Use of Renin-Angiotensin System Blockers Increases Serum Potassium in Anuric Hemodialysis Patients

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Keywords
Hyperkalemia · Renin angiotensin system · Hypertension · Dialysis · Cardiovascular

Abstract
Background: Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are increasingly used in uremic patients (pts). However, their effect on serum potassium (sK) concentrations in anuric pts on chronic hemodialysis treatment (HD) is controversial. The aim of the study was to evaluate sK before and after the start of ACEi/ARB therapy.

Methods: In the period 1/1/2015 – 31/12/2015, 112 out of 240 prevalent HD pts on thrice weekly HD treatment followed at our institution started the ACEi/ARB therapy. The mean age was 67 ± 14 years, 67/112 were men, dialysis vintage was 6–212 months. In the 3 months before (PRE; N=36 HD sessions) and after (POST; N=36 HD sessions) the start of ACEi/ARB therapy, the following variables were evaluated in pre dialysis after the long interdialysis interval: sK (mean of 12 determinations; mmol/L), maximum sK (maximum K value observed during observations; mmol/L), serum sodium (sNa; mmol/L), pre dialysis systolic blood pressure (SBP; mm Hg) and diastolic blood pressure (DBP; mm Hg), body weight (BW; Kg), interdialytic weight gain (IWG; Kg), Kt/V, serum bicarbonate concentrations (sBic; mmol/L), protein catabolic rate (PCRn; g/KgBW/day). SBP, DBP, IWG are the mean of the 24 HD sessions. Out of 112 patients, 102 were on antihypertensive therapy. The duration of HD and blood and dialysate flow rates were kept constant. Data are expressed as mean ± SD. Student t test for paired and unpaired data for normally distributed variables, Mann-Whitney test for medians, χ² test for categorical data were employed to compare groups. A significant difference was defined as p < 0.05. Results: sK increased from 5.0 ± 0.4 mmol/L PRE to 5.7 ± 0.5 mmol/L POST (p < 0.0001). sKmax increased from 5.3 ± 0.5 mmol/L PRE to 6.2 ± 0.6 mmol/L POST (p < 0.0001). The percentage of pts with normal sK concentrations decreased from 82% PRE to 29% POST (p < 0.0001). Mild hyperkalemia increased from 18 to 52% (p < 0.001); in 31% of the patients, it was necessary to reduce the K dialysate concentration. None of the patients had severe hyperkalemia PRE, but 19% developed severe hyperkalemia POST (p < 0.0001) necessitating treatment withdrawal. Mean......
sK in these pts varied from 5.2 ± 0.3 mmol/L PRE to 6.5 ± 0.2 mmol/L at the moment of withdrawal (p < 0.0001) and sKmax from 5.5 ± mmol/L PRE to 6.9 ± 0.3 mmol/L (p < 0.0001). After withdrawal of ACEi/ARB, sK and sKmax concentrations decreased to basal levels within 1 month. There were no significant changes of BW, IWG, SBP, DBP, Na, Hb, Kt/V, sBic, and PCRn in both periods. Conclusions: ACEi/ARB therapy is associated with an increased risk of hyperkalemia in anuric hemodialysis patients. The proportion of patients with normal sK concentrations decreased from 82 to 29% and with mild hyperkalemia increased from 18 to 52%. Severe hyperkalemia necessitating the interruption of ACEi/ARB therapy developed in 19% of patients. This suggests great caution in the widest utilization of this class of drugs in HD patients.

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**Introduction**

Cardiovascular disease is the primary cause of mortality and morbidity in the end-stage renal disease (ESRD) population and occurs in as many as 50–60% of ESRD patients [1]. Hypertension has been recognized as one of the principal contributors to death in these patients, its prevalence ranging from more than 80% in the United States [2], about 50% in Great Britain [3], and 70% in Italy [4]. The renin-angiotensin-aldosterone system (RAAS) plays key roles in the regulation of blood pressure, blood volume and cardiovascular function. Therapeutic manipulation of the RAAS by the use of angiotensin converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB) is an important treatment strategy for hypertension, heart failure, and diabetic patients.

