Serum uric acid level and renal function tests in hypertensive patients treated by captopril

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ABSTRACT

Objective: To evaluate the effect of captopril on the serum uric acid level and renal function tests in hypertensive patients, in relation to the age and gender patients , and dose and duration of captopril use.

Patients & methods: This is a case control study conducted in the Consultatory Clinic for Internal Medicine in Ibn-Siena Teaching Hospital in Mosul/Iraq, from the 15th of October 2009 to the 15th of June 2010. A total number of 100 patients (56 males and 44 females) with mild to moderate primary hypertension, non diabetic, neither having renal diseases nor other chronic illnesses, were taken and divided into two groups: First group included 50 patients using captopril (captopril group) for more than three months , The second group included 50 newly diagnosed untreated hypertensive patients (control group). Serum uric acid, serum urea, creatinine, sodium and potassium concentration were measured using special kits and creatinine clearance (Crcl) were calculated by Cockroft and Gault equation and all were compared in the two groups.

Results: Serum uric acid decreased significantly in captopril group while the renal function tests did not show any significant difference in comparison with the control group. There was a significant reduction of creatinine clearance in the captopril group in the older patients using captopril than younger patients. There were no significant effect of the dose and the duration of captopril use on serum uric acid and renal function tests , except that increasing the dose of captopril lead to a significant increase in serum potassium. Also, there was a significant increase in serum uric acid, urea , and creatinine and a significant reduction of crcl in males patients than in females patients in both groups.

Conclusion: Captopril is a safe drug for the treatment of patients with essential hypertension regarding renal function tests beside that captopril therapy causes a significant reduction of serum uric acid, but no significant effects for the dose and duration of use of captopril on serum uric acid and renal function tests except that increasing the dose of captopril lead to a significant increase in serum potassium. There were a significant reduction of mean Crcl in the captopril group with increasing of the age. Male hypertensive patients were more prone for renal impairment than female hypertensive patients.

Key words: captopril, uric acid, urea, creatinine

الخلاصة

الهدف : لتقييم تأثير الكابتوبريل على مستوى الحامض البولي في مصل الدم واختبارات وظيفة الكلى لدى مرضى فرط ضغط الدم وعلاقته بعمر وجنس المريض وجرعة ومدة استخدام الكابتوبريل.

الطرق المتبعة والمرضى: هذه تصميم دراسة حالة أجريت في العيادة الاستشارية للطب الباطني في مستشفى أبن سينا التعليمي في الموصل / العراق، للفترة من 2009/10/15 إلى 2010/6/15 م0 تم اخذ 100مريضا من كلا الجنسين (56ذكر و 44 أنثى) المصابين بفرط ضغط الدم الأساسي من الدرجة الخفيفة إلى المتوسطة والذين لا يعانون من داء البول السكري ، ولا من أمراض الكلية المزمنة أو أية أمراض مزمنة أخرى، وقد تم تقسيمهم إلى مجموعتين :

المجموعة الأولى تضمنت ٥٠ مريضا ممن كانوا يتناولون الكابتوبريل لأكثر من ثلاثة أشهر لمعالجة فرط ضغط الدم (مجموعة الكابتوبريل) . المجموعة الثانية تضمنت 50 مريضا مشخصين بإصابتهم حديثا بفرط ضغط الدم وغير معالجين بعد وقد اعتبرت كمجموعة سيطرة في هذه الدراسة 0 تركيز الحامض البولي، اليوريا، الكرياتنين و الصوديوم والبوتاسيوم في مصل الدم تم قياسها بعدد يدوية خاصة وتصفية الكرياتنين تم حسابها بمعادلة كوكروفت كولت وقورنوا بالمجموعتين.

