to study the characteristics of its ocular effects in greater detail.

The present study relates to a series of investigations aimed at determining the mydriatic effect of the drug and its inhibition and reversibility by adrenergic alpha 1 blockade, as well as its possible influence on refraction, accommodation and visual acuity. Effects on intraocular pressure were also studied both in normal subjects and in patients suffering from primary open-angle glaucoma at a very early stage of disease. In addition, the effects of the drug on a number of ocular variables of major interest for assessing the risk of angle-closure glaucoma were also determined.

MATERIALS AND METHODS

Forty-five volunteers (16 men, 29 women), aged from 40 to 78 years (mean age: 59.2 ± 11), comprising 30 healthy subjects and 15 patients with primary open-angle glaucoma, were recruited into the study.

Informed consent was obtained from all subjects, and the study was approved by the Local Ethical Committee. The research was conducted in accordance with the principles laid down in the Declaration of Helsinki.

An open design was adopted, and the study protocol involved two experiments:

—the aim of the first was to examine the characteristics of the mydriatic effect induced by 2% ibopamine;

—the second was aimed at evaluating, in addition to pupil diameter, the effects of the drug on objective and subjective refraction, natural and corrected visual acuity, IOP, and the following A-scan ultrasound biometric variables: anterior chamber depth, lens thickness, axial length, lens/axial length factor (LAF) and relative lens position (RLP).

Experiment 1

The study of the mydriatic effect was conducted in 15 healthy volunteers (7 men, 8 women), aged from 54 to 78 years (mean age: 68.1 ± 8), divided into three groups (A, B and C) each of 5 subjects.

In group A, the extent and duration of the mydriasis induced by 2% ibopamine were determined. One drop of the drug was instilled into only one eye, randomly selected, with repeat administration after 5 min. Two drops of saline solution were administered according to the same procedure in the fellow eye, used as control.

In group B, we assessed the reversal of the mydriatic effect of 2% ibopamine produced by instillation of the $alpha_1$-blocker 0.5% dapiprazole. One drop of 2% ibopamine was instilled into both eyes of the 5 group B subjects, with repeat administration after 5 min. Forty min after instillation of the drug, one drop of 0.5% dapiprazole was administered in only one eye, randomly selected, whereas the fellow eye, used as control, was treated with one drop of saline solution.

In group C, we assessed the possibility of preventing the onset of 2% ibopamine-induced mydriasis. One drop of 0.5% dapiprazole was instilled into only one eye, randomly selected, whereas the fellow eye was treated with saline solution. One drop of 2% ibopamine was administered in both eyes 40 min after instillation.

Pupil diameter was measured in each of the three groups prior to instillation of the drugs and then at 30, 40, 60, 90, 120, 240 and 480 min, using the Bonora and Bonomi method (12) by means of a millimeter scale applied to the screen of an autorefractometer after focusing and in constant lighting conditions.

Experiment 2

The effects of 2% ibopamine on objective and subjective refraction, natural and corrected visual acuity, IOP and A-scan ultrasound biometry parameters were investigated in 30 subjects (9 men, 21 women), aged from 40 to 70 years (mean age: 54.8 ± 9.6), comprising 15 healthy subjects and 15 patients with previously undetected and untreated primary open-angle glaucoma. Both healthy and glaucomatous subjects were recruited into this part of the study, because the drug has been reported to cause different effects in glaucoma patients, at least as far as IOP is concerned (13). The primary open-angle glaucoma diagnosis was defined on the basis of the presence of IOP ≥ 22 mm Hg and of glaucoma-type abnormalities of the optic disk (stereo optic disk photographs) and/or visual field (Humphrey visual field, central 30–2 threshold program, statpac 2 software, single field analysis) in at least one eye. All patients had a nonoccludable chamber angle.

In the case of both normal subjects and glaucoma patients, the protocol envisaged, according to an open design, the instillation of one drop of 2% ibopamine in only one eye, randomly selected, with repetition of the administration after 5 min. Two drops of saline solution were instilled according to the same procedure in the fellow eye, used as control.