In recent years, ACEi and ARB have been increasingly used in patients with ESRD with the aim to reduce fatal and nonfatal cardiovascular events and left ventricular mass [5]. However, recent evidence suggests that ACEi and ARB may not be superior to other antihypertensive agents in reducing cardiovascular risk in advanced kidney disease [6] and are often associated with an increased risk of hyperkalemia, particularly when administered in combination [7]. ACEi and ARB may have different effects on potassium levels that reflect differences in their actions on potassium homeostasis. Patients with diabetes, heart failure, or chronic renal failure treated with these drugs are at an increased risk of hyperkalemia compared with those without these conditions [8]. However, their effect on serum potassium (sK) concentrations in anuric patients on chronic HD treatment is still controversial.

Increased sK levels may induce characteristic electrocardiographic changes that can vary depending on the severity and rapidity of sK changes. sK ≥6 mmol/L are generally considered to be clinically significant and are estimated to complicate 1.4% of hospital admissions in general population [9, 10] and are associated with increased all-cause mortality, cardiovascular mortality, and arrhythmogenic death in HD patients [11]. The aim of the study has been to evaluate sK concentrations before and after ACEi/ARB therapy introduction in a cohort of prevalent anuric uremic patients on thrice weekly HD treatment.

**Patients and Methods**

A retrospective analysis of prospectively acquired data to evaluate sK changes before and after the assumption of ACEi/ARB therapy was done from 1 January 2015 to 31 December 2015. The study was part of standard antihypertensive treatment in prevalent HD patients of the O.U. of Nephrology, ASST Spedali Civili and University of Brescia. The primary outcome was the evaluation of pre-HD sK and peak-sK concentration changes in the 3 months before and after the introduction of the ACEi/ARB therapy. The secondary outcome was the proportion of patients who developed moderate or severe hyperkalemia after ACEi/ARB therapy introduction, and the proportion of patients requiring the reduction in dialysate K concentration or drug discontinuation. The study protocol, conducted according to the principles of Declaration of Helsinki, has been approved by the institute’s committee on human research. Informed consent was obtained from all study participants.

**Selection Criteria**

All the prevalent oligo-anuric patients on regular 3 times weekly HD treatment for at least 6 months who introduced ACEi or ARB as part of their current treatment of hypertension according to the attending doctor clinical judgment and prescription, double RAAS blockade (ACEi + ARB) therapy association was not allowed.

**Exclusion Criteria**

Those who had a stroke or myocardial infarction within the previous 3 months, active malignancy, or cachexia were not included in the study.

**Source of Data**

Data were acquired from a computerized data file that included all demographic, clinical, and laboratory data of the patients prospectively collected according to specific standard of care procedures followed in our Dialysis Unit.

**Study Protocol**

In the 3 months before (36 HD sessions) and after (36 HD sessions) the introduction of ACEi/ARB therapy, the following variables were evaluated in pre-dialysis after the long interdialysis interval: m-sK (mean value of 12 determinations; mmol/L), peak-sK

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Hyperkalemia and ACEi/ARB Therapy

Results

From a total prevalent HD population of 240 patients, 112 patients (67 men, 45 women), mean age 67 ± 14 years (range 22–89), on regular chronic HD treatment for 6–212 months (median 44 months), met the inclusion/exclusion criteria. Underlying renal diseases included chronic glomerulonephritis in 13 patients, renal vascular disease in 19 patients, diabetes in 20 patients, tubule-interstitial nephritis in 11 patients, polycystic kidney disease in 13 patients, and undiagnosed nephropathy in 36 patients.

Seventy-seven patients (pts) were on bicarbonate HD with high-flux synthetic membranes (Helixone FX80, Recovlear 400), 35 on online-HDF with high-flux synthetic membranes (Helixone FX Cordiax, Polysulph 210H), Blood flow rate ranged from 250 to 350 mL/min (median 300); dialysate flow rate was 500 mL/min. Dialysate fluid composition was sodium 140 mmol/L, potassium 2–3 mmol/L, calcium 1.5 mmol/L, bicarbonate 32 mmol/L, acetate 4 mmol/L, and glucose 1 g/L.

Table 1 shows the baseline clinical and laboratory characteristics of the 112 patients treated with ACEi/ARB drugs. Median urinary output was 50 mL/24 h (IQR range 0–200 mL/24 h). Cardiovascular disease was present in 40% of the patients and diabetes was in 18%. One hundred 2 patients (91%) were already on anti-hypertensive therapy. Of these patients, 26 pts (23%) were treated with beta blocker, 41 pts (37%) with calcium channel blocker, 15 pts (13%) with calcium channel blocker + beta blocker, and 20 pts (18%) with doxazosin or clonidine.

