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# Effect of monatepil, a calcium channel blocker in ocular hypertensive rabbits

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ABSTRACT

*Introduction:* Increased ocular hypertension is one of the main characteristics of glaucoma. Monatepil belongs to a class of calcium channel blockers with special characteristic of α1-adrenergic receptor blocking effect. Calcium channel blockers and α1-adrenergic receptor blocker act as antihypertensive agents.

*Aim:* Monatepil has been studied for its effect on ocular hypertension in experimental glaucoma and for its mechanism of action for effect in glaucoma.

*Material and methods:* After pretreatment with topical monatepil (1%), 5% dextrose has been administered intravenously through marginal ear vein in healthy New Zealand white rabbits. Pilocarpine (1%) was used as the reference standard. Freshly prepared 50 units of α-chymotrypsin was injected in the posterior chamber of the eye to induce chronic model of glaucoma. After achievement of steady ocular hypertension, single dose treatment with monatepil (1%) and pilocarpine (1%) was given. To find possible mechanism of action, interaction of monatepil with pilocarpine and indomethacin has been studied.

*Results and discussion:* Topical administration of monatepil prevented acute increase in intraocular pressure. Monatepil (1%) and pilocarpine (1%) produced a significant decrease in intraocular pressure in α-chymotrypsin induced chronic ocular hypertensive rabbits. Indomethacin (1%) and pilocarpine (1%) pretreatment did not alter intraocular pressure lowering effect of monatepil.

*Conclusions:* Monatepil give beneficial effect in ocular hypertension by enhancement of aqueous humor outflow.



## 1. Introduction

Elevated intraocular pressure (IOP) is one of the leading causes of glaucoma, the irreversible blindness in the word. Elevated IOP is the most prominent cause of optic nerve damage which is considered as the hallmark in glaucoma. Improper treatment of elevated IOP can result in permanent blindness.

Apart from that, β-adrenergic blockers, parasympathomimetics, α2-adrenoceptor agonists, prostaglandin analogs,

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carbonic anhydrase inhibitors, α1-adrenergic receptor blockers and angiotensin converting enzyme inhibitors are available for glaucoma treatment.[1–3] Beta-blockers are the golden standard for treatment ocular hypertension. But they get into systemic circulation after topical instillation in eye and cause many systemic effects.[4] However, glaucoma is considered as the serious chronic disorder of eye, ideal agents are not available till date for treatment of the disease. Hence there is an urgent need of the ideal agent.

Steady state IOP is the result of balanced formation and outflow of aqueous humor. Aqueous humor dynamics is affected by calcium flux. Hydrostatic component plays important role in maintenance of arterial blood pressure as well as ciliary body perfusion and thereby aqueous humor dynamics. Also it is affected by the osmotic component by an effect on the active secretion of ions like calcium, sodium, etc., through ciliary epithelium.[5] Calcium channel blockers (CCBs) have been studied by several scientists for their effects on aqueous humor dynamics. However, the effect of CCBs on IOP is controversial since long due to obtained results of various studies, i.e. CCBs failed to cause reduction in IOP in rabbits when administered orally.[6] While, topical application of nifedipine, diltiazem and nifedipine has been reported to lower IOP effectively dose dependently in rabbits.[7] Reports indicated IOP lowering effect of verapamil in human volunteers also.[8] Monatepil is the newer drug of calcium channel blocker which also possess α1-adrenergic receptor blocking effect. α1-Adrenergic receptor blockers like prazosin are reported for enhancement of aqueous humor outflow.[9]

## 2. Aim

The present study was aimed to investigate effect of monatepil maleate on ocular hypertension in rabbits and to find out possible mechanism of action.

## 3. Material and methods

The protocol of the experiment was approved by Institutional Animal Ethics Committee as per the guidance of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. Monatepil solution (1%) was prepared in polyethylene glycol 400. The formulation was first tested in rabbit's eyes for ocular safety. No ill effects were observed.

### 3.1. *Acute model of ocular hypertension*

The basal IOP was measured for all the rabbits under the study. The drugs, monatepil maleate (1%) and pilocarpine (1%), as reference standard, was administered topically in one eyes 15 min before dextrose (5%) administration (15 mL/kg) through marginal ear vein.[10] Another eye served as control. Changes in the IOP were measured till it became normal at every 15 min interval. Schiotz indentation tonometer was used to measure IOP.

### 3.2. *α-Chymotrypsin induced chronic glaucoma*

Healthy New Zealand white rabbits of either sex (weighing from 1.5 kg to 2.5 kg) were selected for the experiments. Animals were sedated with intravenous administration of 1 mg/kg diazepam and 25 mg/kg ketamine. A dose of 50 units of α-chymotrypsin (a freshly prepared solution in the saline) was irrigated into posterior chamber of eye through cannula.[10] Rabbits with steady elevated IOP (above 30 mmHg) were selected for the study. Monatepil maleate and pilocarpine (1%) were administered in animals in one eye and the other eye served as control. IOP was measured at the different time intervals (i.e. 0, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min).

