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Ibopamine – A New Alpha-Adrenergic and D1-Dopaminergic Drug

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1. Introduction

Ibopamine (3,4 di-isobutyrylester of N-methyldopamine) at 2% concentration, when instilled in the conjunctival sac, stimulates ocular D1-dopaminergic and α -adrenergic receptors [1,2]. It is a pro-drug of epinine (N-methyldopamine) (Figure 1). It has positive inotropic effects: it improves cardiac function and it is effective in the treatment of congestive heart failure. The pharmacological ocular characteristics of ibopamine are as follows:

- It increases aqueous humor production following D1-dopaminergic stimulation;
- It is a provocative test for evaluating the function of aqueous humor outflow structures;
- It can be used to treat ocular hypotension;
- It induces a noncycloplegic mydriasis (α -adrenergic action);
- It is very useful, apart from genetic testing, to detect a predisposition to ocular hypertension and even glaucoma in relatives of glaucoma patients.

In the conjunctival sac, ibopamine is fastly hydrolysed to epinine by the esterases of the aqueous humor and ocular tissues. This hydrolysis suggests that epinine is the active component of the molecule. The half-life of ibopamine in the aqueous humor is short (about 2 minutes) and epinine formation precedes the mydriatic effect [3,4] (Figure 1). It has been proved that after the instillation of ibopamine, only epinine can be found in the aqueous humor [3].

When hydrolysed to epinine, ibopamine stimulates the α -adrenergic and D1 dopaminergic receptors. The mydriatic effect of ibopamine is due to the stimulation of the α -adrenergic receptors of the dilating muscle of the pupil. Since ibopamine has no effect on the ciliary muscle, the mydriasis is not accompanied by cycloplegia. Mydriasis can be antagonized and

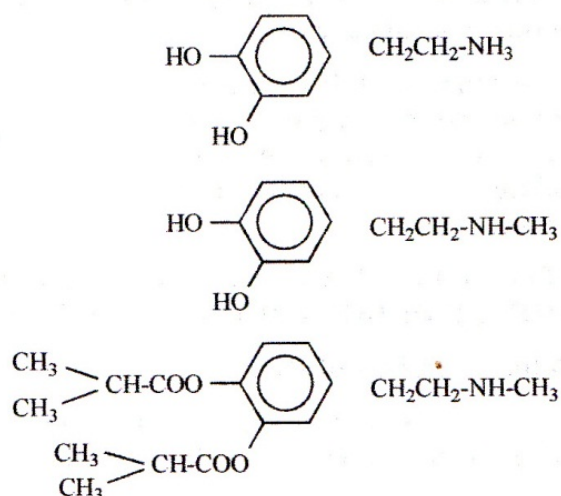


Figure 1. Dopamine → Epinephrine → Ibopamine (3,4 diisobutyryl ester of N-methyldopamine).

reversed by pre-treatment by α -blocking agents (such as thymoxamine and dapiprazole). Some Randomized Clinical Trials (RCTs) show that the D1 dopaminergic activity of the drug increases aqueous humor production and intraocular pressure (IOP) in open-angle glaucoma (POAG) patients [5].

Ibopamine has low toxicity both at systemic and local levels. LD₅₀ is 2056 mg/Kg, 4930 mg/Kg and 1786 mg/Kg in mice, rats and guinea pigs respectively. Ibopamine is well tolerated without any significant change to the haematological and behavioural parameters. 2% ibopamine eye drops show that ibopamine is well tolerated at local level, without systemic side-effects and tachyphylaxis phenomena. One drop of 2% ibopamine contains 1 mg of the compound, while the oral dosage is higher than 400 mg/day. Electrophysiological assessment showed that ibopamine is not retinotoxic at all [6].

2. Clinical use

2.1. Non-cycloplegic mydriatic activity

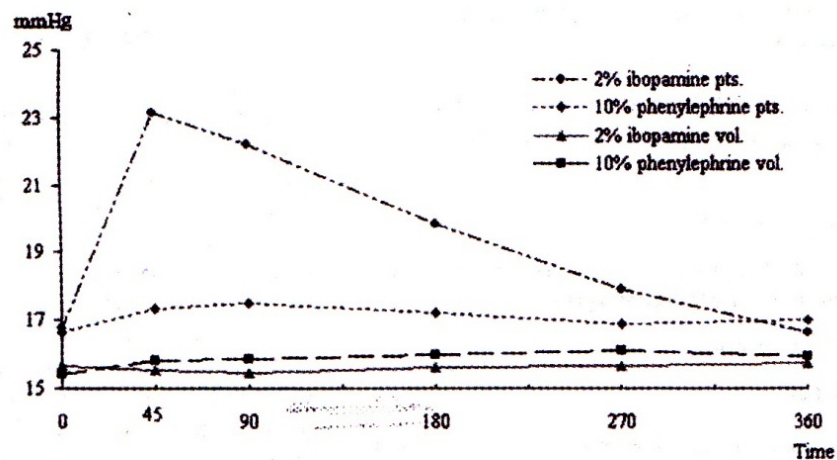
In binocular indirect examination of fundus oculi with scleral indentation, fluorescein and indocyanine angiography, and in the laser treatment of retinal lesions, ibopamine can induce a fast, short-lasting (2-3 hours) maximal mydriasis without cycloplegic effects or local a/or systemic side-effects [7]. The mydriatic effect of ibopamine can be prolonged if repeatedly administered (every 30 minutes). Ibopamine-induced mydriasis can be reversed by local application of α -blockers such as thymoxamine and dapiprazole. Ibopamine can substitute phenylephrine in association with tropicamide a/or cyclopentolate to avoid the typical discomfort of cycloplegia mostly in adults [7]. Ibopamine eye drops is effective in inducing pre-operative mydriasis, without effects on the cardiovascular system [7]. In the post-operative period ibopamine can induce a fast and short-lasting mydriasis to induce pupil dilatation.

