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Ramipril and Risk of Hyperkalemia in Chronic Hemodialysis Patients

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ABSTRACT

Angiotensin converting enzyme (ACE) inhibitors provide well known cardiorenal-protective benefits added to antihypertensive effects in chronic renal disease. These agents are underused in management of patients receiving hemodialysis (HD) because of common concern of hyperkalemia. However, few studies have investigated effect of renin angiotensin aldosterone system (RAAS) blockade on serum potassium in hemodialysis patients. We assessed the safety of ramipril in patients on maintenance HD. We enrolled 28 adult end stage renal disease (ESRD) patients treated by maintenance HD and prescribed them ramipril in doses of 1.25 to 5 mg per day. They underwent serum potassium concentration measurements before ramipril introduction and in 1 to 3 months afterwards. No significant increase in kalemia was found. Results of our study encourage the use of ACE inhibitors in chronically hemodialyzed patients, but close potassium monitoring is mandatory.

Key words: *angiotensin converting enzyme inhibitors, hyperkalemia, hemodialysis*

Introduction

Chronic kidney disease accelerates atherosclerosis, myocardial disease, and valvular disease and promotes cardiac arrhythmias. These factors present strong risk for cardiovascular mortality, which is leading cause of death among these patients. Retrospective studies have identified renal dysfunction as the most significant prognostic factor for long-term mortality[1] and patients with chronic renal failure have the highest mortality rate in chronic diseasepopulation[2]. Also, multiple studies in patients with class II and III of heart failure have shown decreased survival related to the renal impairment[3]. Deterioration of renal function is mediated by glomerular capillary hypertension, and ACE (angiotensin converting enzyme) inhibitors, which selectively lower glomerular pressure, should be most effective in inhibiting progression to ESRD (end stage renal disease). Patients with ESRD have worse outcome considering cardiac death even in comparison with diabetic patients. Treating a patient with ESRD presents a challenge to a clinician and ACE inhibitors are a treatment option. Hyperactivation of the RAAS (renin angiotensin aldosteron system) is a target for therapy in ESRD and ACE inhibitors have been proven to reduce LVH and possibly improve survival[4]. A retrospective study found that only approximately 20 percent of patients with ESRD and CAD (coronary artery disease) receive ACE inhibitors[1].

ACE inhibitors are officially contraindicated in severe renal failure and common concern is hyperkalemia. The mechanisms responsible for potassium homeostasis are renal, gastrointestinal and skin potassium excretion. The most important mechanism is the renal excretion and the major site of renal regulation of potassium excretion occurs in the distal tubules and collecting ducts. The stimulation of potassium secretion is related to the ability of aldosteron to stimulate sodium potassium ATPase (adenosine triphosphatase) activity in cells of distal tubule. ACE inhibition is associated with aldosteron reduction and has potential indirect natriuretic and potassium retaining effects. Urine flow rate increases urinary po-

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tassium excretion and hyperkalemia is a common complication of oliguric renal failure and urinary tract obstruction[5]. It is less commonly associated with non-oliguric renal failure and is rarely associated with prerenal azotemia unless prerenal azotemia results from Addison's disease. A particular caution is required in the management of the patient who is already receiving dialysis. Danger of hyperkalemia seems to be major discourage for their prescription in those patients.

We have previously undertaken a cross-sectional study in 194 maintenance HD patients and showed that 63 of them that received RAAS inhibitors did not differ in kalemia in comparison with 131 patients without that medication[6]. In our study we used ramipril, which had major indication based on trial data for the following: a) cardiovascular prevention (HOPE)[7] b) heart failure, post-myocardial infarction (AIRE)[8] c) diabetic nephropathy (MICRO-HOPE)[9] d) chronic renal disease (REIN)[10]. The results encouraged us to perform a prospective study on kalemia change following prescription of ramipril in ESRD treated with HD. We hypothesized that introduction of ramipril treatment would not significantly increase serum potassium concentration in maintenance HD patients.

Objective of the study was an examination of increased risk of hyperkalemia in chronic hemodialysis patients upon blockade of renin-angiotensin system by angiotensin converting enzyme inhibitors. Endpoints included significant change in kalemia and incidence of severe hyperkalemia.

