A Comparative Clinical Study of Effects of Monotherapy with Oral Captopril and Lisinopril on Intraocular Pressure of Glaucomatous Patients

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ABSTRACT

Background: Angiotensin I-converting enzyme (ACE) activity has been demonstrated in aqueous humor and other ocular tissues. Coincidence of glaucoma with hypertension or heart failure, the main indications of ACE inhibitors is not uncommon particularly in adults.

Aim of Study is to explore the initial response of intraocular pressure (IOP) to short courses of oral captopril and lisinopril in both normal volunteers and glaucomatous patients.

Patients & Methods: This study included 60 subjects with normal blood pressure whom assigned to receive either captopril tablets (12.5 mg twice daily) or lisinopril tablets (10 mg once daily) for 4 successive days. Each group included 15 volunteers (with normal IOP) and 15 glaucomatous patients (with open angle glaucoma). IOP and blood pressure were measured at pre-treatment, and then after 1, 3, and 4 days of treatment.

Results: Captopril-induced decrement in mean IOP of normal volunteers was highly significant with percentages ranged 4.1-6.6 % (right eyes) and 0.4-4.6 % (left eyes). Percentages of decline in mean IOP of glaucomatous patients ranged from 3.7-7.4 % (right eyes) and 1-9.2 % (left eyes) but statistically, such decrements were variable in significances along the days of captopril treatment.

Lisinopril-induced decrement in mean IOP of normal volunteers was found statistically variable in significances with percentages ranged 3.2-8.9 % (*right* eyes) and 1.7-5 % (*left* eyes). Although it was statistically variable in glaucomatous patients' *right* eyes with percentage ranged from 1.4-6.3 %, the decline in mean IOP of their *left* eyes was highly significant throughout the trial period and its percentage ranged 4.7-8.7 %.

***Conclusions*:** Each of oral captopril and lisinopril has an initial ocular hypotensive effect and thus might be preferred in treatment of patients with arterial hypertension who are vulnerable to or with raised IOP.

دراسة سريرية مقارنة لتأثيرات كلا من دواء الكابتوبريل وكذلك دواء الليزينوبريل المعطيان عن طريق الفم بشكل منفرد على ضغط العين للمصابين بداء الزرقاء

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الخلاصة

خلفية البحث: لقد تم الكشف عن فعالية الانزيم المحول للانجيوتنسين -1 في ماء القرنية وأنسجة أخرى في العين. من جانب آخر فليس من غير الشائع وخاصة عند البالغين أن يتزامن داء الزرقاء مع كلا من ارتفاع ضغط الدم أو عجز القلب المرضين اللذين هما من أهم دواعي استخدام الأدوية المثبطة للانزيم المحول للانجيوتنسين -1

هدف الدراسة: هو لأكتشاف الأستجابة الأولية لضغط العين عند استخدام كلا من دواء الكابتوبريل وكذلك دواء الليزينوبريل المعطى عن طريق الفم بشكل منفرد ولفترات قصيرة لكل من المتطوعين الأصحاء وكذلك للمصابين بداء الزرقاء

المرضى وطرق البحث: تضمنت هذه الدراسة 60 شخصا من ذوي ضغط الدم الطبيعي وقد تم توزيعهم الى مجموعتين احداهما يعالج الأشخاص فيها بدواء الكابتوبريل (12.5 ملغم مرتان يوميا) و من هم في المجموعة الأخرى يعالجون بدواء الليزينوبريل (10 ملغم مرة واحدة يوميا) لمدة 4 أيام متتابعة. كل مجموعة تشمل كلا من ذوي ضغط العين الطبيعي (15 متطوع) وكذلك من المصابين بارتفاع ضغط العين (داء الزرقاء ذا الزاوية المفتوحة) (15 مريضا). وقد تم قياس كلا من ضغط العين وضغط الدم قبل الشروع بالعلاج ومن ثم بعد يوم وبعد ثلاثة أيام وبعد أربعة أيام من بدء العلاج

