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The effects of 2% ibopamine eye drops on the intraocular pressure and pupil motility of patients with open-angle glaucoma

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PURPOSE. *Ibopamine is a prodrug of N-methyldopamine that has a non-cycloplegic mydriatic action due to its α-adrenergic properties and is able to induce, when topically given, a transient increase of intraocular pressure (IOP) in eyes with hydrodynamic disorders.*
METHODS. *This is a randomized, crossover, open-labeled, two- center study. Forty patients (20 open-angle glaucoma patients and 20 healthy subjects) were treated with ibopamine 2% eye drops and phenylephrine 10% eye drops.*
RESULTS. *Ibopamine induced a significant increase in IOP only in glaucomatous eyes ($p<0.001$) without a significant hypertensive effect in normal eyes. Ibopamine and phenylephrine showed a similar mydriatic activity but ibopamine was able to induce an hypertensive effect only in glaucomatous eyes.*
CONCLUSIONS. *The results confirm the use of ibopamine as provocative test in detection of hydrodynamic disorders.(Eur J Ophthalmol 2004; 14: 508-13)*

KEY WORDS. *Aqueous humor outflow, Dopaminergic D1-agonist, Ibopamine, IOP*

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INTRODUCTION

Ibopamine is a prodrug of N-methyldopamine which has a non-cycloplegic mydriatic action due to its α-adrenergic properties and is able to induce, when topically given, a transient increase of intraocular pressure (IOP) in eyes with hydrodynamic disorders (1-3). Previous fluorophotometric investigations showed that the increase of IOP after the instillation of ibopamine is partly the result of an increased production of aqueous humor by the ciliary body following the stimulation of D1 dopamine receptors (4, 5). This drug does not induce systemic side- effects, including hypertension and other sympathomimetic cardiovascular effects and, after topical use, ocular tolerability is always good even with repeated instillations of the drug. This test may also disclose a hydrodynamic disorder in the pseudoexfoliation syndrome (6, 7). Several clinical reports proved the usefulness of ibopamine to make a diagnosis of glaucoma (8-18). This test is simple to perform, is positive in 92% of patients with open-angle glaucoma, and is negative in the healthy eye. The increase in aqueous humor production induced by ibopamine is very useful in the management of ocular hypotony following vitreo-retinal surgery or antiglaucomatous filtering surgery and as a predic-

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tive test of corticosteroid-responsive patients after PRK (19). The goal of this study was to compare a sympathomimetic agent; that mainly affects α-adrenoceptors, and the activity of ibopamine on D1 receptors, whose stimulation is related to an increase in aqueous humor production. The primary aim of this study was to evaluate the ocular hypertensive effect of ibopamine in patients with open-angle glaucoma vs healthy subjects. Two percent ibopamine was compared with a reference mydriatic agent having α-adrenergic activity but not dopaminergic activity (10% phenylephrine) that is therefore unable to induce IOP increase as the result of increased aqueous humor production. To compare the degree and duration of the mydriatic activity of both the above eye drops was the second aim of this study.

TABLE I - BASIC THERAPY OF GLAUCOMA

Therapy	n.	Duration of treatment (months) Mean	Minimum	Maximum
Timolol	12/20	60.6	1	156
Betaxolol	4/20	33.5	14	48
Levobunolol	4/20	43	4	84

PATIENTS AND METHODS

Twenty patients with primary open-angle glaucoma (POAG) aged between 46 and 75 years (9 men and 11 women) and twenty healthy volunteers aged between 46 and 73 years (5 men and 15 women) were enrolled in the trial. The diagnosis of POAG was based on these parameters: IOP between 21- and 26 mmHg or higher, Humphrey 24-2 visual field results with two contiguous points on the total deviation plot at the less than 2% level, and optic disc damage. Treatment with