The variables assessed in this experiment were the following:

—pupil diameter: measured according to the Bonomi and Bonora method (12);

—objective refraction, using a Nidek AR-800 autorefractometer (Nidek Co., Gamagori, Japan), and subjective refraction;

—natural and corrected visual acuity: determined using a Monoyer decimal test card at a distance of 5 meters;

—IOP: measured with a Goldmann applanation tonometer after anesthesia with 0.4% benoxinate in a single-dose solution;

—A-scan ultrasound biometric variables: anterior chamber depth, lens thickness, axial length, lens/axial length factor (LAF), and relative lens position (RLP) (14). We adopted the standardized A-scan biometric immersion technique using the Ophtascan S instrument (Biophisic Médical, Clermont Ferrand, France) and a non-focused 8 MHz transducer-probe with tissue sensitivity T = 68 dB. After topical anesthesia (0.4% benoxinate eye drops in single-dose disposable), the examination was performed using an eye cup with methylcellulose or 0.9% saline solution as a coupling medium. A-scan patterns were displayed at T −15 dB to T −20 dB levels. Each scan was frozen when four high, sharply rising echo-spikes were observed. The single best reading was considered for measurement purposes. The lengths of the various ocular segments were computed in mm, "peak to peak," using two US speeds: 1532 m/sec for the aqueous and vitreous and 1640 m/sec for the lens. The accuracy of the technique is 0.1 mm (15).

One hour prior to administration of the drug, each subject underwent baseline determination of refraction, visual acuity, pupil diameter and IOP. Measurement of these variables was repeated 30, 40, 60, 90, 120, 240 and 480 min after instillation of the drug. For the purposes of reducing the likelihood of corneal abrasions, IOP was measured only at 40 and 120 min.

The A-scan ultrasound biometry variables were determined 30 min prior to administration of the eye drops and 40 min after administration.

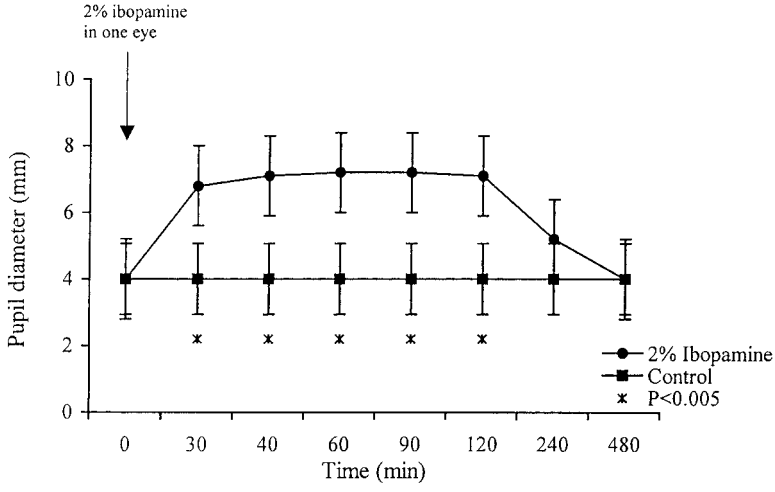

FIGURE 1. Effect of 2% Ibopamine on Pupil Diameter.

RESULTS

Experiment 1

Figure 1 illustrates the pupil diameter trend after instillation of 2% ibopamine in 5 healthy subjects (group A). As compared to baseline values (3.9 ± 1.14 mm), a significant increase in pupil diameter had occurred after only 30 min in the treated eyes (6.9 ± 1.34 mm) with mydriasis peaking at 40 min (7.3 ± 1.20 mm). The diameter then remained unchanged up to 90 min and by 480 min had returned to the baseline value. No significant change in diameter occurred in the control eyes at any time during the observation period.

Figure 2 shows the trend for reversal of 2% ibopamine-induced mydriasis as a result of administration of 0.5% dapiprazole in 5 healthy subjects (group B). Reversion to baseline pupil diameter