النتائج: لقد كان التناقص المحدث بفعل الكابتوبريل في معدل ضغط العين للأشخاص ذوي ضغط العين الطبيعي هام جدا وبنسبة تراوحت بين 4,1 - 6,6 % (للعيون اليمنى) و 0,4 – 4,6 % (للعيون اليسرى) وأما التناقص في معدل ضغط العين للمصابين بارتفاع ضغط العين فقد تراوح 3,7 – 7,4 % (للعيون اليمنى) 1- 9,2 (للعيون اليسرى) ولكن احصائيا كان هذا التناقص متذبذب الأهمية احصائيا طيلة فترة العلاج بالكابتوبريل. و لقد كان التناقص المحدث بفعل اللزينوبريل في معدل ضغط العين للأشخاص ذوي ضغط العين الطبيعي متذبذب احصائيا وبنسبة تراوحت بين 3,2 - 8,9 % (للعيون اليمنى) و 1,7 – 5 % (للعيون اليسرى) وأما التناقص في معدل ضغط العين للمصابين بارتفاع ضغط العين فقد كان متذبذب الأهمية احصائيا بالنسبة للعيون اليمنى حيث تراوحت بين 1,4- 6,3 % وأما بالنسبة للعيون اليسرى فقد كان التناقص هام جدا احصائيا طيلة فترة العلاج بالليزينوبريل وقد تراوحت النسبة بين 4,7 – 8,7 % .

الأستنتاج: ان كلا من دواء الكابتوبريل وكذلك دواء الليزينوبريل المعطى عن طريق الفم بشكل منفرد ولفترات قصيرة له تأثير ابتدائي مخفض لضغط العين لذا يمكن تفضيل كلا منهما في علاج المرضى المصابين بارتفاع ضغط الدم الذين هم مرشحون للاصابة بارتفاع ضغط العين (داء الزرقاء)

INTRODUCTION

Human intraocular pressure (IOP) is determined by three factors; the rate of aqueous humor production by the ciliary body, the resistance to aqueous outflow across the trabecular meshwork-schlemm's canal system, and the level of episcleral venous pressure [1,2]. The accepted range for normal intraocular pressure is between 10-21 mm Hg [1, 2, 3].

Glaucoma refers to a group of diseases that have certain common features, including intraocular pressure too high for the continued health of the eye, cupping and atrophy of the optic nerve head, and visual field loss. Several agents that cause inhibition of the enzyme cholinesterase, antagonism of beta - adrenoceptors and stimulation of muscarinic receptors are commonly used as ocular hypotensive agents in glaucoma [1, 4, 5].

Angiotensin I-converting enzyme (ACE) activity has been demonstrated in aqueous humor and other ocular tissues by various authors [6,7,8]. Wagner et al [9] demonstrated gene expression of renin, angiotensinogen and ACE in various parts of the human eye.

Captopril and lisinopril are specific competitive inhibitors of ACE; the enzyme which is responsible for the conversion of angiotensin I to a potent endogenous vasoconstrictor substance, angiotensin II. Administration of either captopril or lisinopril results in a reduction of peripheral arterial resistance in hypertensive patients. The duration of effect is a dose related and abrupt withdrawal of either one has not been associated with a rapid increase in blood pressure [10]. ACE inhibitors have also been reported to interfere with autonomic nervous system and produce various effects such as facilitation of vagal bradycardia [11], inhibition of response to sympathetic spinal outflow[12] and inhibition of vasoconstrictor response to noradrenaline[13].

Aim of Study:

The present comparative clinical study aimed to explore the IOP changes that could be induced by short courses of systemically (orally)–administered ACE inhibitors (namely captopril and lisinopril) in both volunteers and glaucomatous patients.

PATIENTS & METHODS

Along the period of about one year, this clinical study included sixty subjects with normal blood pressure among the attendees of the ophthalmologic consultation unit of Al-Kadhimiya Teaching Hospital. Ethics committee approval was obtained and all of the included sixty subjects were agreeing to be involved in this trial study. They were randomly assigned to receive either captopril tablets (in a dose of 12.5 mg twice daily for 4 successive days) or lisinopril tablets (in a dose of 10 mg once daily for 4 successive days). Each group included 30 subjects: 15 of them had normal IOP (volunteers) whereas the other 15 had open angle glaucoma (glaucomatous patients); those were already isolated from their anti-glaucomatous therapy just prior the commencement of this study. Exclusive criteria included: pregnant or lactating women, presence of hypertension, heart failure, or history of previous glaucoma surgery.

IOP was measured by Goldmann applanation tonometry (mean of three consecutive readings) with the patient in a sitting position at the slit lamp. It requires a cobalt blue light source and a small droplet of fluorescein on the ocular surface. A tiny pressure sensor attached to a spring-loaded arm is gently placed against the tear film, and the doctor reads the pressure through the microscope under the blue light[14]. Such measurements were achieved by the same ophthalmologist in the ophthalmologic consultation unit of Al-Kadhimiya Teaching Hospital. Both IOP (of both eyes) and blood pressures (BP) for each included one were measured at 4 occasions: pre-treatment, and then after 1, 3, and 4days of treatment with either captopril or lisinopril.

A special concern was guided to elicit any detectable adverse effect whenever it evolves.