TABLE II - DISPOSITION OF PATIENTS

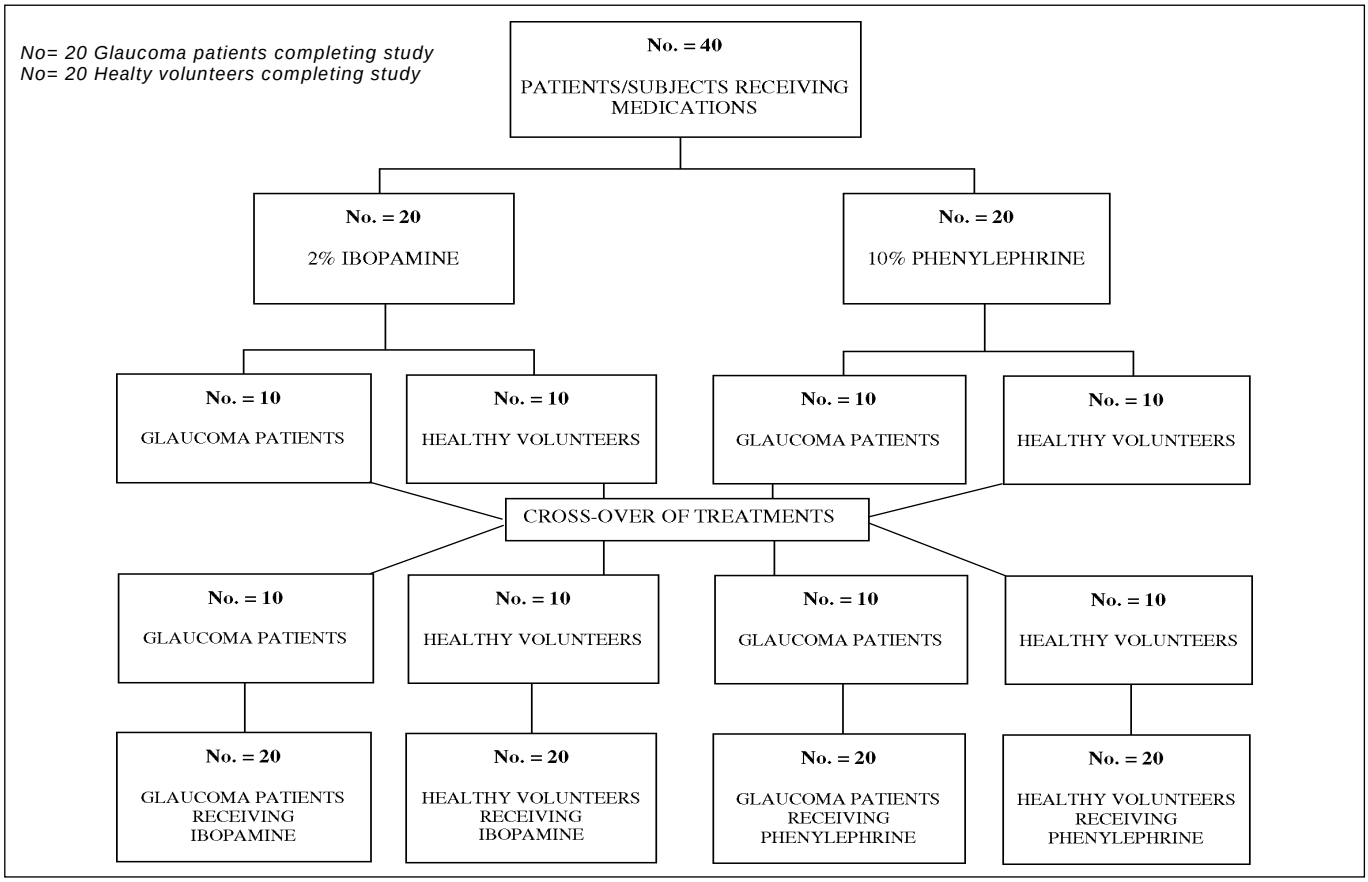


TABLE III - DISTRIBUTION BY AGE, HEIGHT AND WEIGHT

		Age (year)	Height (cm)	Weight (kg)
Glaucomatous patients	n.	20	20	20
	Mean	61.8	163.3	66.5
	Standard Deviation	9.22	5.55	8.87
	Min	46	150	50
	Max	75	172	80
Healthy volunteers	n0.	20	20	20
	Mean	58.3	166.8	69.6
	Standard Deviation	8.02	6.40	11.41
	Min	46	150	55
	Max	73	175	92

TABLE IV - DISTRIBUTION BY SEX AND COLOR OF EYES

		Glaucomatous patients	Healthy volunteers
		n.	n.
Sex	Males	9	5
	Females	11	15
Color of eyes	Blue	1	1
	Grey	2	3
	Green	2	1
	Light brown	9	7
	Dark brown	5	6
	Blue-grey-green	1	2

TABLE V - PUPILLARY DIAMETER (MM) BEFORE EACH TREATMENT PERIOD

	1st period		2nd period	
	patients	subjects	patients	subjects
n.	20	20	20	20
Mean	2.6	2.6	2.8	2.6
S.E.	0.06	0.07	0.13	0.07
Min	2.1	2.0	2.4	2.0
Max	3.2	3.0	5.0	3.0

topical beta-blockers started from 33 to 60 months (Tab. I) and was not discontinued.

