;hfChanges in serum potassium and serum creatinine in hypertensive patients treated with Captopril with or without amlodipine

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Abstract

Background. Renal function and serum potassium are affected by many drugs. Angiotensin Converting Enzyme inhibitors and calcium channel blockers used to treat hypertension and non steroidal anti-inflammatory drugs used for musculoskeletal diseases. Those drugs affect both the renal function and the serum potassium. The aim of this study was to find the impact of these drugs on the renal function and serum potassium.

Methods. A prospective study includes 60 patients in Al Hussain Teaching hospital in Kerbala. Sixty patients were involved in this study 27 male and 33 female, their age ranges between 41 and 65 years with a mean age of 52.98 years.

All patients had hypertension and 34 of them had diabetes mellitus also. All patients started on captopril, 13 of them amlodipine added for them to control blood pressure, and 11 used none steroidal anti-inflammatory drugs. Serum potassium and serum creatinine were checked twice before starting treatment and the average value recorded and checked again after 3 months. Physical examination was done during the follow-up visits to look for symptoms and signs of hyperkalemia e.g. weakness, fatigability, parasthesia, or areflexia. Electrographic recording done to look for changes of hyperkalemia.

Results.

A significant increase in serum potassium and creatinine after starting treatment in the whole group. Regard the gender there were significant differences in both the serum potassium and serum creatinine in female patients but the differences were not significant in male patients.

There was a significant difference in serum potassium in patients receiving captopril alone but not in serum Creatinine. There was difference in serum potassium and serum creatinine in the group of patients receiving captopril and amlodipine and statistically were significant. Changes were significant in diabetic patients but not in hypertensive patients.

Conclusion. Captopril, amlodipine result in an increase in serum potassium and in serum creatinine in patients treated for hypertension.

التغيرات الحاصلة في مستوى البوتاسيوم والكرياتانين في مصل الدم في المرضى المصابين بارتفاع ضغط الدم المعالجين بالكابتوبريل مع او بدون الاملودبين

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الكلمات المفتاحية: كابتوبريل ,املودبين ,مضادات الالتهاب غير الستيرويدية ,مستوى البوتاسيوم في مصل الدم , مستوى الكرياتنين في مصل الدم.

الخلاصة:

وضيفة الكلية والبوتاسيوم في مصل الدم تتأثر بعدد من العقاقير الطبية. مثبطات أنزيم انجيوتنسر التحويلي وحاصرات قنوات الكالسيوم التي تستعمل لعلاج ارتفاع ضغط الدم والعقاقير المضادة للالتهابات غير الستيرويدية والتي تستعمل لإمراض العضلات الهيكلية تؤثر على وظائف الكلية ومستوى والبوتاسيوم في مصل الدم.

الهدف من هذا البحث هو إيجاد تأثير هذه العقاقير على وظائف الكلية و مستوى والبوتاسيوم في مصل الدم.

هذا البحث اجري في مدينة الإمام الحسين الطبية التعليمية و شمل 60 مريضا 27 من الذكور و 33 من الإناث تتراوح أعمارهم بين ال41 سنة و ال65 سنة من العمر وبمعدل قدره 52.98 سنة.

جميع المرضى كانوا مصابين بارتفاع ضغط الدم أربعة وثلاثون منهم كان مصابا بداء السكري كذالك. كافة المرضى تمت معالجتهم بالكابتوبريل و ثلاثة عشر تم إضافة الاملودبين للسيطرة على ارتفاع ضغط الدم. احد عشر مريضا كان يتناول مضادات الالتهابات غير الستيرويدية. مستوى والبوتاسيوم والكرياتنين في مصل الدم تم قياسه مرتين قبل بدا العلاج ومعدل القراءتين تم حسابه وقد أعيدت القراءة بعد ثلاثة أشهر وبنفس الطريقة.

الفحص ألسريري اجري خلال المتابعة للتحقق من إعراض ومظاهر ارتفاع والبوتاسيوم مثل الشعور بالضعف و الإنهاك والخدر العصبي وانخفاض الانفعالات العكسية. تخطيط القلب اجري لكافة المرضى للتحقق من وجود التغيرات التي تنتج عن ارتفاع والبوتاسيوم في مصل الدم.

النتائج: كانت الزيادة معنوية في مستوى والبوتاسيوم والكرياتنين بعد بدا العلاج في كل المجموعة. بالنسبة للجنس فكانت هناك زيادة معنوية عند الإناث ولكنها غير معنوية عند الذكور.

كذالك كانت الزيادة معنوية في مستوى والبوتاسيوم عند المرضى الذين يتناولون الكابتوبريل. وكانت الزيادة معنوية في المرضى الذين يتناولون الكابتوبريل الاملودبين معا. كانت الزيادة معنوية في المرضى المصابين بارتفاع ضغط الدم وداء السكري.