Table 1. Baseline clinical and laboratory characteristics of the patients studied

<table>
<thead>
<tr>
<th>Patients on study</th>
<th>112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>67±14</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>67 (60)</td>
</tr>
<tr>
<td>Dialysis vintage, months*</td>
<td>44 (6–212)</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>45 (40)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>20 (18)</td>
</tr>
<tr>
<td>Antihypertensive therapy, n (%)</td>
<td>101 (90)</td>
</tr>
<tr>
<td>Body weight, Kg, mean ± SD</td>
<td>69±17</td>
</tr>
<tr>
<td>Urinary output, mL/24h*</td>
<td>50 (0–200)</td>
</tr>
<tr>
<td>IDWG, Kg, mean ± SD</td>
<td>2.9±1.0</td>
</tr>
<tr>
<td>Pre HD SBP, mm Hg, mean ± SD</td>
<td>132±8</td>
</tr>
<tr>
<td>Pre HD DBP, mm Hg, mean ± SD</td>
<td>72±10</td>
</tr>
<tr>
<td>HD, n (%)</td>
<td>77 (69)</td>
</tr>
<tr>
<td>HDF-ol, n (%)</td>
<td>35 (31)</td>
</tr>
<tr>
<td>Kt/V, mean ± SD</td>
<td>1.46±0.21</td>
</tr>
<tr>
<td>PCRn, g/KgBW/day, mean ± SD</td>
<td>1.04±0.26</td>
</tr>
</tbody>
</table>

* Median (IQR).

IDWG, interdialytic weight gain; Pre HD SBP, pre dialysis systolic blood pressure; Pre HD DBP, pre-dialysis diastolic blood pressure; HD, bicarbonate hemodialysis; HDF-ol, online hemodiafiltration; IQR, interquartile range.
Table 2 shows the type and dosage of ACEi/ARB therapy: 53 out of 112 (47%) of the patients were treated with an ACEi and 59 out of 112 (53%) were treated with an ARB. No change in dosage was done. None had either drug in combination.

Change in sK Concentrations

Table 3 shows the pre-HD m-sK and peak-sK before and after 3 months of therapy in patients treated with ACEi or ARB drugs. Both m-sK and peak-sKmax increased significantly in both groups of patients. There was no significant difference in pre-HD m-sK concentrations between patients treated with ACEi or ARB drugs either before or after the introduction of each class of drug. For this reason, we considered all patients as a whole group in further analysis.

Figure 1a shows the m-sK pre-HD of the whole group of patients before ACEi/ARB introduction and after 3 months of ACEi/ARB therapy; m-sK increased from 5.0 ± 0.4 to 5.7 ± 0.6 mmol/L (p < 0.0001). Peak-sK increased from 5.3 ± 0.5 to 6.2 ± 0.6 mmol/L (p < 0.0001; Fig. 1b).

Figure 2 shows the proportion of patients with normal m-sK and mild or severe hyperkalemia before and after ACEi/ARB therapy. Patients with normal serum K concentrations decreased from 92 out of 112 (82%) before ACEi/ARB therapy to 33 out of 112 (29%) after ACEi/ARB therapy (p < 0.0001). Mild hyperkalemia increased from 20 out of 112 patients (18%) to 59 out of 112 (52%; p < 0.001). None of the patients had severe hyperkalemia before ACEi/ARB therapy, but after 3 months of ACEi/ARB therapy, 22 out of 112 (19%) developed severe hyperkalemia (p < 0.0001) necessitating drug interruption.

Pre-HD m-sK concentrations in patients that developed mild hyperkalemia varied from 5.1 ± 0.3 mmol/L before ACEi/ARB therapy to 5.8 ± 0.2 (p < 0.0001) after 3 months of ACEi/ARB therapy. None of these patients withdrew ACEi/ARB therapy, but 20 out of 63 (31%) reduced dialysate K concentration (from 3 to 2 mmol/L).

Figure 3 shows the pre-HD m-sK and peak-sK in the 22 patients that developed severe hyperkalemia before and at the time of ACEi/ARB therapy suspension (on average 1.5 ± 0.4 months after the start of therapy). m-sK varied from 5.2 ± 0.3 mmol/L before ACEi/ARB therapy to 6.5 ± 0.2 mmol/L at the moment of suspension of therapy (p < 0.0001). Peak-sK varied from 5.5 ± 0.3 mmol/L before ACEi/ARB introduction to 6.9 ± 0.3 mmol/L at the moment of suspension of therapy (p < 0.0001). After the suspension of ACEi/ARB therapy, m-sK returned to basal levels within 1 month (from 6.5 ± 0.2 to 5.2 ± 0.4 mmol/L; p < 0.0001).