النتائج: وجود انخفاض معنوي في تركيز الحامض البولي في مصل الدم لدى المجموعة التي تتناول الكابتوبريل عند مقارنتها بمجموعة السيطرة ، و لم تظهر فحوصات وظيفة الكلى أي فرق معنوي لدى المجموعة التي تتناول الكابتوبريل عند مقارنته بمجموعة الضبط . أظهرت النتائج كذلك انخفاضا معنويا في تصفية الكرياتينين لدى المجموعة الأكبر عمرا التي تتناول الكابتوبريل من المجموعة الأصغر عمرا. لم يكن هناك أي تأثير معنوي للجرعة المستخدمة ولفترة العلاج للكابتوبريل على تركيز الحامض البولي في مصل الدم و اختبارات وظيفة الكلى ، باستثناء انه مع زيادة جرعة الكابتوبريل كانت هنالك زيادة معنوية في مستوى البوتاسيوم في مصل الدم. كذلك كان هنالك زيادة معنوية في مستويات كل من الحامض البولي ،اليوريا، الكرياتنين في مصل الدم ونقص معنوي في معدل تصفية الكرياتنين لدى المرضى الذكور مقارنة بالمرضى الإناث في كلا المجموعتين.

الاستنتاج : ان الكابتوبريل دواء أمين في علاج فرط ضغط الدم الأساسي (الأولي) فيما يتعلق باختبارات وظيفة الكلى بالإضافة إلى ان العلاج بالكابتوبريل يسبب انخفاضا معنويا في مستوى الحامض البولي في مصل الدم. ولكن ليس هناك تأثير معنوي للجرعة المستخدمة ولفترة استخدام الكابتوبريل على تركيز الحامض البولي في مصل الدم و اختبارات وظيفة الكلى ما عدا انه زيادة جرعة الكابتوبريل تؤدي إلى زيادة معنوية في مستوى البوتاسيوم في مصل الدم كذلك يوجد انخفاضا معنويا في تصفية الكرياتينين لدى المجموعة التي تتناول الكابتوبريل مع زيادة العمر .وكما ظهر أن مرضى فرط ضغط الدم الذكور هم اكثر عرضة لإضعاف وظيفة الكلى من مرضى فرط الدم النساء.

مفتاح الكلمات: كابتوبريل، الحامض البولي ،اليوريا، الكرياتنين

Hypertension is regarded as an important public health challenge, because of the associated morbidity and mortality and the cost to the society[1]. The prevalence of renal impairment increase progressively with increasing levels of BP[2]. Clinically, there is often a vicious circle: Hypertension causes renal damage, which causes more hypertension[3]. The control of hypertension undoubtedly can slow, if not stop, the progression of renal impairment[4]. Therefore, the identification and control of hypertension is the most practical way to slow the progression of renal disease[5].

Hyperuricemia is commonly associated with hypertension and it is present in 25% of untreated hypertensive subjects, and in 50% of subjects taking diuretics and in 75% of subjects with malignant hypertension[6].

The increase in serum uric acid in hypertension may be due to decrease in renal blood flow since a low renal blood flow will stimulate urate reabsorption. Hypertension also results in micro vascular disease and this can lead to local tissue ischemia. In addition the release of lactate that blocks urate secretion in the proximal tubule ischemia results in increased uric acid synthesis[7]. Uric acid is independently and specifically associated with cardiovascular and renal events in hypertensive patients, by playing a role in pathogenesis of hypertension and chronic renal diseases [8].

Clinical data on the effects of angiotensin converting enzyme inhibitors (ACEIs) on serum uric acid level and renal function tests are controversial. The primary objective of this study was to evaluate the effect of captopril monotherapy on the serum uric acid level and renal function tests (serum urea, serum creatinine, creatinine clearance, and serum electrolytes) in hypertensive patients, in relation to the age and gender of patients and the dose and duration of captopril use and to compare with the control. Blood pressure was measured as secondary outcome.