الاستنتاجات: الكابتوبريل الاملودبين يؤديان إلى زيادة في والبوتاسيوم و والكرياتنين في مصل الدم في المرضى المصابين بارتفاع ضغط الدم.

Introduction

Normal serum potassium is 3.5-5.5 mmol/l and so hyperkalemia is defined as serum potassium above 5.5 mmol/l [(1)]. Others define hyperkalemia as serum Potassium greater than 5 mmol/l which occurs as a result of either release of potassium from cells or decreased renal loss [(2)].

Hyperkalemia is potentially a life threatening metabolic problem caused by a variety of factors and its prevalence in hospitalized patients is between 1 and 10% [(3, 4)].

Drug induced hyperkalemia is an important cause of morbidity and mortality and may occur in ambulatory as well as in inpatient setting [(5)].

Drugs can cause hyperkalemia by a variety of mechanisms including reduction in renal potassium excretion due to hypoaldosteronism, reduction in potassium excretion, increase in extracellular shift, and increase in potassium supply[6].

Patients at risk are those with underlying diseases affecting potassium handling such as chronic renal failure, and those taking a combination of drugs known to cause hyperkalemia(5). Angiotensin converting enzyme (ACE) inhibitors cause a decline in the renal function due to decreased kidney perfusion[7]. Normal serum creatinine is 0.68-1.36 mg/dL[8].

ACE inhibitors are used in medical practice to treat hypertension though they may be used for diabetic nephropathy, cardiac failure, and for other reasons[7].

Among their side effects is hyperkalemia by blocking the conversion of angiotensin I to angiotensin II which results in aldosteron release[2]. The risk increases in those with diabetes mellitus (DM), renal insufficiency or when combined with non-steroidal anti inflammatory drugs (NSAID) [2]. Up to 38% of patients taking ACE inhibitors are at risk of developing hyperkalemia [9]. NSAID causes decreased afferent arteriolar flow, suppressing renin and aldosteron secretion [10]. They can cause nephrotoxicity even with newer generations as selective cyclo-oxyegenase inhibitors [11]. NSAID increases the risk of hyperkalemia by more than 40% [9]. An elevated serum potassium concentration in a patient with mild to moderate renal failure should not be ascribed to renal failure alone, other causes should be investigated including drugs [12].

If DM is uncontrolled and when the blood sugar is very high, there will be an internal potassium imbalance [13]. Hyperkalemia usually is asymptomatic, but manifestations as weakness, parasthesia, areflexia, ascending paralysis, gastrointestinal symptoms (nausea, vomiting, and diarrhea) may occur [1, 13].

Electrocardiographic (ECG) changes in patients with hyperkalemia are an ominous features of potentially fatal arrhythmias, but hyperkalemia could be life threatening even if the ECG is normal [14], however about half of patients with serum potassium level exceeding 6 mmol/l had normal ECG [15, 16].

This study aims to evaluate the effect of captopril, amlodipine and NSAID on serum potassium and serum creatinine

Patients and Methods

A prospective study was conducted in Al Hussein Teaching Hospital on sixty hypertensive patients either attending the consultation clinic or admitted to the medical ward for the period from the second of January 2011 to the 24th of December 2012. They were 33 female and 27 male patients. All patients had hypertension, 34 of them had diabetes mellitus in addition. They were not receiving hypotensive medications, and were started initially on captopril. The doses were adjusted according to blood pressure control during follow-up, and thirteen patients needed the addition of amlodipine 5-10 mg/ day to control blood pressure. Patients receiving other antihypertensive drugs were excluded. History of concurrent receiving of NSAID was recorded in 11 patients.

Serum potassium and serum creatinine were checked twice and average value recorded before starting treatment and every 3 months. Venous samples were sent to the laboratory at once to avoid false results due to hemolysis. The units used were mmol/l for serum potassium and mg/dl for serum creatinine. Normal serum potassium considered 3.5-5.5 mmol/l. Normal serum creatinine is 0.68-1.36 mg/dL.

We arranged follow-up visits every 3 months during which blood pressure was checked and adjustment of the dose of captopril was done according to blood pressure reading, captopril dose ranged from 25-150 mg with or without the addition of amlodipine. The number of visits varies from 2-4 visits.

We did physical examination during the follow-up visits for patients to look for symptoms and signs of hyperkalemia such as weakness, fatigability, parasthesia, or areflexia. We did electrographic recording to look for changes of hyperkalemia eg. Prolonged PR interval, absents P wave, tenting of T wave, or broadening of QRS complex.

The research ethical committee in Kerbala Health Directorate approved this study.

