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Effects of ibopamine eye drops on intraocular pressure and aqueous humor flow in healthy volunteers and patients with open-angle glaucoma

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PURPOSE. *On the basis of intraocular pressure measurements and fluorophotometry we assessed the effects of 2% ibopamine eye drops on aqueous humor production in normal and glaucomatous eyes.*

METHODS. *Thirty subjects (15 healthy volunteers and 15 open-angle glaucoma patients with ocular hypertension) were included in a placebo-controlled study with random assignment of treatment from masked containers. All subjects underwent ophthalmologic examinations and intraocular pressure (IOP) measurements. Fluorophotometry was done in both eyes at baseline (without treatment) and during treatment. Each subject was treated with 1 drop of 2% ibopamine in one eye and 1 drop of placebo in the fellow eye 30 minutes before fluorophotometric scans and every hour after the first instillation (for a total of 4 times). Safety was evaluated by recording adverse events and ocular symptoms and signs. Aqueous humor flow data were analyzed using the paired t-test, comparing ibopamine and placebo-treated eyes.*

RESULTS. *No changes in IOP were detected in normal eyes, whereas glaucomatous eyes showed a mean increase of 4 mmHg (95% CI 3.46-4.51) from baseline. The difference in IOP between healthy eyes and those with glaucoma was significant ($p<0.0001$). In normal eyes and patients with glaucoma ibopamine led to a significant increase in aqueous humor flow compared with placebo-treated eyes ($p<0.01$). The safety profile of ibopamine was very good.*

CONCLUSIONS. *The results seem to confirm that ibopamine increases aqueous humor production in normal and glaucomatous eyes, raising IOP only in eyes with glaucoma. (Eur J Ophthalmol 2003; 13: 370-6)*

KEY WORDS. *Ibopamine, Aqueous humor flow, Fluorophotometry, Glaucoma*

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INTRODUCTION

Ibopamine (3,4 di-isobutyryl ester of N-methyldopamine) is an alpha-adrenergic and dopaminergic drug that, after ocular instillation, has non-cycloplegic mydriatic activity and increases aqueous humor production both in normal and glaucomatous eyes (1-3). The increase in aqueous humor production by the ciliary body seems to be related to stimulation of D1 dopamine receptors (4). It is seen only in glaucomatous eyes, with an increase in intraocular pressure (IOP), which is independent of the mydriatic effect,

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as it was still present after pre-treatment with thymoxamine (5).

Systemic exposure to ibopamine eye drops is clinically negligible; after instillation, plasma levels were lower than the limit of detection (6). Topical ibopamine does not induce systemic side effects and is very well tolerated by the eye even after repeated instillations (7, 8).

The specific pharmacodynamic characteristics of ibopamine, particularly its effect on aqueous humor production, suggest its use in the early diagnosis of ocular hydrodynamic disorders and to resolve ocular hypotony, which is often a real concern in clinical practice (8, 9).

We therefore designed this fluorophotometric study to further evaluate the effects of ibopamine eye drops on aqueous humor dynamics and to establish any relationship with IOP changes in subjects with normal or glaucomatous eyes.

METHODS

The study was placebo-controlled. The eye to be treated with 2% ibopamine was chosen randomly and the treatments were administered from masked containers. Ibopamine and placebo eye drops were supplied in identical multi-dose dispensers containing sterile lyophilized powder and the solvent for reconstitution. Each subject/patient was treated with 2% ibopamine in one eye and placebo in the other.

Subjects/patients

The clinical trial was carried out at the AIBILI Clinical Trial Center of the University of Coimbra (Portugal) in the period November 1999-July 2000, in conformity with GCP/ICH guidelines and the Declaration of Helsinki, with all amendments. Before the study started, the local ethics committee approved the study protocol and the informed consent form. All subjects/patients signed informed consent before accrual.

A total of 15 healthy volunteers (6 males and 9 females) and 15 patients (6 males and 9 females) with bilateral primary open-angle glaucoma (POAG) were to be enrolled. Healthy volunteers with no medical or family history of glaucoma or ocular hypertension were selected in an age range of 21-45 years, with gonioscopically open angle, IOP lower than 18 mmHg after at least two tonometric measurements, visual field within normal limits, and an ophthalmoscopically normal optic nerve head.

