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# SHORT-TERM EFFECT OF CAPTOPRIL ON INTRAOCULAR PRESSURE

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**Abstract :** The angiotensin converting enzyme (ACE), which is responsible for the conversion of angiotensin-I to angiotensin-II, and metabolism of bradykinin is found to be present in human ocular tissue and it manifests a variety of physiological and pharmacological effects. Angiotensin increased the intraocular pressure (IOP) in animals. Even, the topical instillation of ACE inhibitors have been reported to reduce the IOP in rabbits. We, therefore performed this randomized, double masked, parallel groups-design and placebo controlled study, to investigate the acute effect of captopril (6.25 mg, 12.50 mg, and 25.00 mg) and placebo on IOP, systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate in healthy human volunteers. These parameters were monitored for 4.0 h after the administration of drugs. Captopril 12.50 mg and 25.00 mg significantly reduced the IOP and SBP ($P<0.05$). Captopril 6.25 mg also had a tendency to lower the IOP and significantly decreased the SBP ($P<0.05$). The mechanism involved in the decrease of IOP and blood pressure with captopril could be due to inhibition in the formation of angiotensin-II and sparing of bradykinin.

**Key words :** captopril intraocular pressure
angiotensin converting enzyme

## INTRODUCTION

The renin-angiotensin-aldosterone system is predominantly involved in the regulation blood pressure and fluid volume in the body. The initiating event in this cascade is the release of renin which converts angiotensinogen to angiotensin-I, an inactive deca-peptide. In turn, the angiotensin-I is cleaved of its two amino acids by angiotensin converting enzyme (ACE), to form angiotensin-II, a potent vasopressor octa-peptide (1, 2). ACE is also implicated in the degradation of bradykinin, a potent nona-peptide vasodilator autocoid (3).

In ocular tissue, the ACE has been detected in aqueous humour (4–6), choroid and ciliary body (7). The intravenous administration of angiotensin-I increased intraocular pressure (IOP) in rabbits (8). Even the intracameral administration of angiotensin-II decreased aqueous humour

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outflow in monkeys (9) and hence, the IOP could be expected to rise in them. Keeping into view the role of angiotensin in the above studies, the inhibitors of ACE may therefore be anticipated to lower the IOP. This has been further substantiated by the fall of IOP when ACE inhibitors were instilled topically in eyes of the rabbits (10). We therefore, conducted this study, to investigate the effect of captopril, a prototype ACE inhibitor, on IOP in healthy human volunteers.

## METHODS

Forty eight healthy human volunteers of either sex participated in this study after their informed written consents. The subjects having any history of eye surgery, eye disease, systemic diseases, taking any drug systemically or alcohol, and smokers were excluded from the study. The design of the trial was randomized, double masked, parallel groups and placebo controlled.

Drugs : captopril 6.25 mg
captopril 12.50 mg
captopril 25.00 mg
control placebo

The subject reported the Clinical Pharmacology laboratory at 9.00 AM. Their IOP, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured in lying down position for the basal readings. The IOP was measured with Schiotz's tonometer. The SBP and DBP were measured with mercury manometer at Korotokoff sounds first and fifth respectively. The HR was checked manually for one min. Immediately after recording these basal parameters, a single oral dose of the drug was administered with a glass of water, under supervision. The subjects were instructed not to take any other fluid during the course of study. The IOP, SBP, DBP, and HR were again recorded in the same position at 0.5h, 1.0h, 2.0h, 3.0h, and 4.0h after the intake of drug.

The adverse drug reactions volunteered by the subjects were also monitored during the study. The statistical analysis was performed by Wilcoxon rank test and Student's 't' test wherever appropriate. The value of P less than 0.05 was kept as a level of statistical significance.

## RESULTS

The study was performed in 48 subjects (12 in each group). Their age ranged from 20 to 25 years and weight from 50 th 70 kg.