Patients with pseudoexfoliative or pigmentary dispersion syndrome were not enrolled in this study. Healthy volunteers were randomly selected from the outdoor department with the following inclusion criteria: IOP < 18 mmHg and normal optic disc and visual field. Before entering the study, each patient was fully informed by the investigators about the purposes of the research and the expected duration of the patient's participation. The study was performed according to Good Clinical Practices. The study conformed to the requirements of the "Declaration of Helsinki" and subsequent reviews. This study was an open-labeled, cross-over, randomized, controlled clinical trial of 2% ibopamine versus 10% phenylephrine eye drops. The randomization and cross-over of treatments allowed minimization of bias (Tabs. II, III, IV).

Wash-out between first and second test was at least 3 days. Before tonometry, patients were locally treated with 0.4% oxybuprocaine hydrochloride eye drops. Patients and subjects were evaluated with applanation tonometry at baseline, 5, 45, 90, 180, 270, and 360 minutes after drug instillation. Pupillary diameter was also assessed (Tab. V).

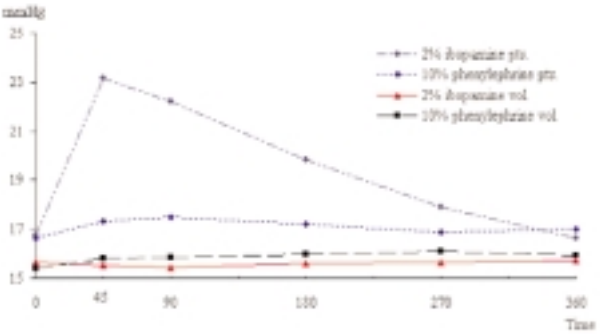
Efficacy was evaluated in both eyes by different parameters such as ocular pressure, mydriasis, and photomotor reflex. Eyes with an increase > 3 mm Hg in IOP at 45 minutes following instillation were considered positive to ibopamine (1). Safety was evaluated monitoring the adverse events such as burning, lacrimation, hyperemia, blood pressure, and heart rate. Efficacy and tolerability parameters were evaluated by analysis of variance for continuous data (ANOVA) and with Friedman's chi-square test and Wilcoxon's test for categorical data.

RESULTS

Comparing the two basal values, the authors noted a significant difference between patients and healthy volunteers (p= 0.001) (Fig. 1, Tab. VI).

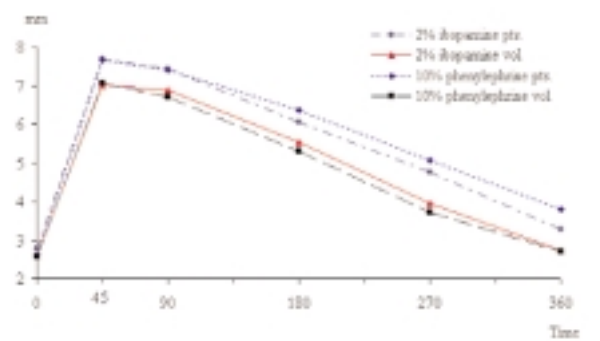
All patients were positive to ibopamine test independently from the type of hypotensive drug in use. No increase was observed in healthy volunteers after treatment with both drugs.

The analysis performed to evaluate the time trend



Maximum increase	Area under the curve	
Ibo pts. vs. Ibo vol.	p = 0.0001	p = 0.0001
Ibo pts. vs. Phn pts.	p = 0.0001	p = 0.0001
Ibo vol. vs. Phn vol.	p = n.s.	p = 0.01
Phn pts. vs. Phn vol.	p = n.s.	p = n.s.

Fig. 1 - *Introcular pressure.*



Maximum increase	Area Under the Curve	
Ibo pts. vs. Ibo vol.	p = n.s.	p = n.s.
Ibo pts. vs. Phn pts.	p = n.s.	p < 0.05
Ibo vol. vs. Phn vol.	p = n.s.	p = n.s.
Phn pts. vs. Phn vol.	p = n.s.	p = 0.0002

Fig. 2 - *Pupillary diameter.*

TABLE VI - INTRAOCULAR PRESSURE (mmHg/mean ± SD)