Patients with glaucoma were enrolled according to the following criteria: age range 45-80 years, male or non-reproductive-age female, bilateral gonioscopically open angle, bilateral IOP higher than 24 mmHg after 7 days of wash-out, bilateral visual field with signs of optic neuropathy, bilateral glaucomatous cupping of optic nerve head.

Patients with diabetes, chorioretinal pathologies, maculopathies, non-glaucomatous neuro-optic pathologies, severe myopia, opacities of the optic media, previous ocular surgery, recurrent uveitis, secondary glaucoma and narrow-angle glaucoma were excluded. Eligible patients were asked to interrupt any previous glaucoma treatment. No concomitant treatments were allowed during the study.

Efficacy and safety

This study schedule comprised three visits: screening (day -7), baseline (day 0), final (day 7). At the screening, each subject/patient underwent the following evaluations: medical history and ophthalmological visit, which included examination of the anterior segment (cornea, anterior chamber, iris, iridocorneal angle, lens), status of the adnexa (eyelids, conjunctiva, tear film, lacrimal apparatus), pupil diameter and IOP measurements (two applanation tonometries with a 45-min interval).

At baseline POAG patients were assessed by IOP measurements in order to verify the inclusion/exclusion criteria. To determine basal corneal autofluorescence and the anterior chamber volume, four scans were done in each eye. All subjects/patients were also assessed for the “ibopamine test” (7): two applanation tonometries were done before and 45 minutes after ibopamine instillations (1 drop + 1 drop with a 5-min interval in both eyes). The test was considered positive when an IOP increase higher than 3 mmHg was observed.

Each subject/patient was also examined by fluorophotometry (without ibopamine) in both eyes. The aqueous humor flow was measured with the Fluorotron Master Coherent, with an adapter for anterior chamber measurements (10). The fluorophotometric assessment was done according to the following procedures: 4 drops of a 10% fluorescein solution (1 drop at 5-min intervals in both eyes) were instilled and 10 minutes

after the last instillation, both eyes were rinsed thoroughly using eye baths containing saline; 4 hours after rinsing the eyes 4 consecutive fluorophotometric scans were taken in each eye. This procedure was repeated 3 times at 1-h intervals (for a total of 4 times).

At the final visit the fluorophotometric examination was repeated concomitantly with 2% ibopamine instillations, using the same procedures as the baseline assessment. Ibopamine was administered according to the scheme reported in Table I. The rate of disappearance of fluorescein in the anterior chamber was considered indicative of the flow rate through the anterior chamber and, consequently, of the rate of aqueous humor production by the ciliary bodies.

Subjects/patients were evaluated on the basis of the ophthalmological findings and were questioned about symptoms or adverse events.

Statistics

In order to characterize each sub-population, descriptive statistics were provided separately and tabulated for age, sex, weight, height, race, eye colour and other parameters recorded at baseline. The changes in IOP after the ibopamine provocative test in POAG patients and healthy volunteers were compared by analysis of variance (ANOVA) for repeated measures. Subjects were compared with patients as the between factor and the measurements on the two eyes of each subject/patient as the within factor.

Aqueous humor flow was analyzed using the paired t-test in the two sub-populations, comparing ibopamine and placebo treated eyes. Changes in aqueous humor flow at the final visit compared to the baseline were also analysed using ANOVA for repeated measures, including comparison of subjects and patients as the between factor, and treatment effect as the within factor.

Each treated eye was considered for local tolerability, evaluated by comparing ocular symptoms and signs at the final visit in comparison with earlier visits. The frequency of adverse events for each treatment group was reported by severity and their potential relation to the study drug.

For all comparisons, the limit of statistical significance was set at $p<0.05$ and the bi-directional hypothesis was considered.

RESULTS

Thirty Caucasian subjects, 15 healthy volunteers and 15 glaucoma patients, were enrolled. The duration of the disease in glaucoma patients ranged from 1 to 240 months. Efficacy in POAG patients was assessed on day 0 and day 7 after mean wash-out periods of respectively 18 days and 25 days.

Demographic and other ophthalmological features before treatment are reported in Table II. No alterations in eye motility, pupillary reflexes, pupillary diameter and lacrimal tests were found. Gonioscopy showed open-angle IV in all subjects/patients. Visual field was normal in healthy volunteers and altered in all glaucoma patients. Fundus examination in glaucoma patients showed cupping of the optic nerve head.