Subjects and Methods

This study included patients with mild to moderate primary hypertension, non diabetic , neither having renal diseases nor other chronic illnesses. Patients with secondary hypertension, severe hypertension, myocardial infarction and heart failure or chronic use of other drugs were excluded from the study.

a total number of 100 patients (56 males and 44 females) were taken and divided into two groups: First group included 50 patients using captopril for more than three months, with age ranged from 37 to 61 years (captopril group). The second group included 50 newly diagnosed untreated hypertensive patients, with age ranged from 36-58 years and matched with the first group by age , sex , and BMI (weight in (kg) by square of height in (meter)) and considered as control group.

$$Crcl = \frac{[140 - Age\ (year)] \times weight\ (kg) \times 1.23\ (male)\ or\ 0.85\ (female)}{Serum\ creatinine\ (\mu mol/l)}$$

Serum sodium and potassium were measured by using FP 20-photometer, reagents supplied by SEAC-Italy.

Standard statistical methods were used to determine the mean and standard deviation (SD). Unpaired student t-test was used to compare the results for measured biochemical parameters between captopril group and the control. ANOVA Test (Analysis of Variance) was used to identify the variation in the different variables in relation to the duration of captopril use .

The sera obtained from the blood samples of all participants in this study were used to measure: Serum uric acid and urea concentration by enzymatic method using kits supplied by Bio Labo, France. Serum creatinine concentration by using a kit supplied by SYRBIO company (Syria) while Creatinine clearance (Crcl) which was estimated by using Cockroft and Gault equation [9].

P-value of ≤ 0.05 was considered to be statistically significant.

The approval of the study protocol by an ethic committee has been obtained from the local health committee of Ministry of Health and College of Medicine, University of Mosul, Iraq.

Results

A total number of 100 hypertensive patients (56 males) and (44 females) were included in this study, 50 of them were used captopril for more than three months and the remaining 50 were newly diagnosed untreated hypertensive patients, were taken as a control group (table 1).

Table 1: General characteristics of the captopril group and the control group.

Character	Captopril group (N=50)	Control group (N=50)	P-Value
Age (years)	46.9 ± 3.9	42.6 ± 4.6	(NS)
Sex:			
Males No.	27	29	(NS)
Females No.	23	21	(NS)
BMI (kg/m^2)	30.49 ± 1.82	31.28 ± 1.92	(NS)

Tables 2 demonstrates that captopril caused a significant reduction in SBP and DBP in comparison to the control group.

Table 2: Comparison between mean of SBP and DBP of captopril group and control group

Parameters	Mean ± SD		P-Value
	Captopril group (n= 50)	Control group (n= 50)	
SBP (mmHg)	140.21 ± 7.33	150.1 ± 8.56	0.041
DBP (mmHg)	82.56 ± 4.79	90.28 ± 5.62	0.036

Table 3: Comparison of serum uric acid and renal function tests between captopril group and control group

Serum concentration of Parameters	Mean ± SD		P-value
	Captopril group (n=50)	Control group (n=50)	
Uric acid (µmol/l)	306 ± 31.37	324 ± 30.45	0.038
Urea (mmol/l)	5.21 ± 0.65	5.62 ± 0.88	(NS)
Creatinine (µmol/l)	85 ± 7.19	82 ± 15.94	(NS)
Crcl (ml/min)	91.34 ± 16.53	89.03 ± 17.94	(NS)
Sodium (mmol/l)	140.76 ± 2.13	140.08 ± 2.06	(NS)
Potassium (mmol/l)	4.3 ± 0.34	4.19 ± 0.41	(NS)

Tables 3 shows that captopril caused a significant reduction of the serum uric acid concentration in the captopril group as compared with the control group but a non significant differences for the renal function tests.

Table 4 demonstrates that there was a significant reduction of mean Crcl in the older patients using captopril than younger patients; while there were no significant differences in mean serum uric acid and other renal function tests in relation to the age of captopril using patients.