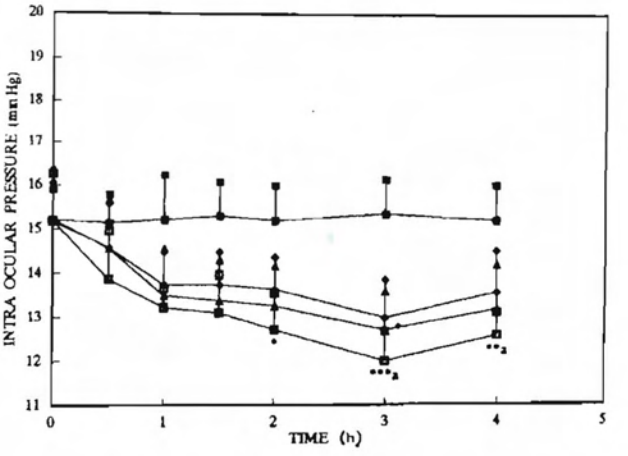


Fig. 1: Effect of captopril (6.25 mg, 12.50 mg and 25.00 mg) and placebo on IOP at different time intervals. Data are $\overline{X}$ + SEM of 12 subjects in each group.

Control; Captopril 6.25 mg; Captopril 12.50 mg; Captopril 25.00 mg.

*P<0.05; **P<0.02; ***P<0.01 vs control at respective time intervals
a = P<0.05 vs basal.

The drugs were administered under supervision and no drop out occurred in this study.

Intraocular pressure: The effect of different drug treatments on the IOP at different time intervals in presented graphically in Fig. 1. There was no difference in the IOP at the baseline level among all the groups. However, a significant fall in IOP was seen with captoril 25.00 mg from 2.0h to 4.0h ($P<0.05$, $P<0.01$, $P<0.02$ respectively) and with captopril 12.50 at 3.0h ($P<0.05$) as compared to the control at corresponding time periods. Captopril 6.25 mg also had a tendency of lowering IOP, though the results did not reach the level of significance. There was no change in IOP in the placebo treated group.

Systolic blood pressure: The effect of different doses of captopril on SBP at different time points is shown in Fig. 2. The administration of captopril (6.25 mg, 12.50 mg, and 25.00 mg) produced a significant drop in SBP ($P<0.05$) as compared to the control at related time intervals and also as regards to their baseline values. Surprisingly, there was a little fall of SBP immediately after the administration of placebo, however it started rising after 1.0 h to reach near its previous level by 2.0h.

Diastolic blood pressure: The effect of captopril (6.25 mg, 12.50 mg, and 25.00 mg) and placebo on DBP is depicted in Fig. 3. Captopril 25.00 mg produced a significant decline in DBP from 1.5 h to 2.0 h as

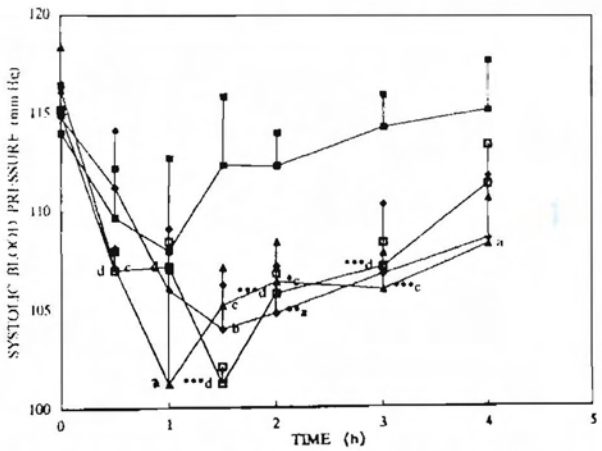


Fig. 2: Effect of captopril (6.25 mg, 12.50 mg and 25.00 mg) and placebo on SBP at different time intervals. Data are $\overline{X}$ + SEM of 12 subjects in each group.

Control; Captopril 6.25 mg; Captopril 12.50 mg; Captopril 25.00 mg.

*P<0.05; **P<0.02; ***P<0.01 vs control at respective time intervals

a = P<0.05; b = P<0.02; c = P<0.01; d = P<0.001; vs respective basals.

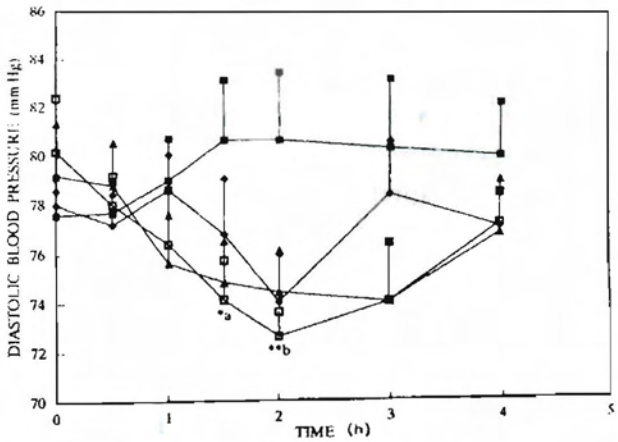


Fig. 3: Effect of captopril (6.25 mg, 12.50 mg and 25.00 mg) and placebo on DBP at different time intervals. Data are $\overline{X}$ + SEM of 12 subjects in each group.