To evaluate effect of monatepil maleate on aqueous humor outflow through uveoscleral pathway, effect of interaction of monatepil maleate and indomethacin (1%) (a prostaglandin inhibitor) has been studied. Indomethacin (1%) was administered topically in left eye. Another eye served as control. After 45 min monatepil solution (1%) was instilled topically in the eye treated with indomethacin. The changes in IOP were recorded at specific time intervals with the help of Schiotz type indentation tonometer. To study effect of pilocarpine and monatepil maleate interaction on IOP, similar method was used as in case of interaction of indomethacin (1%) with monatepil solution (1%). After 45 min monatepil solution (1%) was instilled topically in the eye treated with pilocaroine. The changes in IOP were recorded.

### 3.3. *Statistical analysis*

Paired student *t*-test was employed for determining the statistical significance of most of the data at the probability level of 95%. A split-plot ANOVA analysis was carried out for studying the time dependent interaction between the drugs under study.

## 4. Results

An acute elevation in intraocular pressure (IOP) up to 33 mmHg was observed after intravenous administration of 5% dextrose solution. Pretreatment with monatepil prevented this rise in IOP when compare with eyes served as control (Fig. 1).

In α-chymotrypsin induced glaucoma eyes, topical administration of monatepil (1%) produced a significant fall in IOP when compared with control eyes. Pretreatment with indomethacin (1%) did not produce any significant change in IOP lowering effect of monatepil. Pretreatment with pilocarpine (1%) followed by monatepil (1%) instillation did not further lower IOP in α-chymotrypsin induced chronic glaucoma eyes in rabbits (Fig. 2).

## 5. Discussion

Ocular hypertension is the most common cause of optic nerve damage and blindness in glaucoma. The drugs which are available for treatment of glaucoma (ocular hypertension) are also well established for their cardiovascular effect by either lowering of blood pressure and or reduction of cardiovascular

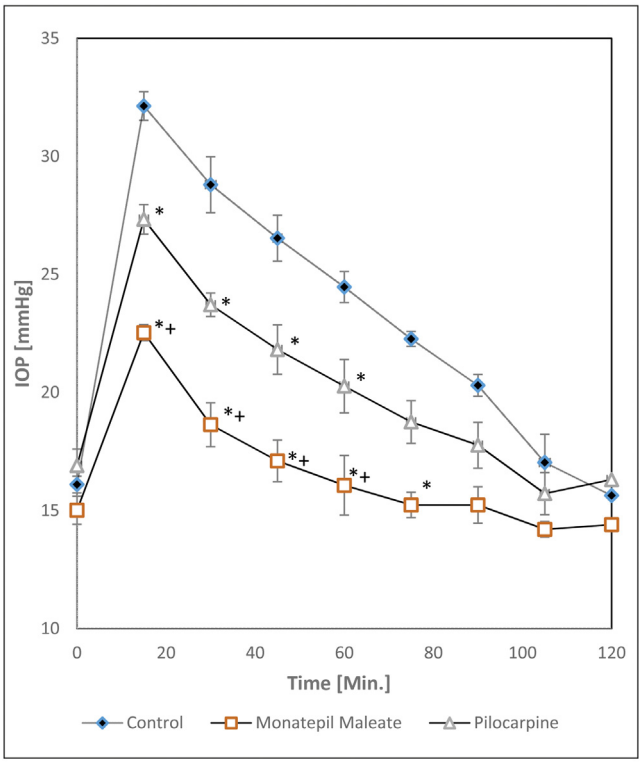


**Fig. 1 – Effect of monatepil maleate (1%) and pilocarpine (1%) on IOP in acute glaucoma model in rabbits. Each point and bar represents mean (± SEM) of 6 observations. *Significantly different from control ($P < 0.05$), + significantly different form pilocarpine ($P < 0.05$).**