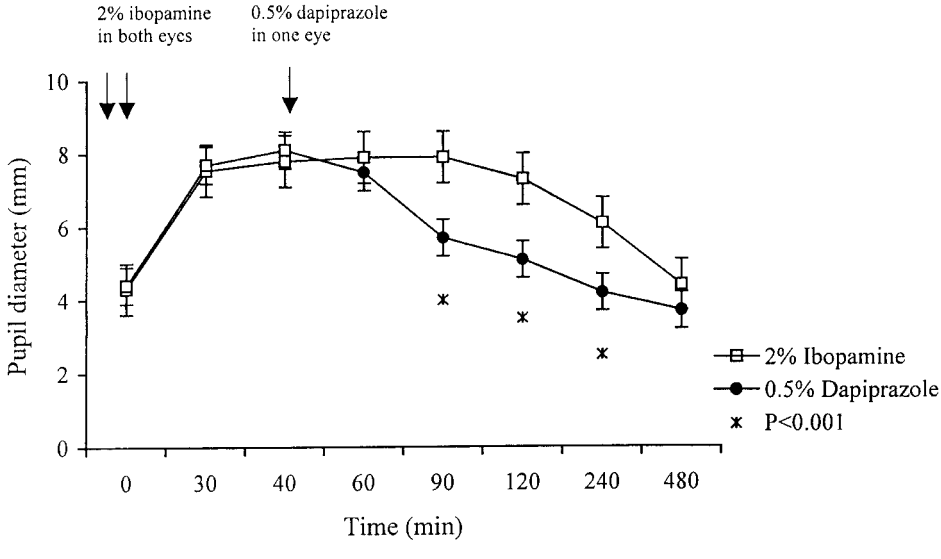

FIGURE 2. Reversal of Mydriasis.

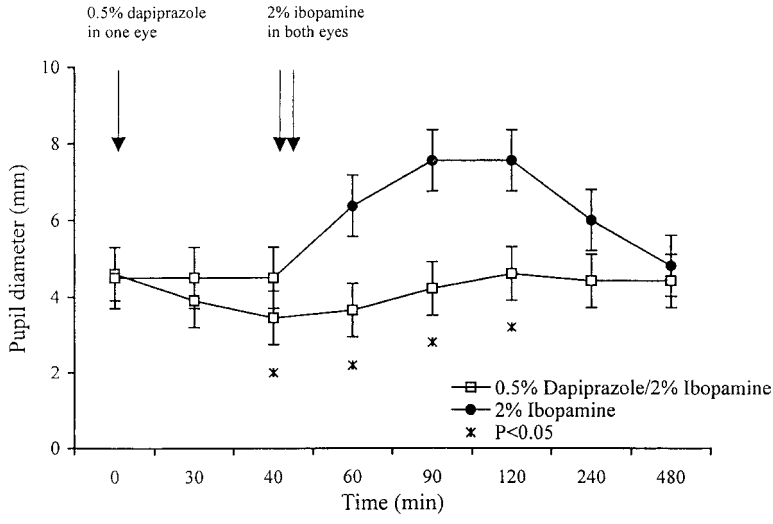

FIGURE 3. Prevention of Mydriasis.

values had taken place in the eyes treated with 0.5% dapiprazole when examined 4 hr after the start of the experiment. The differences as compared to control eyes were statistically significant from the 90-min observation time onwards.

Figure 3 gives the data for the prevention of 2% ibopamine-induced mydriasis as a result of administration of 0.5% dapiprazole in 5 healthy subjects (group C). In the eyes pretreated with 0.5% dapiprazole, 2% ibopamine induced no significant mydriasis as compared to control eyes.

Experiment 2

Table 1 gives the pupil diameter trend after instillation of 2% ibopamine in 15 healthy subjects and 15 glaucoma patients. An increase in pupil diameter compared to baseline was observed after only 30 min in the eyes treated with 2% ibopamine, peak mydriasis values being observed after 40

TABLE 1.
Pupil Diameter (mm)

	Normal (n=15)			POAG (n=15)		
Time	Ibopamine 2%	Control eyes	**P***	Ibopamine 2%	Control eyes	**P***
Baseline	4.9 ± 0.47	4.9 ± 0.47	-	5.20 ± 0.67	5.20 ± 0.67	-
30'	8.16 ± 0.48	4.9 ± 0.47	<0.0001	8.00 ± 0.65	5.16 ± 0.67	<0.0001
40'	9.10 ± 0.62	4.8 ± 0.52	<0.0001	9.22 ± 0.43	4.93 ± 0.70	<0.0001
60'	9.13 ± 0.57	4.7 ± 0.56	<0.0001	9.22 ± 0.43	4.96 ± 0.74	<0.0001
90'	9.13 ± 0.57	4.9 ± 0.51	<0.0001	9.18 ± 0.43	5.16 ± 0.67	<0.0001
120'	8.17 ± 0.92	4.9 ± 0.47	<0.0001	8.06 ± 0.70	5.20 ± 0.67	<0.0001
240'	7.20 ± 0.72	4.9 ± 0.47	<0.0001	7.10 ± 0.73	5.20 ± 0.67	<0.0001
480'	4.9 ± 0.47	4.9 ± 0.47	-	5.20 ± 0.67	5.20 ± 0.67	-

