The effect of Captopril on Renal Function Test

Running Title: *Captopril and renal function.*

Shatha A. Hassan
Junayaa. Sursem
Nahla O. M. Tawfik
College of Dentistry. University of Mosul

Abstract

Objectives: This study was conducted to evaluate the effect of different doses of captopril on renal function test in patient receiving the drug for various periods of time.

Subjects and Methods: Fifty three patients taking captopril therapy (12.5 – 150 mg/day) for management of hypertension or congestive heart failure were included in this study from mosul city. Forty eight apparently healthy subjects of matched age and sex were taken as a control group. They were investigated for blood urea and creatinine concentration and creatinine clearance test was evaluated.

Results: The study revealed that captopril had significant effect ($P<0.05$) in elevation of blood urea and creatinine concentrations with long term of treatment. There were significantly negative correlation ($P<0.05$) between duration of treatment and creatinine clearance levels. In addition, there were significant effect of short and long term treatment ($P < 0.05$) on blood urea concentration when compared with control group.

Conclusions: Captopril had significant effect on renal function tests and that close monitoring of those patients is needed when the drug is given for long time.

Key Words: Captopril, renal function test.

Introduction

The kidney plays a key role in the control of hemodynamic in essential hypertension and heart failure., drugs that increase renal blood flow have beneficial effects in those patients.[1] One of the pharmacological approaches to increase renal blood flow is to inhibit the production of angiotensin II. [2] Angiotensin-converting enzyme (ACE) inhibitors have well-known preferential renal vasodilator effects.[3] Captopril was the first drug to be introduced in the class of ACE-inhibitors. Since 1979 it has been increasingly used for the

treatment of hypertension and congestive heart failure[1,2] , and more recently also for the treatment of proteinuria in diabetic patients., ACE inhibitors and angiotensin receptor blockers are first-line hypertensive agents for patients with type 1 or 2 diabetes mellitus and proteinuria or early chronic kidney disease[4,5,6,7]because these agents reduce blood pressure and proteinuria, slow the progression of kidney disease, and provide long-term cardiovascular protection. In addition captopril is used also for post myocardial infarction therapy, and other forms of nephropathy.[4,5]

ACE inhibitors inhibit the formation of angiotensin II, which is a powerful vasoconstrictor, they also indirectly reduce aldosterone secretion and so suppress the reabsorption of sodium and excretion of potassium in the distal tubule.[1,8] Numerous clinical trials have demonstrated that inhibitors of the renin-angiotensin system, i.e. ACE inhibitors and angiotensin receptor blockers, reduce the progression of chronic kidney disease. [3,5] This paradox can be explained by local activation of the renin- angiotensine system.[1] Dissociation between intrarenal and plasma angiotensin II has been shown in a variety of animal models.[3] Recent studies demonstrated that renal tubular cells are endowed with all the components of renin-angiotensin system.[8,9] All these experimental data suggest that the local renal tissue renin-angiotensin system contributes to progressive renal injury.

This study aimed to assess renal function (blood urea, serum creatinine and estimated creatinine clearance levels) in patients treated with different doses of captopril for different duration of time.

Subjects and methods

Fifty three patients (22female and 31 male) aged between 30-71 years, mean age (52.52 $\pm$ 9.26 yr) were collected randomly from out patient clinic of ibn sena hospital from Mosul City. They were taking captopril for management of their disease conditions (uncomplicated hypertension or chronic heart failure). The dose range from 12.5 – 150 mg/day for different duration of treatment. The control group contain forty- eight healthy subjects(29female and 19 male), with a mean age 58.76$\pm$10.86 (range 40–70 years). None of them have a history of heart disease, diabetes or any other metabolic or endocrine disorders. None of the female subject were pregnant or lactating.

5 ml of venous samples were drawn from each subject and separated into serum. They were used for estimation of blood urea and creatinine concentrations .

Blood urea concentration was estimated by Berthelot enzymatic colorimeteric method, using linear chemicals kit (Spain). [10]The principle of this test is that urea in the sample is hydrolyzed enzymatically into a mmonia and carbon dioxide. Ammonia reacts with salicylate and hypochlorite, in the

presence of the nitroprusside, to form a green indophenol. The color intensity was measured at 580 nm, which was proportional to the concentration of urea in the sample.