No alterations were found in the anterior segment and adnexa examinations of healthy volunteers, while 9 mild alterations (8 bilateral lens opacifications and

TABLE I - SCHEDULE OF 2% IBOPAMINE INSTILLATIONS DURING FLUOROPHOTOMETRIC ASSESSMENT

		1st instillation		**2nd instillation**		**3rd instillation**		**4th instillation**	
Fluorescein instillation * ↓	Eye rinse ↓	ibo/pla ↓	**FPM** ↓	ibo/pla ↓	**FPM** ↓	ibo/pla ↓	**FPM** ↓	ibo/pla ↓	**FPM** ↓
0-15 min	25 min	235 min	265 min	295 min	325 min	355 min	385 min	415 min	445 min

* 1 drop of 10% fluorescein in both eyes every 5 minutes (total 4 drops in each eye)
ibo = 2% ibopamine (1 drop); pla = Placebo (1 drop in the fellow eye); FPM = Fluorophotometric scans (4 consecutive scans at each session)

1 concomitant conjunctival hyperemia) were detected in 8 glaucoma patients. Mydriasis was observed in ibopamine-treated eyes in all subjects/patients except one. No concomitant treatments were administered during the study period. None of those enrolled discontinued the study and all were considered for efficacy and safety.

Intraocular pressure

No differences in IOP were detected in healthy volunteers and POAG patients in the two measurements performed at screening, indicating the absence of diurnal variations. Tonometry, done in both eyes of volunteers and glaucoma patients before and 45 minutes after 2% ibopamine drops, showed no changes in IOP in healthy eyes (mean ± SE 11.13 ± 0.49 mmHg vs. 11.13 ± 0.47 mmHg) but a significant difference in glaucoma eyes (25.83 ± 0.23 mmHg vs. 29.87 ± 0.33 mmHg), the mean increase amounting to 4.03 mmHg (95% CI 3.46-4.51). The difference between the mean changes in healthy volunteers and patients was significant ($p<0.0001$).

None of the volunteers showed an IOP increase higher than 3 mmHg, while 86.7% of glaucoma eyes were positive to the ibopamine test (Fig. 1).

Fluorophotometry

Aqueous humor flow after ibopamine and placebo instillations was compared to baseline (Fig. 2). In healthy volunteers, the mean changes in aqueous humor flow were respectively -0.20 µl/min (95% CI 0.71-0.31) and 1.31 µl/min (95% CI 0.61-2.02) in the placebo and ibopamine treated eyes. The difference between the two groups was significant ($p<0.01$). The flow increase induced by ibopamine was about 46% compared to baseline, and 52% with respect to the fellow eye treated with placebo.

In POAG patients, the mean changes in aqueous humor flow were -0.20 µl/min (95% CI -0.71-0.32) and 1.01 µl/min (95% CI 0.31-1.72) in the placebo and ibopamine treated eyes respectively. The difference between the two groups was significant ($p<0.01$). The increase in flow in glaucomatous eyes treated with ibopamine was 81% compared to baseline, and 52% with respect to placebo.

No differences in aqueous humor production were detected between healthy volunteers and glaucoma patients.

Adverse events

No serious adverse events arose during the study. In total, 26 mild adverse events (24 ocular and 2 systemic) occurred in 13 healthy volunteers and 6 glaucoma patients. The most frequent adverse event in normal (12/19) and glaucoma eyes (4/5) was photophobia, probably related to the mydriatic effect of ibopamine. A systemic adverse event (mild vomiting) – probably related to the fluorescein instillations – occurred in one patient both at baseline and at the final visits.

DISCUSSION

Ocular hypertension is probably due to an impair-

TABLE II - DEMOGRAPHIC AND OPHTHALMOLOGICAL CHARACTERISTICS BEFORE TREATMENT

		Healthy volunteers	**Glaucoma patients**
Sex	M/F	6/9	6/9
Eye colour	dark/light *	12/3	12/3
Age (years)	mean ± SD	28.5 ± 4.98	64.4 ± 7.59
Weight (kg)	mean ± SD	60.0 ± 7.72	69.8 ± 9.31
Height (cm)	mean ± SD	168.0 ± 6.78	160.9 ± 6.95
Ant. chamber volume (µl) **	mean ± SD	178.2 ± 29.67	169.1 ± 34.92
Aqueous humor flow (µl/min) **	mean ± SD	2.9 ± 1.25	1.5 ± 0.71
IOP (mmHg) **	mean ± SD	11.0 ± 2.41	26.5 ± 1.61