Glaucomatous patients	**Ibopamine (no=20)**	**Phenylephrine (no=20)**
Baseline	16.75 ± 1.1	16.65 ± 1.4
45 min.	23.15 ± 1.8	17.35 ± 1.8
90 min.	22.20 ± 1.9	17.50 ± 1.7
180min.	19.85 ± 2.4	17.20 ± 1.6
270min.	17.90 ± 1.8	16.90 ± 1.3
360min.	16.65 ± 1.3	17.00 ± 0.9
Healthy volunteers	**Ibopamine (no.=20)**	**Phenylephrine (no.=20)**
Baseline	15.65 ± 0.7	15.40 ± 0.9
45min.	15.55 ± 1.1	15.80 ± 0.8
90min.	15.45 ± 1.1	15.85 ± 0.7
180min.	15.60 ± 0.8	16.00 ± 0.6
270min.	15.65 ± 0.7	16.10 ± 0.7
360min	15.75 ± 0.7	15.95 ± 0.7

TABLE VII - PUPILLARY DIAMETER (mm/mean ± SD)

Glaucomatous patients	**Ibopamine (no=20)**	**Phenylephrine (no=20)**
Baseline	2.8 ± 0.6	2.6 ± 0.3
45 min.	7.7 ± 0.6	7.6 ± 1.1
90 min.	7.4 ±0.8	7.4 ± 0.9
180 min.	6.1 ± 1.1	6.3 ± 0.7
270 min.	4.7 ± 1.2	5.1 ± 0.6
360 min.	3.3 ± 1.0	3.8 ± 0.3
Healthy volunteers	**Ibopamine (n.=20)**	**Phenylephrine (n.=20)**
Baseline	2.6 ± 0.3	2.6 ± 0.3
45 min.	7.1 ± 0.8	7.1 ± 1.0
90 min.	6.9 ± 0.8	6.7 ± 1.2
180 min.	5.5 ± 0.8	5.3 ± 0.9
270 min.	3.9 ± 1.2	3.7 ± 0.4
360 min.	2.7 ± 1.3	2.7 ± 0.3

of IOP showed a statistically significant increase from 45 to 270 minutes after instillations in patients treated with ibopamine when compared to the other treatment groups (p< 0.001).

The mean values of pupillary diameter obtained at each visit are reported in Figure 2 and Table VII.

No differences were found in healthy volunteers. The analysis performed to evaluate the time trend of photomotor reflex was statistically significant (p= 0.001), showing a return to normality of pupil motility. No adverse events occurred during the study. Age, height, weight, and iris color did not influence the study (p= 0.5).