Serum creatinine concentration was determined by Jaffe's method, using Bicone fluitest creatinine kit (Germany).[10] Creatinine in alkaline solution reacts with picric acid to form colored complex (creatinine picrate) which was measured at 520 nm.

Creatinine clearance was calculated using the Cockcroft – Gault formula.[11]

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{Age}) \times (\text{weight kg})}{72 \times \text{serum creatinine in mg/dl}}$$

For women the result should be multiply by 0.85(because of reduced muscle mass). [12]

Statistical analysis

Data were expressed as the mean ± standard deviation (mean ± SD) throughout the paper. The data were analyzed by SPSS software. Independent *Student's* t – test was used for evaluating the difference between studied and control group using an independent *Student's* t – test, analysis of variance (ANOVA) and Duncan test. The relationship between duration of therapy and the studied parameters were assessed using Pearson correlation coefficient.[13] Differences were considered significant at $p< 0.05$.

Results

The effect of captopril up to 150 mg/ day on renal function was investigated. Figure 1 represents the frequency distribution of different doses of captopril among treated groups.

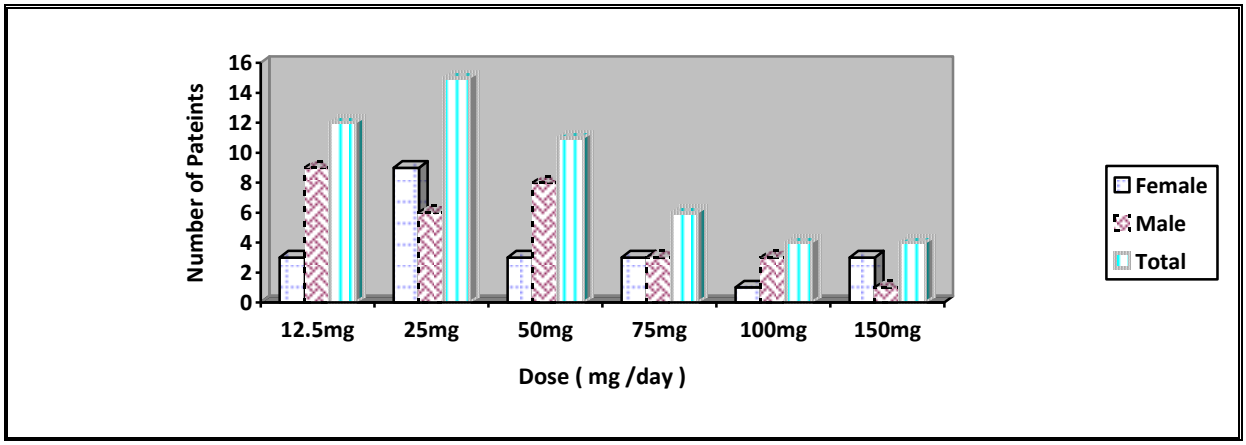

Figure 1. *Frequency distribution of patients among different doses of captopril.*

Table 1 represents the general characteristics (age, weight) and studied parameters for both groups. There were no significant difference (P>0.05), but there were significant differences in age between males (p< 0.05). Significant difference was noticed also between captopril treated group and control group in the serum levels of blood urea in female groups only (p< 0.05), while no significant difference was noticed for both sexes between the treated and control groups for serum creatinine and estimated creatinine clearance levels as shown in table 1.

Table 1. ***Comparison of studied parameters between capotopril users and control group.***

Groups / parameters	Mean ± SD					
	Female		P	Male		P
	Control group (n=29)	Treated group (n=22)		Control group (n=19)	Treated group (n=31)	
Age (year)	53.79 ± 8.92	57.05 ± 11.0	>0.05	50.58 ± 9.68	59.97 ± 10.78*	<0.05
Weight (Kg)	72.62 ± 6.99	76.59 ± 13.98	>0.05	83.57 ± 6.14	79.58 ± 13.97	>0.05
Urea (mmol/L)	4.99 ± 0.87	6.28 ± 2.85*	<0.05	6.04 ± 0.69	6.97 ± 2.24	>0.05
Creatinine (µmol/L)	87.97 ± 13.87	94.03 ± 28.81	>0.05	99.05 ± 16.75	110.36 ± 29.48	>0.05
Cr Cl (ml/min)	89.01 ± 16.44	77.98 ± 30.88	>0.05	74.91 ± 13.07	77.11 ± 30.36	>0.05