Blood Pressure, Serum Sodium, Body Weight, Interdialytic Weight Gain, Serum Bicarbonate, Kt/V, and Normalized Protein Catabolic Rate Changes

Table 4 shows the values of pre-HD SBP and DBP, serum Na concentrations, BW, IDWG, Kt/V, serum bicarbonate concentrations, and nPCR in the 112 patients treated with ACEi or ARB drugs. No significant changes were observed.

Discussion

Our study clearly indicates that in prevalent anuric uremic patients on regular thrice weekly hemodialysis, ACEi or ARB therapy may result in a significant increase in pre-HD m-sK that lead to severe hyperkalemia, necessitating therapy suspension, in 19% of cases. Both ACEi and ARB are considered effective medications that can decrease cardiovascular morbidity and mortality with mechanisms partially independent from the normalization of high blood pressure [14, 15]. As such, their clinical use is very common even in HD patients. However, data concerning the side effect of hyperkalemia in patients on regular HD are still controversial [16]. For this reason, we conducted this observational study with the aim of evaluating the pre HD serum K concentrations after the introduction of an ACEi or an ARB as part of standard antihypertensive therapy in prevalent anuric HD patients. The vast majority of our patients (91%) were already on an antihypertensive treatment, most commonly with a calcium channel blocker and/or a beta

Table 2. Type and dosage of renin-angiotensin-aldosterone system blocker drugs in the 112 patients under study

<table>
<thead>
<tr>
<th>Drug</th>
<th>patients, n (%)</th>
<th>dose, mg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>41 (37)</td>
<td>5 (2.5–10)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>11 (10)</td>
<td>10 (5–20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>patients, n (%)</th>
<th>dose, mg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>44 (39)</td>
<td>50 (25–100)</td>
</tr>
<tr>
<td>Valsartan</td>
<td>16 (14)</td>
<td>80 (40–80)</td>
</tr>
</tbody>
</table>

* Median (IQR). IQR, interquartile range.
blocker. We decided to introduce an ACEi/ARB drug at low dosage (Table 2) because randomized [14] and clinical [17] trials suggested that the inhibition of the RAAS could contribute to reduce morbidity and mortality in dialyzed uremic patients and could improve left ventricular hypertrophy even independently from their hypotensive effect. As such, as shown in Table 4, in our patients, systolic and diastolic blood pressure levels did not change significantly, thereby showing on the average a good blood pressure control either before or after the introduction of ACEi/ARB treatment [18]. Notwithstanding this (Fig. 1a, b), 3 months of ACEi or ARB assumption resulted in a significant increase in pre-HD m-sK independent on the type of RAAS blocker used. In fact, as shown in Table 3, the magnitude of the increment in serum K concentrations, was very similar in patients treated with an ACEi or an ARB drug, and this was further confirmed by the fact that serum K concentrations either before or after the introduction of each class of drugs were not significantly different in the 2 groups of patients. Moreover, as shown in Figure 2, the proportion of patients with normal serum K concentrations decreased sharply from 82% before ACEi/ARB therapy to 29% after ACEi/ARB therapy ($p < 0.0001$), while the proportion of those with mild hyperkalemia (5.5 ≤ sK ≤ 6.0 mmol/L), increased from 18% before to 52% after ACEi/ARB therapy ($p < 0.001$). According to our protocol, ACEi/ARB were not stopped, but in 20 out of 63 patients (31%), it was necessary to reduce the dialysate K concentration from 3 to 2 mmol/L.
Another important observation was the finding that while none of the patients had severe hyperkalemia (sK >6 mmol/L) before ACEi/ARB therapy, 19% of the patients developed this complication after ACEi/ARB introduction ($p < 0.0001$) necessitating treatment interruption. In these patients (Fig. 3), m-sK and peak-sK varied from 5.2 ± 0.3 and 5.5 ± 0.3 mmol/L before ACEi/ARB therapy to 6.5 ± 0.2 and 6.9 ± 0.3 mmol/L at the moment of suspension of therapy ($p < 0.0001$; on the average 1.5 months from the start of treatment). This sequence of events is in agreement with reports of hyperkalemia following the blockade of the RAAS in patients with chronic renal failure still not on dialysis [19] and confirm previous data from Knoll et al. [20] that the risk of hyperkalemia continues even after regular dialysis therapy has been initiated and diuresis is lost. Since our patients had virtually no residual renal function, the observed increased risk of hyperkalemia is consistent with previous studies suggesting that the blockade of RAAS may have important effects on the extra-renal handling of potassium homeostasis. In a study involving anephric dialysis patients, the disposal of an acute potassium load was enhanced by mineralocorticoid administration and impaired by spironolactone suggesting a role of aldosterone on extrarenal cellular uptake of potassium [21]. Other studies have shown that intestinal potassium excretion is increased significantly in patients with renal failure [22], supporting the hypothesis that patients with end-stage renal disease adapt to decreased renal potassium excretion by increasing colonic potassium secretion. However, despite these adaptations, oligo anuric patients have limited reserve to tolerate any additional insult [23]. Addition of ACEi/ARB therapy can increase the risk of hyperkalemia interfering with the colonic secretion [24] and the extracellular removal of potassium [21]. This seems to be the most likely explanation of the phenomenon given that, as shown in Table 4, there were no concomitant significant variations in body weight, interdialytic weight gain, Kt/V, serum Na concentrations, serum bicarbonate concentrations, and protein catabolic rate either before or after ACEi/ARB treatment, thus excluding that each one of these variables could have exerted any significant influence on the variation in sK concentrations. In further support to this assumption is the observation that in these patients, the suspension of ACEi/ARB therapy returned sK concentrations to basal levels within 1 month (sK from 6.5 ± 0.2 to 5.2 ± 0.4 mmol/L; $p < 0.0001$). We chose to interrupt ACEi/ARB administration in patients who developed severe hyperkalemia due to the lack of effective agents for outpatient treatment of this condition [25]. Sodium polystyrene sulfonate may cause serious gastrointestinal adverse events that limit its extended use [26]. It is possible that the introduction of more effective and well-tolerated oral agents could change the future approach [23].