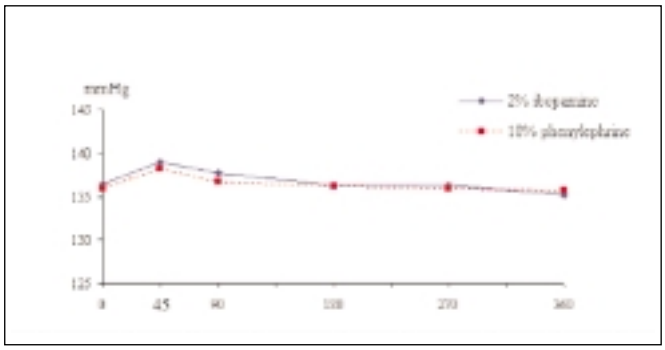


Fig. 3 - *Glaucomatous patients - Systolic blood pressure.*

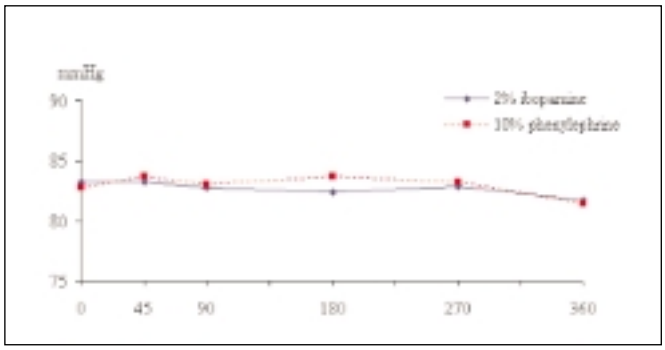


Fig. 4 - *Glaucomatous patients - Diastolic blood pressure.*

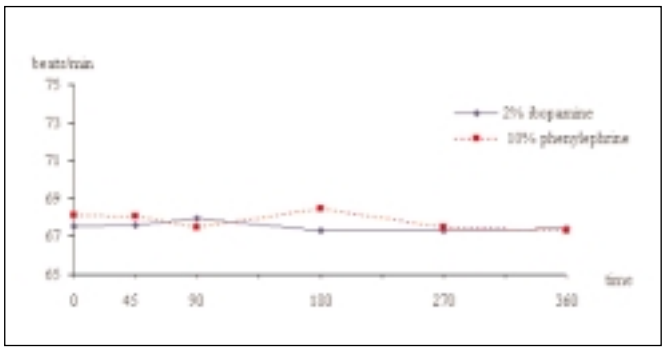


Fig. 5 - *Glaucomatous patients - Heart rate.*

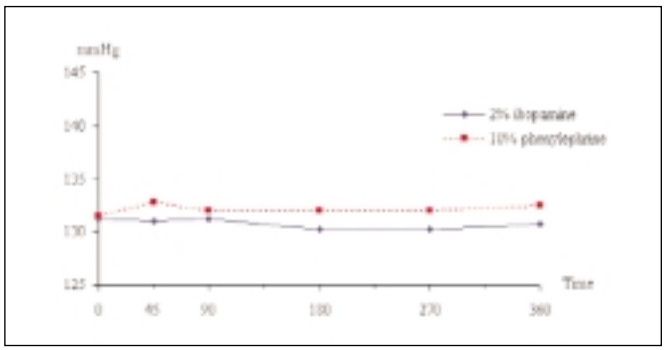


Fig. 6 - *Healthy volunteers - Systolic blood pressure.*

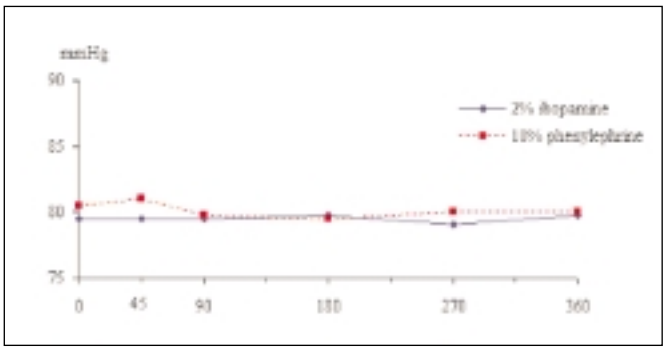


Fig. 7 - *Healthy volunteers - Diastolic blood pressure.*

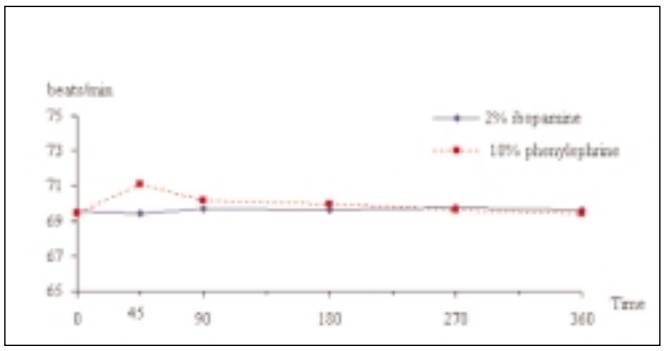


Fig. 8 - *Healthy volunteers - Heart rate.*

DISCUSSION

Previous data showed that ibopamine is able to increase IOP in eyes with impaired aqueous humor outflow and that this effect was attributed to the specific activity of ibopamine on the D1 dopamine receptors, the stimulation of which leads to an increase in the production of aqueous humor. A comparison was also performed with a reference mydriatic agent having α-adrenergic activity but not dopaminergic activity (10% phenylephrine) and, therefore, being unable to induce a rise in IOP. The randomized clinical trial (RCT) was performed according to a cross-over design, evaluating the time course of IOP, pupillary diameter, and vital signs at different times up to 360 minutes after instillations (Figs. 3-8).

Already after the first tonometry performed 45 minutes after instillations a significative increase in IOP (6.40±1.45 mmHg) was observed in all glaucomatous patients treated with 2% ibopamine, thus indicating a partial obstruction of the outflow. Healthy volunteers treated with 10% phenylephrine did not show any statistically significant variation in IOP (Fig. 1). Healthy volunteers treated with 2% ibopamine and 10% phenylephrine showed no statistically significant change in IOP (Fig. 1). The safety profile of both treatments was good. Thus, the results of this study support previous data concerning the characteristic activity of ibopamine on aqueous humor production and confirm its potential employment as an interesting and simple tool for the ophthalmologist in the detection of alterations in aqueous humor outflow, beyond tonometry and ophthalmoscopy.

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