***significant difference at P< 0.05.**

Table 2 and 3 represent the comparison between the levels of the studied parameters between short term (≤ 1month), and long term (1 - ≥ 10 years) capotopril users and control group. There were significant elevation of blood urea level by 21.3% for short term treated group (P<0.001) and by 23% for long term treated group (p< 0.001). The changes also involves creatinine level by 6.5% elevation in short term treatment and a 13.17% elevation for long term treatments but both were insignificant changes (P>0.05) table 2 and 3. Estimated creatinine clearance levels were declined by -0.12% and -8.4% for short term and long term treatments respectively but this was statically insignificant for short and long term treated groups as in table 2,3.

Table 2. ***Comparison of studied parameters between short term (≤ 1month) capotopril users and control group.***

parameters	Mean ± SD		
	Control group (n=48)	Treated group ≤ 1month (n=8)	P
Age (year)	52.52 ± 9.26	60.38 ± 11.82	>0.05
Weight (Kg)	76.62 ± 8.54	83.38 ± 14.66	>0.05
Urea (mmol/L)	5.41 ± 0.95	6.56 ± 0.72***	<0.001
Creatinine (µmol/L)	92.35 ± 15.88	98.35 ± 26.49	>0.05
Cr Cl (ml/min)	83.43 ± 16.78	83.34 ± 33.19	>0.05

***significant difference at *** P<0.001.**

Table 3. ***Comparison of studied parameters between long term (1 - ≥ 10 years) capotopril users and control group.***

parameters	Mean ± SD		
	Control group (n=48)	Treated group 1 - ≥ 10 years (n=42)	P
Age (year)	52.52 ± 9.26	58.47 ± 10.79**	<0.01
Weight (Kg)	76.62 ± 8.54	77.45 ± 13.76	>0.05
Urea (mmol/L)	5.41 ± 0.95	6.70 ± 2.71***	<0.001
Creatinine (µmol/L)	92.35 ± 15.88	104.51 ± 30.81*	>0.05
Cr Cl (ml/min)	83.43 ± 16.78	76.43 ± 30.02	>0.05

****significant difference at ** P< 0.01, *** P< 0.001.**

Studying the influence of duration of treatments on the renal function as shown in table 4 demonstrated that there were significant elevation of blood urea (P<0.05) in 5-10 years treated group. Serum creatinine was significantly elevated (P<0.05) at ≥ 10 years treated group associated with a decline in estimated creatinine clearance in the ≥ 10 years treated groups (P<0.05).

Table 4. ***Effect of duration of treatment on the studied parameters.***

Durations / Parameters	Mean ± SD			
	Treated group ≤ 1 year (n=8)	Treated group 1-5 years (n=35)	Treated group 5-10 years (n=6)	Treated group ≥ 10 years (n=4)
Urea (mmol/L)	6.48 ± 1.91 a	6.94 ± 2.44 a	8.22 ± 5.54 b	8.05±5.53 ab
Creatinine (µmol/L)	86.93 ± 37.85 a	99.51 ± 21.62 a	141.44±63.75 ab	117.866±45.36 b
Cr Cl (ml/min)	86.43 ± 16.78 b	78.39 ± 18.78 b	42.48± 24.34 ab	55.12±17.48 a

***Different letters horizontally mean significant difference at P≤ 0.05**

There were a significant negative correlations between the duration of treatment and creatinine clearance level (P<0.05, r= s- 0.245) as shown in figure 2.

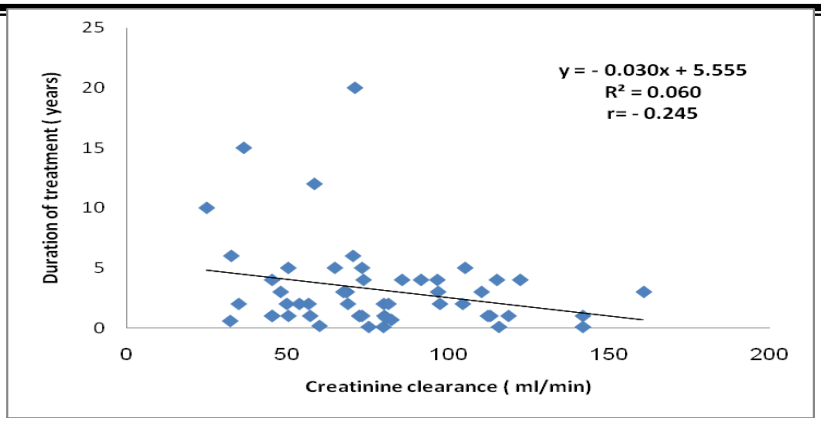

Figure 2. *Correlation between duration of treatment with captopril and creatinine clearance level* .