Statistical Analysis:

The obtained data were presented as mean ± S.E.M. (standard error of mean). The results were analyzed statistically using Student paired *t*-test for assessing the effect of employed drug for a given group of patients. While Student (unpaired) *t*-test for independent data was used to test the significance of the difference between any two groups. Differences were accepted as insignificant, significant or highly significant if $p>0.05$, $0.01 < P \leq 0.05$, or $p \leq 0.01$ respectively [15, 16].

RESULTS

I- CAPTOPRIL GROUP:

Tables (1) demonstrated the gender and age analysis of patients received oral captopril. There was highly significant difference between the mean age of normal volunteers (46.53 ± 4.43 years) and that of glaucomatous patients (56.53 ± 3.53 years).

There was no detectable adverse effect that could be observed among the included volunteers and glaucomatous patients received oral captopril for the trial period, i.e., 4 successive days.

1. Response of Mean IOP: (Figure 1-A & Associated Table)

A) Normal Volunteers Subgroup: (n=15)

The decrement in mean IOP of volunteers' *right eyes* was highly significant along the trial period. Its percentage ranged from 4.13 %(day 4) to 6.61 %(day 1).

Mean IOP of *left eyes* also decreased highly significantly after 1 day but then insignificantly after 3 and 4 days of captopril treatment. Decrement ranged from 0.42% (day 4) to 4.64% (day 1).

B) Glaucomatous Patients Subgroup: (n=15)

The observed decline in mean IOP of *right* eyes of glaucomatous patients received oral captopril found to be highly significant, significant, and then not significant after 1,3, 4 days of treatment respectively. Decrement percentage ranged from 3.7 % (day4) to 7.41 % (day 1). The mean IOP of *left* eyes of same glaucomatous patients decreased highly significantly after 1 and 3 days but then insignificantly after 4 days of treatment. Decrement percentage ranged from 1% (day 4) to 9.23 % (day 3).

2. Response of Mean BP: (Figure 1-B & Associated Table)

A) Normal Volunteers Subgroup: (n=15)

The decrement in mean *systolic* BP was highly significant along the trial period. Decrement percentage ranged from 5.98 % (day 1) to 9.24 % (day3).

Mean *diastolic* BP decreased, although not significant, after 1 day but then progressed to be highly significantly at day 3 and 4 of treatment. Decrement percentage ranged from 1.71 % (day 1) to 9.83 % (day3).

B) Glaucomatous Patients Subgroup: (n=15)

The decrement in mean *systolic* BP was not significant, significant, and then highly significant after 1, 3, 4 days of treatment respectively. Decrement ranged from 2.3% (day 1) to 4.59% (day 4).

Mean *diastolic* BP declined highly significantly along the trial period with a decrement percentage ranged from 4.24% (day 1) to 7.2% (day 3).

II- LISINOPRIL GROUP:

Tables (2) showed the gender and age analysis of patients received oral lisinopril. There was significant difference between the mean age of normal volunteers (46. 93 ± 4.77years) and that of glaucomatous patients (56. 33 ± 5.2 years).

Along the trial period (4 days), there was no detectable adverse effect among the included volunteers and glaucomatous patients received oral lisinopril.

1. Response of Mean IOP: (Figure 2-A & Associated Table)

A) Normal Volunteers Subgroup: (n=15)

The decrement in mean IOP of volunteers' *right* eyes was highly significant after 1 and 3 days of treatment and significant by the end of trial period. Decrement percentage ranged from 3.24% (day 4) to 8.91% (day 3).

Mean IOP of *left* eyes decreased significantly after 1 day but then insignificantly after 3 and 4 days of treatment. Decrement percentage ranged from 1.68% (day 4) to 5.04% (day 1).

B) Glaucomatous Patients Subgroup: (n=15)

The observed decline in mean IOP of *right* eyes of glaucomatous patients received oral lisinopril found to be highly significant at days 1 and 3 and then not significant at day 4 of treatment. Decrement ranged from 1.37 % (day4) to 6.32 % (day 3).

The mean IOP of *left* eyes of same glaucomatous patients decreased highly significantly throughout the trial period. Decrement percentage ranged from 4.72 % (day 4) to 8.66 % (day 3).

B) Response of Mean BP: (Figure 2-B & Associated Table)

A) Normal Volunteers Subgroup: (n=15)

The decrement in mean *systolic* BP was highly significant along the trial period. Decrement percentage ranged from 6.99 % (day 1) to 10.48 % (day 4).

Mean *diastolic* BP decreased although not significant after 1 day but then progressed to be highly significantly at day 3 to be insignificant again by day 4 of treatment. Decrement percentage ranged from 3.48 % (days 1 & 4) to 6.09 % (day3).