Subjects and Methods

Study included 28 patients (10 women, 18 men), mean age 58±11 years, treated by maintenance HD for median time 4.5 years (from 1 to 19 years) in Osijek University Hospital Center, Osijek, Croatia. They suffered from common basic renal diseases that cause ESRD (Table 1). They received HD three times a week for 4 to 4.5h. Bicarbonate dialysis was applied in all patients. No change in dialytic solution or in dialysators was done during the study. Main inclusion criterion was potential cardiovascular benefit from ACE inhibitor therapy, i.e. those with left ventricular hypertrophy, diabetes mellitus, unregulated arterial hypertension, chronic heart failure and history of myocardial infarction. Exclusion criteria were as follows: current medication with RAAS inhibitor, chronic or frequent hypotension (systolic blood pressure 100 mmHg or less, not only intradialytic) and predialysis kalemia of 6 mmol/L and above that value, even only once during the previous two-month regular check-ups (since on maintenance dialysis).

Diagnosis of arterial hypertension was considered if patient already had such diagnosis or was taking antihypertensives. Twenty nine of total 194 patients receiving HD in the centre fulfilled the criteria and accepted the proposed treatment with ramipril. They underwent predialysis serum potassium concentration determination before the therapy introduction and again 1–3 months afterwards, thrice in 7 days, respectively. Potassium

TABLE 1
CHARACTERISTICS OF THE PATIENTS (N=28)

Characteristic	Value
Age (years)	58±11
Gender (males)	18
Duration of chronic hemodialysis (years)	median 4.5 (min. 1 – max. 19)
Renal disease (n):	
Glomerulonephritis	14
Interstitial nephritis	5
Autosomal dominant polycystic kidney disease	3
Diabetes mellitus	4
Other	2
Residual diuresis (mL/day)	median 150 (min. 0 – max. 1000)
<100 mL/day (n)	12
100–500 mL/day (n)	10
>500 mL/day (n)	6
Arterial hypertension (n)	15
Medication (n)	
Diuretics	10
Calcium antagonists	17
Beta blockers	11
Alpha blockers	7
Propafenon	1
Nitrates	9
Digoxin	2
Insulin	2

was determined by routine method in the hospital laboratory, as usual, with caution to avoid artificial hyperkalemia. One patient dropped out of the study during a run-in phase, due to hyperkalemia of 6 mmol/L in one of the three predialytic potassium measurements before the drug introduction. He was not included in the statistical analysis. Predialytic blood pressure measurements were recorded just before 6 consecutive HD sessions, along with already scheduled potassium determination. The measurement was done by nurse in supine position, after at least 10 minutes rest. Mean arterial pressure (MAP) was calculated according to the standard equation- diastolic + 1/3 (systolic-diastolic), for all measurements. For three MAP values before ramipril introduction and 1–3 months afterwards mean MAP was calculated, respectively. That two mean MAP values were used for statistical analysis. Mean potassium serum concentration was calculated for three predialysis values before the drug introduction and for three predialysis potassium values 1–3 months afterwards, respectively. Those two mean potassium values were used for statistical analysis. Residual diuresis and other antihypertensive medication were recorded. Anuria was considered when daily urine output was less than 100 mL. Additional sub-

groups were analyzed divided according to daily urine output of 500 mL and more or less than that. All patients denied taking resins regularly. The patients were prescribed small doses of ramipril (Tritace, Sanofi-Aventis Group, Paris) 1.25, 2.5 or 5 mg upon conventional antihypertensive therapy to achieve diastolic blood pressure under 90 mmHg. Endpoints were change in kalemia and incidence of severe hyperkalemia (≥6.0 mmol/L).

Statistics

Statistical analysis was performed using software package SPSS 17.0 (SPSS inc, Chicago, IL, USA). Depending on the type of variable and normality of distribution, descriptive statistics used frequencies, means±SD and median (range) to present the data. Potassium concentration distribution was normally distributed and paired t-test was used for comparison analysis. Paired t-test was although used for further examination of differences between normally distributed variables throughout the study. $p<0.05$ was considered statistically significant. For comparison between 2 independent samples Mann-Whitney test was used because of small size of the subgroups, irrespective of the distribution. Sample size suffices for relevant statistical conclusion, while for minimal significant difference in serum potassium concentration of 0.3 mmol/L and presumed standard deviation in the difference in kalemia (according to our previous study) of 0.4 mmol/L 12.5 pairs of observations is needed (2×0.3/0.4 – Altman's nomogram).