Table 4 : Distribution of serum uric acid concentration and renal function tests according to age of the patients in captopril group

Age (year) / Parameters	Mean ± SD			P-value
	30-39 (n=17)	40-49 (n=18)	≥ 50 (n=15)	
Uric acid (µmol/l)	309 ± 30.23	307 ± 31.82	308 ± 31.1	(NS)
Urea (mmol/l)	5.8 ± 0.72	5.44 ± 0.6	5.91 ± 0.76	(NS)
Creatinine (µmol/l)	80 ± 17.1	81.32 ±18.4	80.42 ± 19.3	(NS)
Crcl (ml/min)	90.3 ±18.1	82.6 ± 16.1	80.1 ± 15.41	0.03
Sodium (mmol/l)	139 ±1.9	140.53 ± 2.21	140.92 ± 2.33	(NS)
Potassium (mmol/l)	4.2 ± 0.44	4.3 ± 0.36	4.45 ± 0.49	(NS)

Table 5 shows a non significant differences in the mean serum uric acid and renal function tests except that mean serum potassium level was significantly increased with increasing of the dose of captopril .

Table 5: Distribution of captopril dose on serum uric acid and renal function tests in captopril group.

Dose / Parameters	Mean ± SD			P-value
	25-50 mg/day (n=15)	75-100 mg/day (n=21)	150 mg/day (n=14)	
Uric acid (µmol/l)	306 ± 31.90	308 ± 32.0	307 ± 29.65	(NS)
Urea (mmol/L)	5.21 ± 0.62	5.32 ± 0.66	5.20 ± 0.73	(NS)
Creatinine (µmol/l)	84 ± 17.24	85 ± 17.19	86 ± 16.92	(NS)
Crcl (ml/min)	90.38 ± 16.2	90.99 ± 16.9	91.79 ± 16.8	(NS)
Sodium (mmol/l)	139.84±2.17	141.51 ± 1.8	140.61 ±2.91	(NS)
Potassium (mmol/l)	4.23 ± 0.41	4.53 ± 0.52	4.79 ± 0.32	0.043

Table 6 : Distribution of serum uric acid concentration and renal function tests according to duration of therapy in captopril group

Duration(years) / Parameters	Mean ± SD			P-value
	1 (n=12)	1-3 (n=19)	> 3 (n=18)	
Uric acid (µmol/l)	307 ± 33.8	306 ± 31.65	304 ± 32.4	(NS)
Urea (mmol/l)	5.4 ± 0.8	5.7 ± 0.83	5.32 ± 0.51	(NS)
Creatinine (µmol/l)	83 ± 16.52	86 ± 17.34	83.91 ± 17.22	(NS)
Crcl (ml/min)	88.2 ±15.7	90.86 ± 17.2	93.51 ± 16.82	(NS)
Sodium (mmol/l)	140.32 ±1.9	139.8 ± 2.94	139.51 ± 2.6	(NS)
Potassium (mmol/l)	4.15 ± 0.64	4.4 ± 0.65	4.19 ± 0.24	(NS)

Table 6 shows that there was no significant effect of duration of captopril therapy on serum uric acid and renal function tests in captopril group.

Tables 7 demonstrates that there were a significant increases of mean serum uric acid , serum urea, serum creatinine and significant reduction in the mean of Crcl in the males patients than females in captopril group; while there were no significant differences in mean serum sodium and potassium in relation to the gender of the patients.

Table 7: Effect of gender on the studied parameters in the captopril group

Gender / Parameters	Mean ± SD		
	males (n=27)	females (n=23)	P-value
Uric acid (µmol/ l)	334 ± 30.3	306±30.8	0.042
Urea (mmol/ l)	5.8 ± 0.84	5.2 ± 0.91	0.04
Creatinine (µmol/ l)	91.3 ± 15.7	77 ± 15.9	0.032
Crcl (ml/min)	81.8 ± 17.9	98.41 ± 16.3	0.042
Sodium (mmol/ l)	140.55 ± 1.77	138.9 ± 2.2	(NS)
Potassium(mmol/ l)	4.25 ± 0.49	4.42 ± 0.38	(NS)

Discussion

This study found that the use of captopril has resulted in a significant reduction of the mean SBP and DBP as compared with the control group, these results are in agreement with other studies [10,11], who reported that captopril significantly decreased BP by blockade of the renin angiotensin aldosterone system (RAAS) by its selective lowering of angiotensin II blood level and may be, through dilating the efferent glomerular arterioles, restore the ability of the kidney to excrete salt and water as well as control glomerular hyperfiltration.