* dark = Hazel or brown; Light = Blue, green or grey
** n = 30 eyes

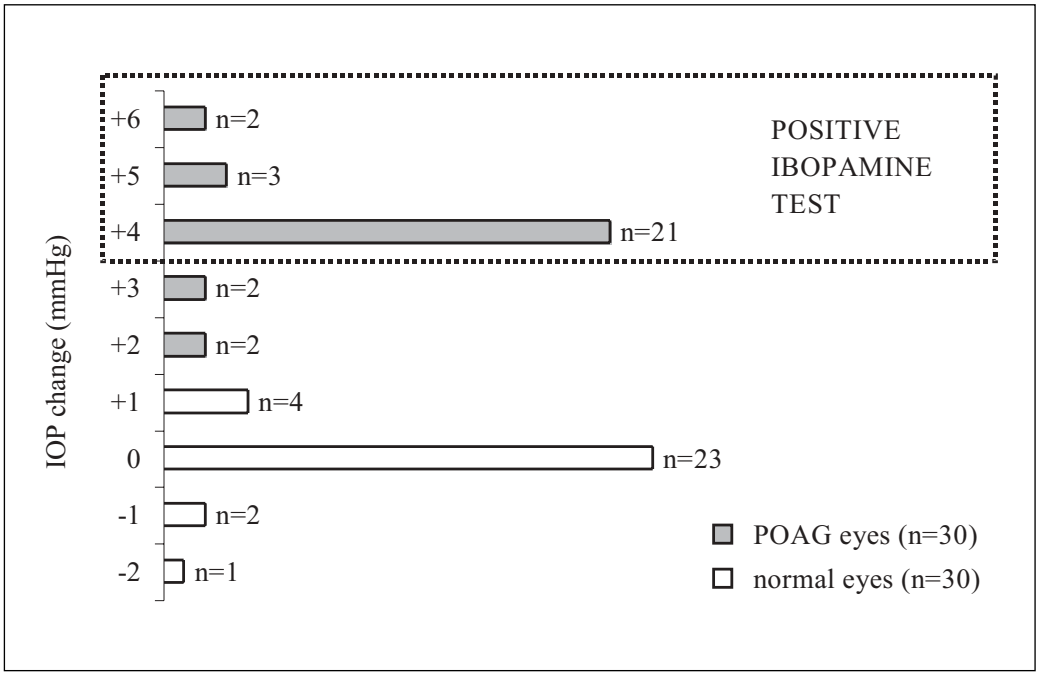

Fig. 1 - *Numbers of eyes by IOP changes after the ibopamine provocative test.*

ment of the outflow pathway combined with an alteration in aqueous humor production (7). In one study, ibopamine raised IOP in 92% of patients with ocular hydrodynamic disorders but not in normal subjects (5). This increase was not related to the mydriatic effect, as it was still present after pre-treatment with thymoxamine, and occurred with no changes in the depth of the anterior chamber (5, 7). After ibopamine, the combination of increased production of aqueous humor and the altered outflow pathway results in an increase in IOP in POAG eyes, but not in normal eyes because of the self-regulation of the outflow. In normal eyes trabecular outflow is pressure-dependent.

The effect of ibopamine on IOP is what underlies its use in post-surgical ocular hypotony in patients treated with corticosteroids, where the stimulation of aqueous humor production in the ciliary bodies by ibopamine normalized IOP values after a 30-day four-times-daily regimen (8). In these cases, steroid-induced alterations of the outflow pathway probably enhanced ibopamine's effect on IOP recovery. However, after discontinuation of ibopamine mean IOP dropped back to the pre-treatment values. These results seem to exclude a phenomenon of tachyphylaxis after chronic treatment with ibopamine, as confirmed in more recent reports (11).

In this study, mean aqueous humor flow in POAG patients was lower than in healthy volunteers (Fig. 2). This difference probably reflects the difference in mean age of the volunteers and patients (28.5 vs. 64.4 years) since aqueous flow diminishes anyway with age (12). In addition, a residual effect on flow rate due to long-term use of β-adrenergic antagonists cannot be excluded, although no significant changes were observed between day 0 and day 7 in the flow rate in placebo-treated POAG eyes.

The present study confirms the ocular hypertensive effect of ibopamine in POAG patients, possibly related to the 52% increase in flow observed by fluorophotometry compared to placebo. The fact that there was no such effect in POAG eyes treated with placebo confirms that the increase in aqueous flow after ibopamine is related to the drug's effect and probably not to any existing alterations due to the glaucoma.