*Repeated measures one way ANOVA test
POAG= primary open angle glaucoma

TABLE 2.
Intraocular Pressure (mmHg)

Time	Normal (n=15)			POAG (n=15)		
	Ibopamine 2%	Control eyes	P*	Ibopamine 2%	Control eyes	P*
Baseline	14.8 ± 2.13	14.9 ± 2.40	NS	22.2 ± 1.74	21.7 ± 1.09	NS
40'	14.5 ± 1.72	14.4 ± 2.19	NS	24.8 ± 1.37	21.6 ± 1.29	<0.0001
120'	13.8 ± 1.88	14.4 ± 1.72	NS	24.0 ± 1.51	20.6 ± 1.84	<0.0001

*Repeated measures one way ANOVA test
NS = not significant
POAG= primary open angle glaucoma

min in the glaucoma patients and after 60 min in normal subjects. The diameter then remained unchanged up to 60 min and up to 90 min, respectively, in the glaucoma patients and healthy subjects. No significant changes in pupil diameter occurred in the fellow eyes at any time during the observation period.

Table 2 gives details of the IOP results. In healthy subjects, the instillation of 2% ibopamine induced no significant changes in IOP values, whereas it produced an increase in IOP in the glaucoma patients. The differences as compared to control eyes (3.2 mm Hg at 40 min and 3.4 mm Hg at 120 min, respectively) were statistically significant.

No significant difference in natural or corrected visual acuity was observed in either of the groups at any time during the observation period. Refraction values also remained unchanged after instillation of 2% ibopamine (Tables 3 and 4).

Tables 5 and 6 present the values obtained for the A-scan ultrasound biometry variables. No significant changes occurred after instillation of 2% ibopamine.

TABLE 3.
Refraction in Healthy Eyes (D)

Time	Objective refraction			Subjective refraction		
	Ibopamine 2%	Control eyes	P*	Ibopamine 2%	Control eyes	P*
Baseline	0.10 ± 1.26	0.10 ± 1.30	NS	0.10 ± 1.80	0.10 ± 1.00	NS
30' post-treatment	0.13 ± 1.22	0.10 ± 1.32	NS	0.10 ± 1.80	0.10 ± 1.00	NS
40' post-treatment	0.13 ± 1.22	0.10 ± 1.35	NS	0.06 ± 0.85	0.10 ± 1.00	NS
60' post-treatment	0.10 ± 1.25	0.10 ± 1.37	NS	0.06 ± 0.85	0.10 ± 1.00	NS
90' post-treatment	0.21 ± 1.08	0.16 ± 1.21	NS	0.06 ± 0.85	0.08 ± 1.02	NS
120' post-treatment	0.10 ± 1.15	0.13 ± 1.21	NS	0.10 ± 1.80	0.08 ± 1.02	NS
240' post-treatment	0.18 ± 1.20	0.15 ± 1.24	NS	0.10 ± 1.80	0.08 ± 1.02	NS
480' post-treatment	0.16 ± 1.27	0.13 ± 1.30	NS	0.10 ± 1.80	0.08 ± 1.02	NS

* Repeated measures one way ANOVA test
NS = not significant.

TABLE 4.
Refraction in Glaucomatous Eyes (D)

Time	Objective refraction			Subjective refraction		
	Ibopamine 2%	Control eyes	P*	Ibopamine 2%	Control eyes	P*
Baseline	0.20 ± 1.04	0.25 ± 1.45	NS	0.28 ± 0.72	0.26 ± 1.24	NS
30' post-treatment	0.26 ± 1.05	0.30 ± 1.48	NS	0.28 ± 0.72	0.26 ± 1.24	NS
40' post-treatment	0.26 ± 1.00	0.30 ± 1.43	NS	0.28 ± 0.72	0.26 ± 1.24	NS
60' post-treatment	0.33 ± 1.06	0.31 ± 1.33	NS	0.28 ± 0.72	0.26 ± 1.24	NS
90' post-treatment	0.35 ± 1.03	0.31 ± 1.33	NS	0.28 ± 0.72	0.26 ± 1.24	NS
120' post-treatment	0.40 ± 1.05	0.31 ± 1.39	NS	0.28 ± 0.72	0.26 ± 1.24	NS
240' post-treatment	0.38 ± 0.93	0.28 ± 1.37	NS	0.28 ± 0.72	0.26 ± 1.24	NS
480' post-treatment	0.36 ± 0.98	0.36 ± 1.40	NS	0.28 ± 0.72	0.26 ± 1.24	NS

* Repeated measures one way ANOVA test
NS = not significant.