The dose of captopril has negative correlations with blood urea and creatinine levels but these were non statically significant (r= - 0.100 for urea and r= - 0.092 for creatinine).

Discussion

Short and long terms treatment with captropril has got its influence on renal function as shown in this study were blood urea, serum ceatinine levels were elevated but estimated creatinine clearances level was lowered which is in agreement with others. [14-18] Glück et al.[14] investigated the effect of the substitution of captopril up to 450 mg /day after an average of 25 days (short-term) and 26 weeks (long-term). Short-term treatment produced a 15.5% decrease in mean blood pressure and inter-individually variable effects on renal function. That pattern was quite similar to the effects of our study but the drop in our result was not statically significant for estimated creatinine clearance. Smith et al.[12] measured glomerular filtration rate (GFR) , effective renal plasma flow, and creatinine clearance in ten patients with stable chronic renal failure (GFR <50 ml/min) before, during and after 1 month's treatment with captopril. There were no alteration in baseline GFR, effective renal plasma flow, or creatinine clearance, with or without captopril. On the other hand another study found that administration of captopril reduced the risk of development of contrast-induced nephrotoxicity by 79% .[19]

ACE inhibitors inhibit the renin-angiotensin-aldosterone system in patients with chronic kidney disease and in patients with normal baseline serum creatinine levels, causing efferent arteriolar dilation. This can cause an acute decline in GFR of more than 15 % from baseline with proportional elevations in serum creatinine within the first week of initiating therapy.[16-19] This most commonly occurs in patients

with congestive heart failure, in patients using concomitant diuretics or nonsteroidal anti-inflammatory drugs, and in patients receiving

high doses of ACE inhibitors.[20-23] Captopril, particularly when given in high doses to patients with renal insufficiency, may cause proteinuria.[19] In most patients, ACE inhibitors can be continued safely if the rise in serum creatinine is less than30 %. Typically, the level will return to baseline in four to six weeks.[14,23]

In conclusion

If one chooses captopril for hypertension, one should know that the response to captopril may also be dependent on the degree of activation of the renin- angiotensine system and that the drug have considerable effect on renal function, so close monitoring of renal function is very important .

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الخلاصة:

أهداف البحث : تم إجراء الدراسة لغرض تقييم تأثير الجرع المختلفة لعقار الكابتوبريل على وظائف الكلية عند المرضى الذين يستخدمون هذا الدواء ولفترات مختلفة.

المرضى والطرق المتبعة: تضمنت الدراسة53 مريضا من كلا الجنسين يستخدمون عقار الكابتوبريل وبجرع مختلفة (12.5 – 150 mg/day) لغرض علاج ارتفاع ضغط الدم أو هبوط القلب من مدينة الموصل. شملت الدراسة 48 عينة من الأشخاص ألأصحاء من كلا الجنسين كمجموعة سيطرة وتم قياس تركيز اليوريا والكرياتنين وحساب نسبة تصفية الكرياتنين للمجموعتين.

النتائج: أظهرت النتائج وجود ارتفاع معنوي $P<0.05$ في مستويات تراكيز اليوريا والكرياتنين

في المرضى الذين ياخذون العلاج لمدة طويلة. كما انه هناك علاقة سالبة بين فترة العلاج ونسبة تصفية الكرياتنين بالاضافة لوجود فرق معنوي $p<0.05$ بين مجموعة المرضى الذين ياخذون العلاج لفترة قصيرة وطويلة في تركيز اليوريا عند مقارنتها بمجموعة السيطرة.

الاستنتاجات: إن عقار الكابتوبريل له تأثير معنوي على وظائف الكلى ولهذا يجب مراقبة هؤلاء المرضى وخصوصا عند استخدام الدواء لفترات طويلة.