Statistical analysis was performed using statistical package for social science version 16 (SPSS 16) program. All variables were expressed as means, standard deviation (SD) and t test for paired samples were used for statistical analysis of data and a $P < 0.05$ considered for the level of significance.

Results

Sixty patients were involved in this study 27 male and 33 female, their age ranges between 41 and 65 years with a mean age of 52.98 years ± SD of 6.43 year .

The mean serum potassium in the whole group before starting treatment was 4.66 mmol/l and 4.96 mmol/l after treatment, while the mean serum creatinine before treatment was 0.90 mg/ dl, and 1.25 mg/ dl after treatment and there was significant statistical difference between the means of both measures before and after treatment as shown in (Table 1).

Table 1. Serum Potassium ($S K^+$) and Serum Creatinine (S Cr) before and after treatment of all patients

	N	Mean ± SD	P value
$S K^+$ before	60	4.66 ± 0.38(mmol/l)	0.001
$S K^+$ after	60	4.96 ± 0.74(mmol/l)	
S Cr before	60	0.90 ± 0.09(mg/dl)	0.005

	N	Mean ± SD	P value
S K^+ before	60	4.66 ± 0.38(mmol/l)	0.001
S Cr after	60	1.25 ± 0.70(mg/dl)	

All patients had normal serum potassium before starting treatment, 7 patients(11.66%) had a serum more than 5.5mmol/l after 3 months of starting treatment, all of them were receiving captopril 125-150 mg/ day while only one patient(1.66%) developed hypokalemia.

All patients had normal serum creatinine before starting treatment, 10 patients (16.66%) had serum creatinine more than 1.36 after 3 months of starting treatment, all of them were receiving captopril 125-150 mg/ day (Fig 1).

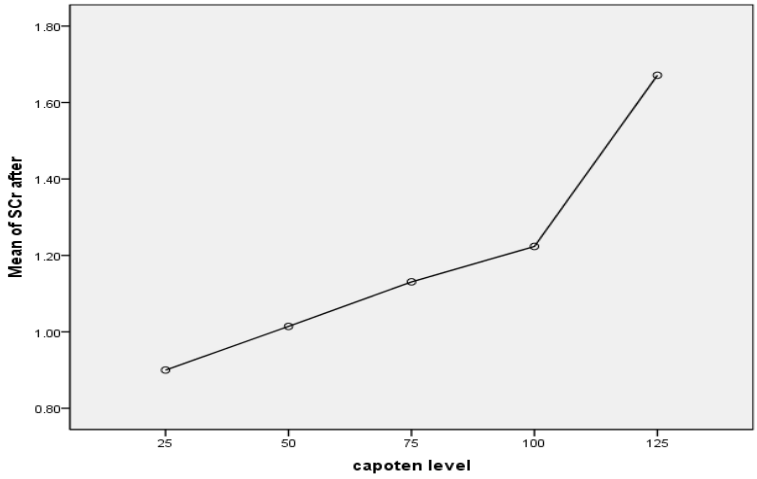

Fig 1 . The mean serum creatinine in relation to the dose of captopril

Regarding gender there were increase in means of both the serum potassium and serum creatinine in both males and females patients before and after treatment and the differences were significant in all except for serum potassium in male patients (Table 2, Table3).

Table 2. Serum potassium and serum creatinine before and after treatment in male patients

Variable	N	Mean ± SD	P value
S K+ before	27	4.64 ± 0.37(mmol/l)	0.289
S K+ after	27	4.82 ± 0.91(mmol/l)	

S Cr before	27	0.89 ± 0.10(mg/dl)	0.031
S Cr after	27	1.26 ± 0.86(mg/dl)	

Table 3. Serum potassium and serum creatinine before and after treatment in female patients

	N	Mean ± SD	P value
S K+ before	33	4.67 ± 0.39(mmol/l)	0.000
S K+ after	33	5.08 ± 0.55(mmol/l)	
S Cr before	33	0.90 ± 0.09(mg/dl)	0.001
S Cr after	33	1.24 ± 0.56(mg/dl)	

There was a significant difference increase in means of serum potassium in patients receiving captopril alone but it was not significant for mean serum creatinine (Table 4). However there were significant statistical difference increase in means of serum potassium and serum creatinine in patients receiving captopril and amlodipine. (Table 5).

Table 4. Serum potassium and serum creatinine and before and after treatment in patients on ACE inhibitors only

	N	Mean ± (SD)	P value
S K+ before	47	4.64 ± 0.41(mmol/l)	0.000
S K+ after	47	4.79 ± 0.73(mmol/l)	
S Cr before	47	0.89 ± 0.10(mg/dl)	0.053
S Cr after	47	1.11 ± 0.63(mg/dl)	

Table 5. Serum potassium and serum creatinine before and after treatment in patients on ACE inhibitors and amlodipine

	N	Mean ± (SD)	P value
S K+ before	13	4.71 ± 0.19(mmol/l)	0.000
S K+ after	13	5.59 ± 0.31(mmol/l)	
S Cr before	13	0.95 ± 0.08(mg/dl)	0.002
S Cr after	13	1.75 ± 0.74(mg/dl)	

While the differences of increase in means of serum potassium and serum creatinine in patients with hypertension alone were not statistically significant (Table 6), the differences of increase in means of serum potassium and serum creatinine in patients with hypertension and diabetes mellitus were statistically significant (Table 7).