2.2. Pathophysiology of IOP

2% ibopamine eye drops increases IOP only in patients suffering from POAG. Ibopamine is useful in different ways:

- Physiological studies on IOP;
- Evaluation of trabecular outflow pathways (pressure-dependent outflow);
- Treatment of ocular hypotony.

The instillation of ibopamine increases the IOP only in about 96% of eyes with POAG [8,9,10] (Figures 2, 3). In normal eyes, 2% ibopamine does not significantly affect IOP, with a possible mild hypotensive effect (1-2 mmHg) (Figure 4). The IOP, in POAG patients, increases by a maximum value of 10-11 mmHg within 45 minutes from the instillation and lasts about 180 minutes [7,8,9,10,11,12,13,14]. To observe this effect, 2 drops of 2% ibopamine have been instilled 5 minutes apart, and IOP was measured 45 minutes after the first instillation. The ibopamine provocative test shows a significant correlation with the highest intraocular pressure in the diurnal tension curve in glaucoma patients [15]. Indeed, in glaucoma patients with early visual field defect, the ibopamine provocative test has shown better sensitivity/specificity than the water drinking test [16]. Ibopamine test does not modify the results of visual field tests in normal individuals [17].



	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.	$p = \text{n.s.}$	$p = 0.01$
Phn pts. vs. Phn vol.	$p = \text{n.s.}$	$p = \text{n.s.}$

Figure 2. Effect on the intraocular pressure of 2% ibopamine and 10% phenylephrine in glaucomatous patients and in normal volunteers.

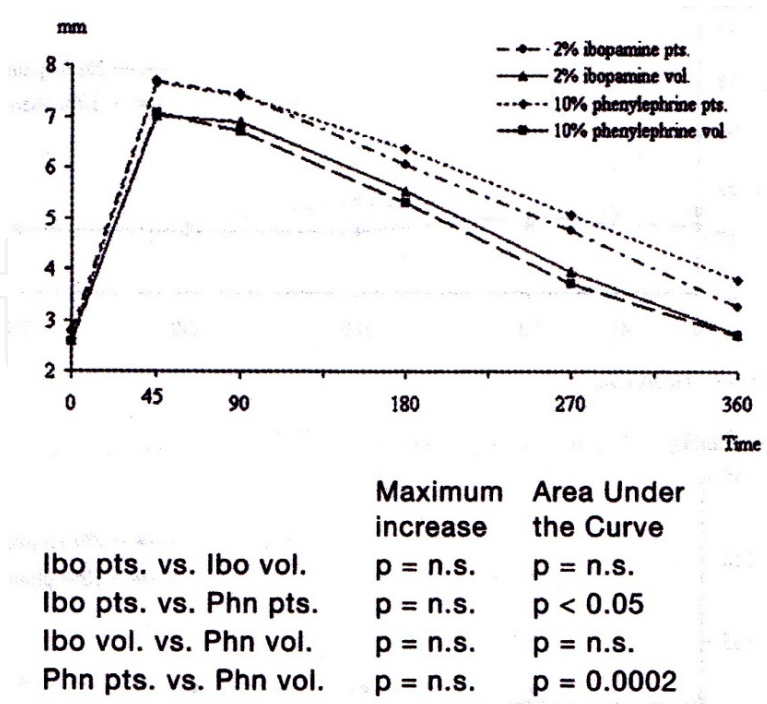


Figure 3. Effect on the pupillary diameter of 2% ibopamine and 10% phenylephrine in glaucomatous patients and in normal volunteers.