Results

One patient dropped out during a run-in phase of the study because of hyperkalemia before ramipril introduction and twenty eight patients completed this prospective 3-month study. No worsening of anemia or other side effects was found. Mean haemoglobin value before the study was 104±10 g/L, and 104±8 g/L after 3 months (t=0.383, p=0.705). There was no need to increase a dose of erythropoietin. Nineteen patients in our study were treated with erythropoietin in a median dose 4000 UI *per* week (2000–8000 UI). Table 2 presents the values of kalemia and MAP before and after introduction of ramipril. Median dose of ramipril was 1.25 mg (21 patiens were given a dose of 1.25 mg ramipril, 5 patients were taking a dose of 2.5 mg ramipril and 2 patients were taking 5 mg ramipril). Mean serum concentration of potassium was similar before and with ramipril treatment (5.0±0.3 *vs.* 5.0±0.4mmol/L, p=0.269). Twelve patients were anuric and they did not show any significant hyperkalemic changes compared with non-anuric patients (Table 3). Most of the patients were taking other medication, including diuretics and beta blockers that could interfere with potassium homeostasis. Fifteen patients had hypertension and were taking antihypertensives. After 3 months on ramipril therapy mean arterial pressure was not significantly changed compared to the basal values (101±10 *vs.* 102±7 mmHg, p=0.691). Kalemia following ramipril medication differed significantly in anuric patients (n=12) in comparison with those (n=16) with residual diuresis (median 4.8 mmol/L, min. 4.1, max. 5.4 *vs* median 5.1 mmol/L, min. 4.4, max. 5.7, z=–2.021, p=0.043), while the pretreatment values were not different. Blood pressure between anuric and non-anuric patients did not differ significantly both before and after ramipril introduction. No difference in kalemia and blood pressure was found between those excreting more than 500 mL of urine daily in comparison with patients with less diuresis, neither before nor with ramipril therapy. Difference in serum potassium concentration and in blood pressure before and following ramipril treatment was not found between the patients taking diuretics, calcium antagonists, beta blockers, or alpha blockers, and those without such therapy, respectively. Nitrates were taken by 9 patients and their blood pressure (MAP) before ramipril introduction was statistically different than in 19 others (median 93, min. 88, max. 104 *vs.* median 103,

TABLE 2
KALEMIA AND BLOOD PRESSURE BEFORE AND 1–3 MONTHS AFTER RAMIPRIL INTRODUCTION (N=28)

	Before ramipril	1–3 months after ramipril introduction	t-value	p
Serum potassium concentration (mmol/L)	5.0±0.3	5.0±0.4	1.129	0.269
Mean arterial pressure (mmHg)	101±10	102±7	–0.401	0.691

TABLE 3
KALEMIA AND MEAN ARTERIAL PRESSURE (MAP) IN RESPECT WITH RESIDUAL DIURESIS BEFORE AND WITH RAMIPRIL THERAPY

	Serum potassium before ramipril (mmol/L) median (min-max)	Serum potassium after ramipril (mmol/L) median (min-max)	MAP before ramipril (mmHg) median (min-max)	MAP after ramipril (mmHg) median (min-max)
Anuric (n=12)	5.1 (4.6–5.5)	4.8 (4.1–5.4)	100 (76–122)	103 (86–119)
With residual diuresis (n=16)	5.1 (4.2–5.5)	5.1 (4.4–5.7)	103 (88–129)	102 (94–110)
Mann-Whitney test value (z)	–0.419	–2.021	–0.675	–0.116
p	0.698	0.043	0.500	0.909

TABLE 4
KALEMIA AND MEAN ARTERIAL PRESSURE (MAP) IN RESPECT WITH VARIOUS MEDICATIONS THERAPY BEFORE AND WITH RAMIPRIL THERAPY