Our study has some strengths including the fact that patients were controls of their own, thus minimizing the possible confounding originating from individual differences in dietary habits or seasonal variations in potassium consumption, and other unmeasured variables. However, the study also has some limitations including the fact that patients were not randomized. As a result, it could be that
some patients with recurrent hyperkalemia at the time the study was started may have been excluded, thus introducing a possible selection bias. However, such a confounding would tend to weaken rather than to potentiate the observed association between RAAS blockade and hyperkalemia, and this gives further strength to our observations.

**Conclusion**

Treatment with ACEi/ARB is associated with an increased risk of hyperkalemia in anuric hemodialysis patients. The proportion of patients with normal m-sK concentrations decreased from 82% to 29% and those with mild hyperkalemia increased from 18% to 52%, necessitating in 31% of cases the reduction of K concentration in the dialysate. Severe hyperkalemia necessitating interruption of ACEi/ARB therapy developed in 19% of patients. This suggests great caution in the increasingly wider utilization of this class of drugs in anuric HD patients.

**Disclosure Statement**

Authors declare that they have no sponsorship or funding arrangements relating to their research and no possible conflicts of interest to disclose.

**Table 4.** Pre-HD systolic and diastolic blood pressure, serum sodium concentrations, body weight, interdialytic weight gain, Kt/V, serum bicarbonate concentrations, and normalized protein catabolic rate before and after 3 months of ACEi/ARB treatment in the 112 patients treated with ACEi or ARB drugs

<table>
<thead>
<tr>
<th></th>
<th>Before ACEi/ARB</th>
<th>After ACEi/ARB</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS, mm Hg</td>
<td>133±8</td>
<td>132±9</td>
<td>NS</td>
</tr>
<tr>
<td>PAD, mm Hg</td>
<td>72±10</td>
<td>71±9</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Na, mmol/L</td>
<td>139.0±1.3</td>
<td>138.3±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight, Kg</td>
<td>68±17</td>
<td>68±17</td>
<td>NS</td>
</tr>
<tr>
<td>IDWG, Kg</td>
<td>2.9±1.0</td>
<td>3.1±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.46±0.21</td>
<td>1.45±0.20</td>
<td>NS</td>
</tr>
<tr>
<td>Serum bicarbonate, mmol/L</td>
<td>23.2±1.3</td>
<td>23.4±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>PCRn, g/KgBW/day</td>
<td>1.04±0.26</td>
<td>1.05±0.25</td>
<td>NS</td>
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</table>

NS, not significant.

**References**