In the present study, along the trial period both lisinopril and captopril had a comparable effect ($p > 0.05$) on mean IOP and mean BP of normal volunteers.

B) Glaucomatous Patients Subgroup: (n=15)

The decrement in mean *systolic* BP was highly significant along the trial period. Decrement percentage ranged from 4.07 % (day 1) to 7.38 % (day 3).

Mean *diastolic* BP declined highly significantly along the trial period. Decrement percentage ranged from 4.15 % (day 1) to 7.47 % (day 3).

In the present study, lisinopril effect on glaucomatous patients' mean IOP and mean BP was found to be comparable ($p > 0.05$) to that of captopril on them along the trial period.

DISCUSSION

Coincidence of glaucoma with hypertension and /or heart failure (the main indications of ACE inhibitors) in same patients is not unusual event; furthermore, in addition to controlling IOP, keeping blood pressures in a normotensive range can a be a secondary tool in managing progressive glaucoma[17]. Thus, this clinical study represented an attempt to elucidate the possible ACE inhibitors - (captopril or lisinopril) – glaucoma (open angle type) interplay.

The 60 included patients in this study were exclusively adults around middle age; furthermore, there was no predominance of a specific gender in the two treatment groups and their subgroups. This pointed out the homogenous nature of the studied groups.

Along the trial period, oral captopril and lisinopril therapy could decrease mean IOP of normal volunteers and glaucomatous patients in comparable rates; yet, such observed reduction was apparently, but not statistically, better in glaucomatous patients than in normal volunteers. The early (since the 1st day of therapy) detectable decrement in mean IOP of normal volunteers in each treatment group emphasizes the prompt response of IOP to systemically administered ACE inhibitors. Despite the rate of reduction did not continue at same manner, mean IOP sustained at values below than its pretreatment measurement by the end of trial period.

In a similar pattern, oral captopril and lisinopril therapy could decrease mean BP (systolic and diastolic) of both normal volunteers and glaucomatous patients in comparable rates.

Results of the present study seemed to be in accordance with Numan NA. and Numan AT (2001) who pointed to the ocular hypotensive effect of lisinopril when applied locally (as eye drops) [18].

Thus, and in absence of noticeable adverse effects, oral ACE inhibitors could be considered to be safe in ocular normotensive patients. Besides, these drugs might also be useful in low pressure glaucoma.

As a postulation for mechanism(s) of oral ACE inhibitors IOP lowering effects, it could be suggested that:

- ACE inhibitors cause reduction in the production of aqueous humor possibly by reducing the blood flow to ciliary body [19].
- ACE inhibitors cause Inhibition of ocular ACE (Kininase II) activity so could prevent breakdown of bradykinin that promote synthesis of prostaglandins [20], which in turn, can lower the IOP by increasing the uveoscleral outflow without affecting the conventional trabecular meshwork outflow [21 - 23]. This suggests that ACE inhibitors can lower IOP even when it is not elevated [5].
- ACE inhibitors have been reported to affect the autonomic nervous system at various levels; cholinesterase inhibition may be involved [5].

CONCLUSIONS

1. ACE inhibitors (namely captopril and lisinopril) have an initial ocular hypotensive effect when given orally.
2. Oral ACE inhibitors might be preferred as treatment for systemic hypertension in patients vulnerable to or with raised IOP.

RECOMMENDATIONS

Further comparative clinical trials with higher doses of oral ACE inhibitors are warranted to explore the maximum efficacy of their ocular hypotensive effect particularly in glaucomatous patients.

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REFERENCES

1- Kathryn A Hecht. Basic and clinical science course. American Academy of Ophthalmology. Section 10, 1994-1995.

2- Kanski Jack J. Clinical Ophthalmology.4th edition, 1999. pp: 186.

3- Forrester John V, Andrew D Dick, et al. The Eye Basic Sciences in Practice.2nd edition. 2002.

4- Richard P Terra, Adam Husney, Jill Ann Smith (2002). http:// health info.nmh.org/Library/ Health Guide /Illness Conditions/topic.asp? hwid=credhw158191.

5- Shah G, Sharma S, Mehta A, Goyal R. Ocular Hypotensive Effect of Ramiprilate in Chronic and Acute Models of Glaucoma in Rabbits. Indian Journal of Pharmacology 1999; 31: 110-115.

6- Immonen I, Friberg K, Sorsila R, Fyhrquist F. Concentration of angiotensin converting enzyme in tears of patients with sarcoidosis. Arch Ophthalmol 1987; 65:27-9.