	Serum potassium before ramipril (mmol/L) median (min-max)	Serum potassium with ramipril (mmol/L) median (min–max)	MAP before ramipril (mmHg) median (min–max)	MAP with ramipril (mmHg) median (min–max)
Beta blockers YES (n=17)	5.1 (4.6–5.5)	5.0 (4.1–5.7)	100 (76–129)	102 (89–119)
Beta blockers NO (n=11)	4.9 (4.2–5.3)	4.8 (4.3–5.6)	98 (92–122)	100 (93–110)
Mann-Whitney test value (z)	–1.627	–0.965	–0.495	–0.118
p	0.111	0.353	0.643	0.926
Alfa blockers YES (n=21)	5.1 (4.2–5.5)	5.0 (4.1–5.6)	100 (76–129)	100 (89–119)
Alfa blockers NO (n=7)	5.3 (4.7–5.5)	4.8 (4.4–5.7)	100 (92–109)	106 (93–110)
Mann-Whitney test value (z)	–1.915	–0.027	–0.053	–0.885
p	0.055	1.000	0.959	0.405
Diuretics YES (n=18)	5.1 (4.7–5.5)	5.1 (4.4–5.7)	99 (76–122)	99 (89–119)
Diuretics NO (n=10)	5.1 (4.2–5.5)	4.8 (4.1–5.4)	106 (88–129)	103 (94–110)
Mann-Whitney test value (z)	–0.312	–1.847	–1.081	–0.528
p	0.759	0.064	0.286	0.621
Calcium antagonist YES (n=11)	5.1 (4.6–5.5)	4.8 (4.4–5.7)	100 (92–122)	100 (93–110)
Calcium antagonist NO (n=17)	5.1 (4.2–5.5)	4.9 (4.1–5.6)	100 (76–129)	102 (89–119)
Mann-Whitney test value (z)	–0.354	–0.071	–0.354	–0.141
p	0.746	0.963	0.746	0.890
Nitrates YES (n=19)	5.1 (4.6–5.5)	4.7 (4.3–5.4)	103 (76–129)	103 (95–119)
Nitrates NO (n=9)	5.1 (4.2–5.4)	5.1 (4.1–5.7)	93 (88–104)	94 (89–110)
Mann-Whitney test value (z)	–0.173	–2.191	–2.096	–1.921
p	0.885	0.028	0.036	0.055

min. 76, max. 129; z=–2.096, p=0.036). The difference disappeared after ramipril introduction. Kalemia did not differ between the subgroups of patients divided according to the nitrates therapy before ramipril, but the values following ramipril therapy differed significantly (median 4.7 min. 4.3, max. 5.4 *vs* median 5.1, min.4.1, max. 5.7; z=–2.191, p=0.028). Table 4 shows values of kalemia and MAP before and after ramipril introduction in the subgroups of patients divided according to different medications, as was stated in the preceding text.

Discussion

We conducted the prospective study to confirm the hypothesis that ACE inhibitors would not affect kalemia in maintenance dialysis patients. Indeed, serum potassium did not increase with ramipril therapy, even though the drug was known to induce hyperkalemia, particularly in renal failure. Previous studies investigated effect of ACE inhibitors on preservation of renal function and included patients with earlier stages of renal dysfunction[11–13]. Very few studies investigated treatment of hemodialyzed patient with ACE inhibitors[14]. Woong found that neither monotherapy (ACE inhibitors or ARB (angiotensin II receptor blocker)) nor combination therapy (ACE inhibitor plus ARB) was associated with an additional risk of hyperkalemia in patients on maintenance haemodialysis. Different results were shown in the prospective study in hemodialysis patients conducted by Knoll et al.[15] They found that the use of ACE inhibitors or angiotensin receptor blockers was associated with significantly higher risk of hyperkalemia. Approximately 20% of patients approaching haemodialysis have diagnosis of heart failure (HF)[16]. ACE inhibitors and beta-blockers have class I recommendation for treatment of left ventricular systolic dysfunction according to the new therapeutic guidelines[17]. Limited data suggest that these agents are underused in patients with ESRD. Roy et al. demonstrated that only 25.5% of patients with ESRD and left ventricular dysfunction receive appropriate treatment[18]. The reasons stated for not prescribing those medications were »concern about adverse reactions». The common concern is worsened hyperkalemia, which is rare but life threatening adverse affect of ACEI. In our study serum potassium level was not affected by ramipril treatment and there were not episodes of severe hyperkalemia during the study period. Serum potassium levels in the anuric group of our patients were even lower than those in non-anuric group. It could be explained by their better compliance to dietary restrictions. The results could contribute those of Wong, which showed that ACEI or ARB therapy was safe in chronic HD patients, even with lower