This study found that the use of captopril caused a significant reduction in serum uric acid in compared with the control. This result is in agreement with other studies on hypertensive patients[12] and diabetic hypertensive patients[13]. The ACEIs captopril, enalapril, ramipril, and lisinopril are able to decrease serum uric acid level by reducing its reabsorption in the proximal tubule when given to patients with uncomplicated essential hypertension[12,14]. Other studies [15,16] found that captopril had no effect on serum uric acid and concluded that this result may be due to that the dose was not sufficient enough to cause a decrease in serum uric acid level.

The present study found that captopril caused no significant changes in the renal function tests (serum urea, serum creatinine, creatinine clearance). This result is in agreement with the result of other studies done by[17,18] who found that there was normal level of serum creatinine in patients treated by captopril in comparison to control group and they concluded that captopril is a safe drug for the treatment of patients with essential hypertension. Furthermore, this result is in agreement with the result of the study done by Cheng et al.,[19] who studied the effect of captopril in 18 hypertensive patients with diabetic nephropathy for 6 months and they found that there were no changes in Crcl but there was a greater tendency to increase serum creatinine in patients with higher pretreatment value so the use of captopril in patients with renal impairment must be balanced against the risk of aggravating the deterioration of renal functions. However other studies[20,21] found that captopril therapy didn't cause any significant change in Crcl and preserves renal functions in hypertensive patients with type II diabetes mellitus by inhibition of ACE which leads to vasodilatation and increase renal blood flow. Captopril by it's effect on renal haemodynamic may lead to decrease the effect of hypertension on the kidney and slow the progression of renal impairment and they concluded that captopril could be used safely and effectively in the management of hypertensive patients with diabetes mellitus.

The present study found that captopril has no effect on serum level of sodium and potassium which are in agreement with the results of the other studies on hypertensive patients[22,23] and in hypertensive patients with heart failure[24]. The results of this was in disagreement with the results of Kutyrina et al.,[25] who reported an increase in serum potassium level after one month of the use of captopril in 13 patients with essential hypertension. They concluded with the study of Williams and Williams[26] that the reduction in aldosterone secretion caused by captopril promotes sodium excretion and potassium retention. Cleland[27], suggested that hyperkalemia is more common with long acting than short acting ACEIs, this probably reflects the differences in the duration of angiotensin II suppression and he suggested that all patients on ACEIs should have measured their serum potassium especially in those on potassium sparing diuretics or with renal impairment[28].

This study found a significant was a significant reduction of mean Crcl in the older patients than younger patients using captopril, this may be due to the decrease of renal blood flow with an advancing age,

because the GFR decrease is about one ml per year with an advancing age[29,30] or due to the decrease renal blood flow because of chronic elevation of BP which may harm glomerular hemodynamic and renal microcirculation[31].

This study reported a significant increase in mean serum potassium level with an increasing of the dose of captopril , this may be due to that increasing the dose of captopril may lead to more inhibition of the RAAS and increasing the probability of hyperkalemia[32], this result is in agreement with the result of other studies[10,33] who studied the effect of captopril dose on renal functions in doses ranged between 25-100 mg and showed that there were no significant changes in serum urea level and Crcl but with mild increase in serum potassium level.

This study found that there was no significant effect of duration of captopril use on the serum uric acid and renal function tests, this result is in agreement with a study of Estrada *et al.,*[15] who studied the effect of duration of captopril use on serum uric acid and renal functions for a period of 6 to 20 months and they found that there were no significant changes in serum uric acid , serum creatinine, Crcl , and serum potassium and they concluded that captopril effects are mostly a dose independent.

Conclusion: Captopril is a safe drug for the treatment of patients with essential hypertension regarding renal function tests beside that captopril therapy causes a significant reduction of serum uric acid, but no significant effects for the dose and duration of use of captopril on serum uric acid and renal function tests except that increasing the dose of captopril lead to a significant increase in serum potassium. There were a significant reduction of mean Crcl in the captopril group with increasing of the age. Male hypertensive patients were more prone for renal impairment than female hypertensive patients.

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