Control; Captopril 6.25 mg; Captopril 12.50 mg; Captopril 25.00 mg.

*P<0.05; **P<0.02; vs control at respective time intervals

a = P<0.05; b = P<0.01; vs respective basals.

compared to control ($P<0.05$, $P<0.02$ respectively) and also as compared to their own basal readings ($P<0.05$, $P<0.02$ respectively). Captopril (6.25 mg and 12.50 mg) also had a tendency of lowering DBP, but the results were not statistically significant.

Heart rate: The effect of different doses of captopril and placebo on HR at different time intervals in represented in Fig. 4. There was no difference in the HR at the basal level and at different time intervals after the administration of different drugs.

Four subjects had headache after the intake of drugs. Three of them belonged to captopril 25.00 mg group and one to captopril 12.50 mg group. No other adverse drug reaction was reported by any volunteer.

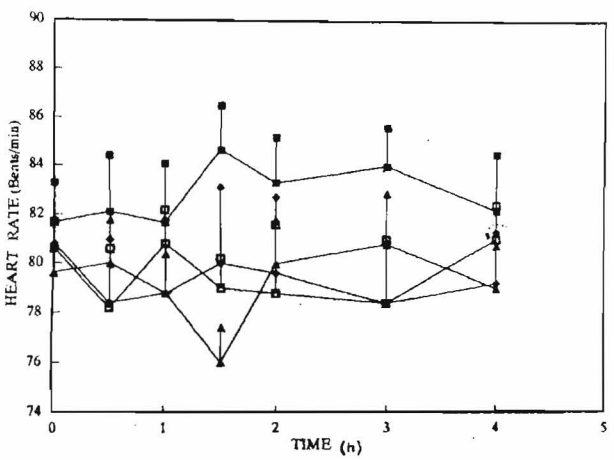


Fig. 4: Effect of captopril (6.25 mg, 12.50 mg and 25.00 mg) and placebo on HR at different time points. Data are $\overline{X}$ + SEM of 12 subjects in each group. Control; Captopril 6.25 mg; Captopril 12.50 mg; Captopril 25.00 mg.

## DISCUSSION

Angiotensin converting enzyme inhibitors block the formation of angiotensin-II and prevent the degradation bradykinin. Captopril is the prototype in this group. ACE inhibitors have been proved to be potent antihypertensive agents (1, 2). However, the effect of angiotensin on IOP is however controversial. Conflicting reports have been documented in the scientific literature. Some researchers reported that angiotensin I and angiotensin II increase the IOP when administered to rabbits and monkeys respectively (8, 9). However, others workers documented that angiotensin II decreased IOP when injected into the vitreous body of rabbits (11) or injected intravenously in cats (12). The contradiction between these opposite findings could be related to the different experimental models used for these studies (8, 9, 11, 12). Inspite of this, on the other hand, the effect of captopril is quite clear and its topical instillation in the rabbits eyes has been known to lower the IOP (10). We also found that the oral captopril caused a fall of IOP in human. The possible mechanism of its causation could be due to the involvement of bradykinin, a vasodilator which remains un-metabolised in the presence of captopril. This could facilitate the drainage of aqueous humor by opening the canal of Shlemn and lower the IOP. However, the second mechanism involving the blocking of agniotensin II formation could still be operating to contribute in decreasing the IOP (8, 9). Furthermore, the captopril also lowered the blood pressure which could also be due to the involvement of angiotensin and bradykinin (1, 2, 13).

In the present study, we adopted a double masked, randomized, placebo control design and this eliminated the bias affecting the study results. We found a fall of IOP in human volunteers and this was a desired effect. Notwithstandingly, in association with the fall of IOP, the blood pressure also dropped which is an undesirable event. This indicates that the oral captopril (though reducing the IOP) would not be of any help in the patient of glaucoma/ocular hypertension as it also possess the blood pressure lowering effect in normotensive subjects. However, the beneficial ocular effect of captorpril on IOP could be potentiated, whereas its harmful effect on blood pressure be nullified by using it topically in the eyes. Our further studies are directed in this direction.

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