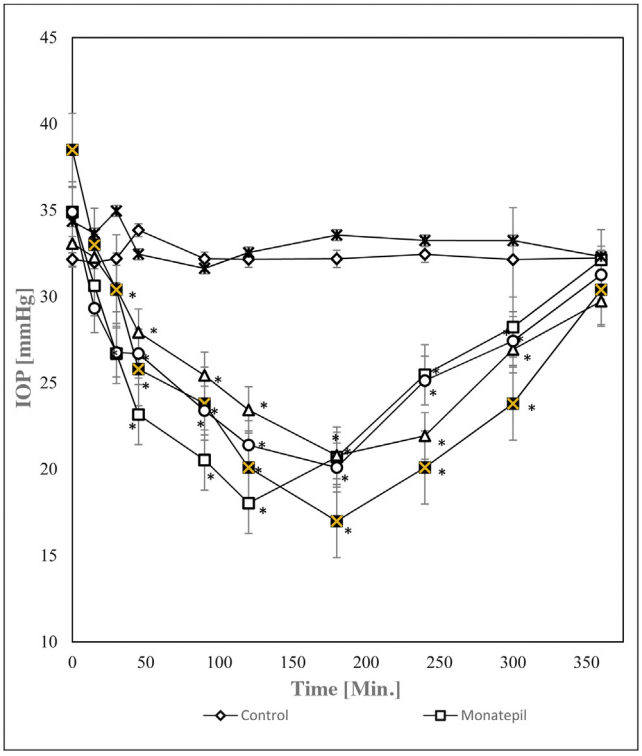


**Fig. 2 – Effect of monatepil maleate (1%), pilocarpine (1%), mixture of pilocarpine (1%) and monatepil maleate (1%), indomethacin and mixture of indomethacin (1%) and monatepil maleate (1%) on IOP in chronic glaucoma model in rabbits. Each point and bar represents mean (± SEM) of 6 observations. * Significantly different from control ($P < 0.05$).**

blood volume by enhancing urine formation. Clinical studies and animals studies indicated involvement of vascular effects in development of ocular hypertension and as a result glaucoma.[10]

One hypothesis that may explain pathophysiology of glaucoma is that in glaucoma there is a decrease in perfusion pressure. It is possible that increase in IOP can cause reduced blood flow toward optic nerves through blood vessel compression.[11] Reduced blood supply to retina as well as optic nerve can impair the anaerobic glycolysis.[12] This phenomena may cause damage to lamina cribrosa which may be the partial cause of optic nerve damage in glaucoma.[13]

We studied the oculohypotensive action of a calcium channel blocker, monatepil in acute and chronic glaucoma in rabbits. A solution (5%) of dextrose induced acute glaucoma is one of the most advantageous as it is easy to perform, faster and reliable method for screening of oculohypotensive drugs. Infusion of 5% dextrose through marginal ear vein would lead to reduced blood osmolality. Hence it will cause increase in aqueous humor formation by transfer of water in the aqueous chamber of eye and thereby increase in intraocular pressure.[14]

In the present study, monatepil and pilocarpine (reference standard) prevented the acute increase in IOP by 5% dextrose infusion (Fig. 1). Steady state elevation in IOP was obtained by administration of α-chymotrypsin in posterior chamber of rabbit eye. α-Chymotrypsin can induce inflammatory reactions in trabecular meshwork which can obstruct aqueous humor drainage and thereby can increase IOP.[15,16] Both monatepil and pilocarpine reduced IOP significantly when instilled in α-chymotrypsin induced chronic glaucomatic eyes (Fig. 2). Hence, the IOP lowering effect of monatepil is significantly higher than pilocarpine.

Prostaglandin analogs are known to reduce IOP by increasing the uveoscleral outflow.[17] Pilocarpine reduces uveoscleral outflow by providing a stretching of the scleral spur through which PGF2α reduces IOP.[18] To explore IOP lowering mechanism of monatepil, we have studied interaction of indomethacin and pilocarpine with monatepil. Topical application of indomethacin was unable to prevent the fall in IOP due to monatepil. The combination of monatepil and pilocarpine did not have any synergistic effect on IOP. This suggests absence of involvement of uveoscleral pathway in lowering IOP by monatepil.

CCBs are reported for their vasodilation effect and for reduction of vascular resistance. CCBs can increase the capillary blood speed in the optic nerve head.[8,19,20] This phenomena may make them a suitable candidate for low tension glaucoma treatment. L-type and T-type calcium channels seem to play role in cellular growth and thus calcium antagonists can inhibit the growth and proliferation of

vascular smooth muscle and fibroblasts. CCBs may also inhibit the synthesis of extra cellular-matrix collagen proteins suggesting beneficial effect in glaucoma.[21]

CCBs Report by Santafe et al. (1997) showed that CCBs decrease aqueous humor secretion, although they also cause a slight but significant reduction of tonographic outflow facility.[7] Also the reduced outflow of aqueous humor caused by raised episcleral venous pressure may be directly increased by calcium inhibition.[5] Apart from IOP lowering effect by improvement in ocular perfusion they may be beneficial in glaucoma for exerting neuroprotective effect on retinal ganglion cells.[22] Monatepil may, at least partly act through this mechanism. In addition to calcium channel blocking activity, monatepil also possesses α1-adrenergic blocking activity.[23,24] Doxazosin, a α1-adrenergic blocker, produces vasodilation by blocking α-adrenoceptors in outflow system. Prazosin α-antagonist produces miosis, which promotes the drainage of fluid through the anterior chamber.[4,25] Monatepil appears to show effect on aqueous outflow through α-adrenergic blocking activity.

## 6. Conclusions

In conclusion, our data suggest that monatepil give oculohypotensive effect probably by enhancing aqueous humor outflow. It can be explored for its candidature as therapeutic molecule for treatment glaucoma.

## Conflict of interest

None declared.

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