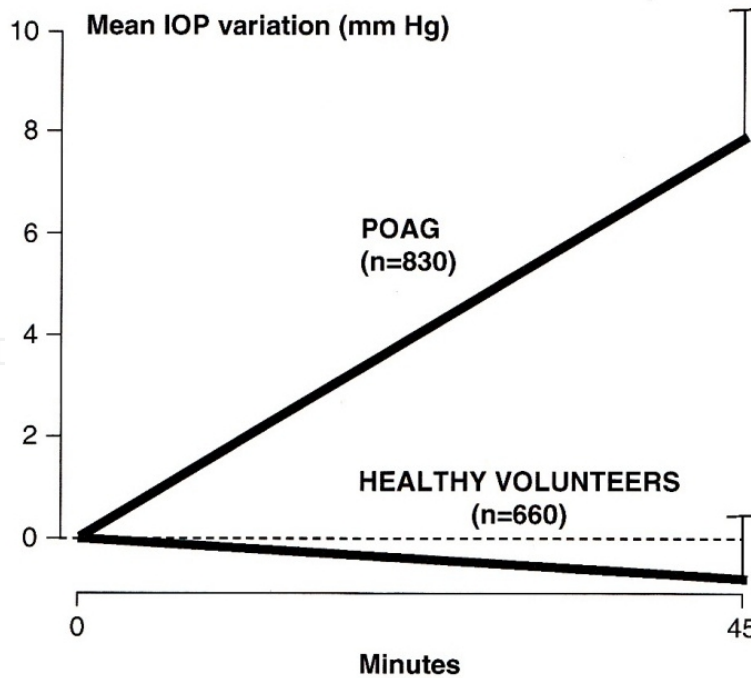


Figure 4. ibopamine induces a transient ocular hypertensive effect (mean, 8.31±2.14 mmHg) in 96% of eyes of patients affected by POAG, whereas in healthy eyes there is a reduction of intraocular pressure (IOP) by 1 to 2 mmHg.

Several studies have been performed to assess the following issues:

- Identification of the responsible receptor (agonist and antagonist);
- Evaluation of the change of the aqueous humor dynamics;
- Evaluation of ibopamine effects when the outflow system was experimentally impaired.

Only the D1 agonist substances, such as fenoldopam, have the same effect as ibopamine on IOP in POAG patients. D1 agonist drugs increase the IOP only in POAG, but never in healthy eyes, stressing the involvement of D1 dopaminergic receptors on the mechanism stimulating the aqueous humor production.

The hypertensive effect of ibopamine in POAG is completely counteracted by the pre-treatment with a selective antagonist of the D1 receptors such as SCH23390. A clear receptorial antagonism for IOP has been identified. Ocular anti-hypertensive drug, such as β -blockers and α -agonists do not antagonize the hypertensive effects of ibopamine in POAG [14]. The partial antagonism performed by glycerol is due to an osmotic reduction of the vitreous mass.

When there is a marked increase of aqueous humor production, due to the D1 dopaminergic effect of ibopamine, the healthy eye increases its outflow maintaining the homeostasis. Instead, in glaucomatous eyes, the impaired trabecular outflow fails to maintain the hydrodynamic equilibrium and IOP increases. Fluorophotometry proves that the D1 dopaminergic stimulation, induced by 2% ibopamine, undoubtedly increases the aqueous humor production.

Ibopamine, when instilled, prior to the Laminaria, into the healthy rabbit eyes does not significantly affect the IOP, while in the eyes treated with Laminaria digitata induces ocular hypertension.

3. Provocative test in glaucoma

Ibopamine 2% eye drops have a positive pressure effect in 50% of suspected normal-tension glaucoma eyes and may differentiate between eyes with normal trabecular outflow capacity and eyes with increased resistance in the trabecular meshwork that are ready to have pressure peaks and deterioration to glaucoma [18].

A long-term treatment with corticosteroids can induce ocular hypertension. They increase the IOP by interfering with the aqueous humor outflow system. By administering dexamethasone at two different concentrations (0.1 and 1%) in eyes suffering from allergic conjunctivitis, the ibopamine test was positive, in a dose-dependent manner, from 33 to 50%.

Ibopamine test is useful in detecting an impairment of the outflow system also in patients affected by pseudoexfoliative syndrome (PEX) [19]. This test is also positive when PEX syndrome is unilateral. It exerts a significant additive effect on mydriasis of PEX eyes induced with 10% phenylephrine-0.5% tropicamide with only minimal increase in IOP [20].

The ibopamine test is positive in 44.33% of offspring of one glaucoma parent without glaucomatous damage. It signifies an impaired function of the outflow structures and, therefore, a predisposition to intraocular hypertension and possible glaucoma in some years [21,22].

Ocular hypotony is a pathological condition of the IOP when it decreases to values below 6-7 mmHg. IOP values below 4 mmHg usually cause progressive damage to the eye [23]. Ocular hypotony can be caused by a damage to ciliary body from trauma or inflammation. In the treatment of ocular hypotony, ibopamine can be administered every 3 hours or 3-4 times daily, associated to corticosteroid therapy [24,25].

4. Conclusion

In conclusion, 2% ibopamine eye drops test is a useful pharmacological tool allowing us to study the pathophysiology of hydrodynamic disorders and in evaluating the outflow impairment. It is useful as a therapeutic drug in ocular hypotony secondary to filtering surgery, vitreo-retinal surgery or long-lasting uveitis. That's why its use is advised in all the Ophthalmological Department in EU and USA.

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