A very similar result was detected in normal subjects treated with ibopamine in terms of flow increase (+ 52% with respect to placebo), but without any change in IOP. The study also confirmed the excellent safety profile of ibopamine.

A significant increase in aqueous flow was already reported after ocular instillation of phenylephrine in

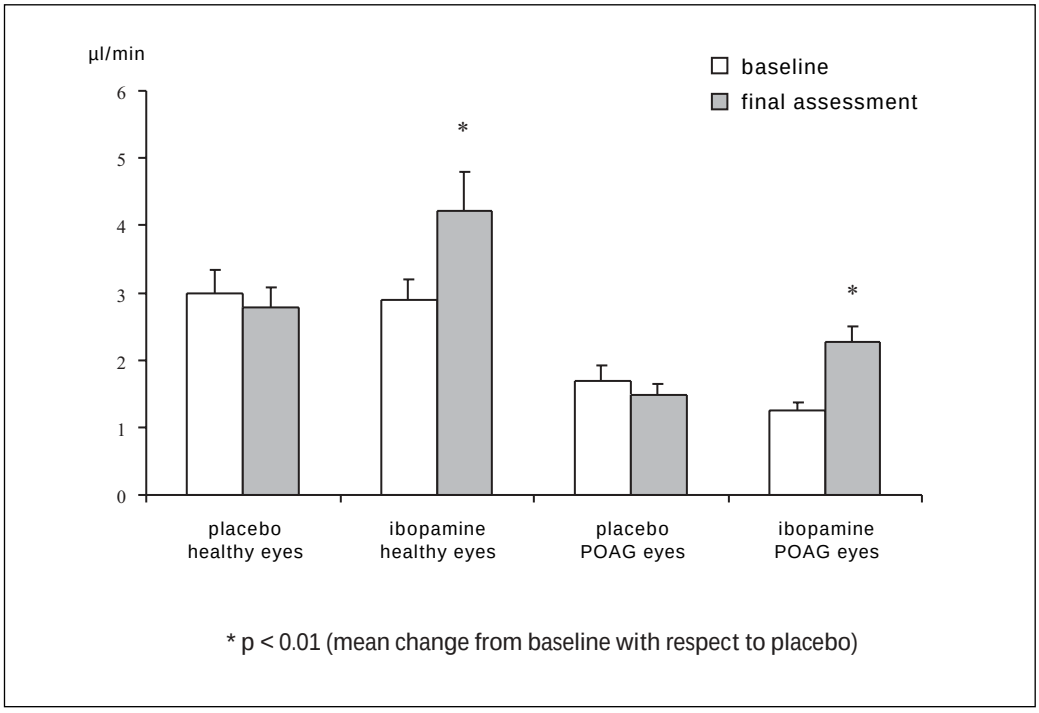

Fig. 2 - *Aqueous humor flow (mean ± SE).*

normal subjects (13, 14). Similar findings were reported more recently in a clinical trial in normal volunteers to determine, by means of fluorophotometry, whether pharmacological dilation of the pupil interferes with measurements of aqueous flow (15). In this study phenylephrine, but not tropicamide, increased the rate of clearance of fluorescein by 40% with respect to placebo, without affecting IOP. This effect on flow was explained as a sort of artifact due to the posterior escape of the tracer related to changes in accommodation and pupil size, in a condition of pupil dilation without cycloplegia that enables subjects to use their eyes between measurements.

This does not fully explain the results in this study. Although the effects on aqueous flow and IOP in normal subjects appear to be similar with ibopamine and phenylephrine, it should be noted that ibopamine, unlike phenylephrine, can significantly raise IOP in POAG patients. A direct comparison of the effects of both drugs in healthy and glaucomatous eyes showed no effects on IOP in normal subjects and a significant increase only in ibopamine-treated POAG patients (16).

On the whole, these findings suggest a positive effect of ibopamine on aqueous humor production which becomes evident in terms of the rise in IOP in patients with hydrodynamic disorders of the outflow pathway. In normal subjects self-regulation of the outflow pathway, by diminishing the outflow resistance, probably counterbalances the increase in aqueous humor, resulting in no changes in IOP. However, additional studies are necessary to clarify the pharmacodynamic characteristics of ibopamine and to better define the changes in the hydrodynamics of aqueous humor, especially in patients with ocular hypertension.

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