kalemia upper normal referent value (5.5 mmol/L in comparison with 6.0 mmol/L in our study). Patients on ramipril treatment had not intolerable side effects. Ramipril had not significant effect on patients' hemoglobin levels and there was no need to increase the dose of erythropoietin. Due to several mechanisms of ACEI interfering with erythropoiesis one could expect worsening of anemia with ramipril, like in a study with enalapril[19]. It is possible that the therapy required longer use of the drug to express such effect. The group's anaemia was at a representative level for chronic hemodialyzed patients, comparable to common state among such group of patients of the same size[20]. According to few reports on that topic and with respect to our findings, it should be wise to consider changing the guidelines or prescription recommendations by declaring that maintenance dialysis should not present contraindication for ACEI treatment. Careful control of potassium is necessary. It is the initial attitude that should be changed. Those patients should be considered for ACEI treatment and excluded if hyperkalemia was recorded. Those drugs should not be *a priori* contraindicated. Diet prescriptions remain also mandatory, especially in the continental patients, shown to be of greater body weight and worse dietary habits than their maritime counterparts[21]**.** The effect on cardiac function could be favorable. However, kalemia itself should always limit their use if high values are determined. Limitations of the study could include the number of the patients and the duration of the study. However, we checked the sample size needed for testing our hypothesis and it turned out that our group of patients suited to the number needed, as it was aforementioned in the methods chapter. Nevertheless, according to our experience ACE inhibitors related hyperkalemia occurs short time after the introduction of the medicine. Therefore, we considered 1 month after introduction of ramipril a sufficient period for the drug induced hyperkalemia to ensue. However, for anemia to worsen, the time could have been to short.

Conclusion

Kalemia in chronically hemodialyzed patient was not affected by ramipril therapy. The results encourage the use of small doses of ACE inhibitors in HD patients. However, close potassium monitoring is mandatory.

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RIZIK POJAVE HIPERKALEMIJE UZ PRIMJENU RAMIPRILA U BOLESNIKA NA KRONIČNOJ HEMODIJALIZI

SAŽETAK

Primjena inhibitora konvertaze angiotenzina I (ACE inhibitora) u kroničnom bubrežnom zatajenju ostvaruje osim antihipertenzivnoga i povoljno zaštitno djelovanje na funkciju bubrega i srčanožilnog sustava. Unatoč poznatom povoljnom protektivnom djelovanju ACE inhibitori se nedovoljno primjenjuju u liječenju bolesnika na kroničnom programu hemodijalize, prvenstveno zbog straha od pojave hiperkalemije. Vrlo su rijetka istraživanja učinka blokade renin-an-

giotenzin-aldosteronskog sustava (RAAS) na vrijednosti serumskog kalija u bolesnika na hemodijalizi. Istraživali smo sigurnost primjene ramiprila u bolesnika na kroničnom programu hemodijalize. Uključeno je 28 odraslih bolesnika sa završnim stupnjem kroničnog bubrežnog zatajenja liječenih ponavljanim hemodijalizama 3 puta tjedno u trajanju od 4 do 4,5 sata. Bolesnicima je propisan ramipril u dozi od 1,25 do 5 mg dnevno. Vrijednost serumskog kalija određivana je 3 puta prije uvođenja ramiprila, te ponovo uz ramipril nakon 1 do 3 mjeseca terapije. Nije nađena statistički značajna razlika u prosječnoj vrijednosti serumskog kalija prije i nakon uvođenja ramiprila (5,0±0,3 *vs*. 5,0±0,4). Rezultati istraživanja pokazuju da je primjena ramiprila sigurna u bolesnika na kroničnom programu hemodijalize uz upozorenje o potrebi redovite kontrole serumskog kalija.