TABLE 5.
A-scan Echographic Parameters in Normal Subjects

A-SCAN ECHOGRAPHIC PARAMETERS	Ibopamine 2%		P*	Control eyes		P*
	Baseline	40' post-treatment		Baseline	40' post-treatment	
Anterior Chamber (mm)	3.24 ± 0.37	3.27 ± 0.36	NS	3.25 ± 0.30	3.28 ± 0.37	NS
Lens (mm)	4.24 ± 0.41	4.14 ± 0.35	NS	4.22 ± 0.37	4.17 ± 0.36	NS
Axial Length (mm)	22.9 ± 0.70	22.9 ± 0.76	NS	22.9 ± 0.83	22.9 ± 0.84	NS
Lens/Axial Length Factor	1.84 ± 0.20	1.81 ± 0.81	NS	1.84 ± 0.19	1.81 ± 0.18	NS
Relative Lens Position	2.33 ± 0.10	2.33 ± 0.09	NS	2.33 ± 0.08	2.33 ± 0.09	NS

* One way ANOVA test
NS = not significant.

TABLE 6.
A-scan Echographic Parameters in Primary Open-angle Glaucoma Patients

A-SCAN ECHOGRAPHIC PARAMETERS	Ibopamine 2%		P*	Control eyes		P*
	Baseline	40' post-treatment		Baseline	40' post-treatment	
Anterior Chamber (mm)	3.18 ± 0.32	3.26 ± 0.25	NS	3.20 ± 0.28	3.23 ± 0.27	NS
Lens (mm)	4.47 ± 0.40	4.46 ± 0.38	NS	4.54 ± 0.43	4.46 ± 0.39	NS
Axial Length (mm)	23.2 ± 0.78	23.2 ± 0.81	NS	23.3 ± 0.89	23.3 ± 0.87	NS
Lens/Axial Length Factor	1.92 ± 0.17	1.92 ± 0.17	NS	1.94 ± 0.15	1.91 ± 0.16	NS
Relative Lens Position	2.34 ± 0.09	2.36 ± 0.10	NS	2.33 ± 0.12	2.27 ± 0.26	NS

* One way ANOVA test
NS = not significant.

DISCUSSION

The results of experiment 1 confirmed the substantial mydriatic effect of the study drug. This effect is actually very considerable, sets in early, lasts for approximately 2 hr and is not accompanied by any refractive effect. Consequently, it does not lead to visual function abnormalities worthy of note. However, though we did not specifically study this aspect, on the basis of the normal subjects' and glaucoma patients' comments, we can conclude that they found an increased sensitivity to light during the ibopamine effect. This is due exclusively to dilation of the pupil, there being no accommodation effects. It should be noted, however, that the use of ibopamine is typically limited in the course of time.

The ibopamine-induced mydriasis appears to be due exclusively to activation of $alpha_1$-adrenergic receptors, as clearly demonstrated by the fact that it is completely inhibited by pretreatment with dapiprazole, a drug known for its ability to block such receptors (16). This finding is in good agreement with the data reported for the use of another alpha-blocker, thymoxamine (8). Of particular interest is the fact that even stable mydriasis induced by ibopamine is rapidly and completely reversed by subsequent dapiprazole treatment. This means that there is good reason to postulate the use of ibopamine to obtain rapid, well tolerated, easily reversible, risk-free diagnostic mydriasis along the lines of the proposals made by Mapstone in relation to the consecutive use of phenylephrine and thymoxamine (17).

Our results also confirm that the instillation of ibopamine does not induce any appreciable effects on IOP in normal eyes, whereas, in eyes affected by initial glaucoma, it causes a significant, though not striking, increase in IOP.

In any event, the innocuous nature of the possible diagnostic use of ibopamine instillation is confirmed by the fact that it does not give rise to changes in any of the biometric variables regarded as important indices in determining the risk of angle closure.

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