7- Ikemoto F, Yamamoto K. Renin angiotensin system in aqueous humor of rabbits, dogs and monkeys. Exp Eye Res 1989; 27:723-5.

8- Abrams KL, Brooks DE, Larata LJ et al. Angiotensin converting enzyme system in the normal canine eye: Pharmacological and physiological aspect. J Ocul Pharmacol 1991; 7:41-51.

9- Wagner J, JanDanser AH, Derkx FHM et al. Demonstration of renin mRNA, angiotensinogen mRNA and angiotensin converting enzyme mRNA expression in the human eye: evidence for an intraocular renin angiotensin system. Br J Ophthalmol 1996; 80:159-63.

10- PDR® Electronic Library, 2001 Medical Economics Company, Inc., Montvale NJ.

11- Rechtmann M, Majewski H. A facilitatory effect of antiangiotensin drugs on vagal bradycardia in the pithed rat and guineapig. Br J Pharmacol 1993; 110:289-96.

12- Antonaccio MJ, Kerwin L. Evidence of prejunctional inhibition of norepinephrine release by captopril in spontaneously hypertensive rats. Eur J Pharmacol 1980; 68:209-12.

13- Okuno T, Konishi K, T Saruta, Kato E. SQ-14,225 attenuates the vascular responses to norepinephrine in rat mesentric arteries. Life Sci 1979; 25:1343-50.

14- Medicine Net.com.Tonometry Symptoms, Causes, Treatment - How is tonometry done (Web site accessed on June, 15 , 2010)

15- Hill A B. A short Textbook of Medical Statistics. Hodder & Stoughton, London. (1977).

16- Daneil WW. Biostatistics: A Foundation for analysis in the Health Sciences. 3rd edition. John Wiley & Sons, New York. 1983.

17- Varma R. Blood Pressure's Impact on Glaucoma: Evidence describes a role for hemodynamics, not just ocular but systemic too. Ophthalmology Treatment;2010,April. (Web site accessed on June, 15, 2010)

18- Numan NA. and Numan AT. Effects of Lisinopril as an Angiotensin Converting Enzyme Inhibitor and Losartan as an Angiotensin Receptor Blocker on Intraocular Pressure. A dissertation presented for the degree of F.I.C.M.S. Ophthalmology to the Iraqi Council for Medical Specialists. 2001.

19- Constad WH, Fiore P, Samson C, Cinnoti AA. Use of angiotensin converting enzyme (ACE) levels in sarcoidosis. Am J Med 1975; 39:365-72

20- Lotti VJ, Pawlowski N. Prostaglandins mediate the ocular hypotensive action of the angiotensin converting enzyme inhibitor MK-422 (enalaprilat) in African green monkeys, J Ocul Pharmacol 1990; 6:1-7.

21- Gabelt BT, Kaufmann PL. Prostaglandins $F_{2\text{-alpha}}$ increases uveoscleral outflow in the cynomologus monkeys. Exp Eye Res 1989; 49:389-402.

22- Nilsson SFE, Samuelson M, Bill A, Stjernschantz J. Increased uveoscleral outflow as a possible mechanism of ocular hypotension caused by prostaglandin $F_{2\alpha}$ -1-isopropylester in the cynomologus monkeys. Exp Eye Res. 1989; 49:707-16.

23- Nilsson SFE, Stjernschantz J, Bill A. $PGF_{2\text{-alpha}}$ increase uveo-scleral outflow. Invest Ophthalmol Vis Sci 1987; 28(suppl):284.

TABLE (1): Gender and Age Distribution of Normal Volunteers and Glaucomatous Patients Received Oral Captopril

Subgroup	No.	Sex (M:F)	Age (Years)	
			Mean ± S.E.M.*	Range
1) Normal Volunteers	15	(7:8)	46.53 ± 4.43	35 – 60
2) Glaucomatous Patients	15	(7:8)	56.53 ± 3.53 HS	43 – 68
TOTAL	30	(14:16)	51.58 ± 1.82	35 - 68

**** S.E.M.= Standard error of mean, S = High significant difference (p≤0.01) compared to that of the other group***

TABLE (2): Gender and Age Distribution of Normal Volunteers and Glaucomatous Patients Received Oral Lisinopril

Subgroup	No.	Sex (M:F)	Age (Years)	
			Mean ± S.E.M.*	Range
1) Normal Volunteers	15	(8:7)	46.93 ± 4.77	33 – 65
2) Glaucomatous Patients	15	(8:7)	56.33 ± 5.2 S	39 – 69
TOTAL	30	(16:14)	51.63 ± 1.97	33 - 69

**** S.E.M.= Standard error of mean, S = significant difference (0.01<p≤0.05) compared to that of the other group***