Table 6. Serum Potassium and serum Creatinine in group of patients with hypertension only

	N	Mean±(SD)	P value
S K+ before	26	4.67 ± 0.42(mmol/l)	0.051
S K+ after	26	4.77 ± 0.91(mmol/l)	
S Cr before	26	0.88 ± 0.09(mg/dl)	0.5444
S Cr after	26	1.21 ± 0.83(mg/dl)	

Table 7. Serum potassium and serum creatinine in group of patients with hypertension and diabetes mellitus

	N	Mean ± SD	P value
S K+ before	34	4.65 ± 0.35(mmol/l)	0.000
S K+ after	34	5.11 ± 0.53(mmol/l)	
S Cr before	34	0.91 ± 0.10(mg/dl)	0.001
S Cr after	34	1.28 ± 0.60(mg/dl)	

Nine patients developed symptoms during follow up, three patients had nausea and vomiting, one of them his serum creatinine was 5.2 mg /dl. Eight patients developed easy fatigability and weakness, two of them had a serum potassium 6 mmol/l, three others 5.8mmol/l.

Discussion

The serum potassium and serum creatinine in the study group was higher after treatment than before treatment and statistically significant. These results were consistent with other studies using the captopril with or without amlodipine or NSAID [2, 17, 18].

Patients using captopril had significant increase in serum potassium and this consistent with other studies conducted by Perazzela 2000 and Samuel et al 2008 [9,18]. In this study 11.66% developed hyperkalemia, all of them were receiving a high dose of captopril, and this is consistent with a study conducted by Samuel et al 2008 in which 10% of his patients developed hyperkalemia whom found a strong dose–effect relationship between therapy with ACE inhibitors and serum potassium[18]. Anton et al 2001 in his study 6% of his patients developed hyperkalemia (serum potassium > 5.5mml/l) [19]. This group of patients had difference in serum creatinine but statistically not significant which contradict other studies[7,17]. Ten patients (16.66%) had serum creatinine more than 1.36 after 3 months of starting treatment, one patient had serum creatinine 5.2mg/dl. Our results are consistent with another study conducted by Anton et al 2001 in which 16% of his patients developed reduced renal function[19], same study indicates that ACE inhibitors use can be associated with a syndrome of "functional renal insufficiency" and/or hyperkalemia, a form of acute renal failure (ARF) most commonly develops shortly after initiation of ACE inhibitor therapy [19]. All of them were receiving captopril 125-150 mg/ and one patient receiving amlodipine as well. Renal failure caused by ACE inhibitors could be reversible in the setting of decreased renal perfusion [7]. It might be the inappropriate high dose of captopril used in treatment of those patients resulted in this high incidence of renal failure in our study.

There were significant differences in serum potassium and serum creatinine in group of patients treated by a combination of captopril and amlodipine. In this study 11.66% developed hyperkalemia and 1.66% developed hypokalemia in comparison with another study in which incidence of hypokalemia in patients using amlodipine was 2.1% and that of hyperkalemia 1.9%[20,21]. The concomitant use of captopril with amlodipine could be the reason for the discrepancy between our results and the studies conducted by Theodore 2012 and Michel et al 2012 in which amlodipine was used alone[20,21].

Changes in serum potassium and serum creatinine were significant in female but the mean serum potassium was higher than in men after treatment compared with Samuel et al 2008 study in which serum potassium was higher in men[18], however this could be related to that higher percent of females on our sample were using NSAID and Amilodipint, though they were not statistically significant .

In patients with hypertension there were changes in both serum potassium and serum creatinine but not significant and this is consistent with other study[22]. Patients with diabetes mellitus had significant changes in both serum potassium and serum creatinine and this is consistent with other studies[23,24].

We noted significant changes in patients receiving NSAID with antihypertensive medications and this is consistent with other study[25].

Limitations

The sample size was relatively small which may account for the results which was not consistent with other studies. The other point was the relatively short duration of follow up of the patients as they need to be followed for at least 1 year.

Conclusions

Captopril used alone or in combination with amlodipine and or NSAID result in an increase in serum potassium and serum creatinine, and this is more risky in patient with DM.

Recommendations

More studies are needed with larger number of patients and the follow up should be for 1 year or more for better results.

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