Original Article

Safety of low-dose spironolactone administration in chronic haemodialysis patients

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Abstract

Background. Prevention of cardiovascular diseases is essential in chronic haemodialysis patients. Recently, low-dose spironolactone has been shown to decrease cardiovascular mortality in patients with severe heart failure. However, since haemodialysis patients are prone to hyperkalaemia, a known side effect of spironolactone, this treatment is not used in this population. We performed a study to assess whether low-dose spironolactone (3×25 mg/week) could be administered without inducing hyperkalaemia in haemodialysis patients.

Methods. The study design included a 2-week baseline period, followed by a 4-week treatment period in which doses of spironolactone were started at 12.5 mg three times/week for 2 weeks, then increased to 25 mg three times/week, and followed by a 2-week wash-out period. Fourteen patients receiving low-dose spironolactone after each dialysis were compared with 21 haemodialysis patients (control group).

Results. Low-dose spironolactone did not change mean serum potassium (4.9 ± 0.7 vs 4.9 ± 0.3 mmol/l: control). The mean plasma canrenone level induced by administration of spironolactone 25 mg three times/week in the 14 treated patients was 13 ± 5.3 ng/ml. Serum aldosterone was not significantly modified by the administration of spironolactone in these patients [before, median 0.35; interquartile range (IQR) 0.11–2.83 nmol/l vs after, median 0.22; IQR 0.12–0.60 nmol/l, NS]. Dietary potassium intake and the use of ion-exchange resin, angiotensin-converting enzyme inhibitors and β-blockers were similar for the two groups throughout the study.

Conclusion. This non-randomized and non-blinded study shows that administration of 25 mg spironolactone thrice weekly is not associated with an increased frequency of hyperkalaemia in haemodialysis patients when they are carefully monitored. More studies are required, however, before concluding that spironolactone administration is safe in the chronic haemodialysis population.

Keywords: cardiovascular; haemodialysis; hyperkalaemia; spironolactone

Introduction

Cardiovascular disorders are common in chronic haemodialysis patients, and account for $\sim$50% of the deaths in this population, which is affected by a mortality rate 10–20 times higher than in the general population [1–4]. New therapeutic strategies are needed to decrease this rate of cardiovascular deaths among haemodialysis patients. The RALES study showed a dramatic reduction of morbidity and mortality in patients suffering from severe heart failure, with inhibition of aldosterone by low-dose spironolactone treatment (25 mg/day) associated with maximal therapy [5]. Aldosterone is a potent mediator of myocardial and vascular fibrosis, and reduced levels of serum markers of cardiac fibrosis were measured after treatment with low-dose spironolactone [6]. Aldosterone is also a potent kaliuretic hormone but, despite concomitant treatment with angiotensin-converting enzyme inhibitors (ACEIs) in 94% of patients, use of low-dose spironolactone did not increase the prevalence of hyperkalaemia [5]. However, no patients with severe chronic renal failure were enrolled in this study. Recently, life-threatening hyperkalaemia during combined therapy with ACEIs and spironolactone has

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been reported in patients with moderate chronic renal impairment [7]. Though renin–angiotensin system blockade currently is recommended in haemodialysis patients, it has been reported to be independently associated with an increased risk of developing hyperkalaemia [8]. Serious hyperkalaemia is reported to occur in 10% of haemodialysis patients and to be responsible for 3–5% of deaths in dialysis [9]. However, the risk of worsening hyperkalaemia with low-dose spironolactone has not been estimated so far in such patients. In chronic renal failure patients, the role of aldosterone in extrarenal homeostasis of potassium (intestinal and cellular) is not well delineated. Patients with chronic renal failure tend to have an increased intestinal excretion of potassium [10]. Anephric haemodialysis patients treated with high doses of spironolactone (300 mg/day) had higher serum potassium levels after an oral potassium challenge without modifying the fecal excretion of potassium [11]. This suggests a role for aldosterone in the cellular uptake of potassium in these patients. With modest dietary potassium intake, administration of spironolactone seemed to influence serum potassium only transiently [11].

Spironolactone has a bioavailability of ∼90% and is metabolized rapidly by the liver. Its active metabolites, canrenone and 7α methylspironolactone, have a long half-life (15–20 h) and 95% plasma protein binding [12]. Both metabolites are partially eliminated by the kidney (∼50%), and spironolactone dosage must be decreased in end-stage renal failure (ESRF). We hypothesized that 25 mg three times weekly in haemodialysis patients will be equivalent to the low-dose spironolactone regimen used (25 mg/day) in patients with normal or slightly impaired renal function [5] and may be administered without increased risk of severe hyperkalaemia.

Subjects and methods

Patients and design of the study

Thirty-five patients on chronic haemodialysis treatment (three sessions a week) were enrolled in a non-randomized and non-blinded study. Fourteen patients agreed to receive spironolactone and were included in the spironolactone group. Of these, 12 were anuric or had a residual urine output of < 300 ml/day. Twenty-one haemodialysis patients declined to receive spironolactone but accepted to be enrolled in the control group. Besides our routine procedures and controls, the protocol of the study included a dietary survey and blood potassium measurements before each haemodialysis session during the study period. The ethics committee of the Department of Medicine approved the study.

Design of the study

The study design included a 2-week baseline period, followed by a 4-week treatment period in which doses of spironolactone (Aldactone®, Pharmacia AG, Switzerland) were started at 12.5 mg three times/week taken just after the

haemodialysis session for 2 weeks, then increased to 25 mg three times/week, and followed by a 2-week wash-out period. Throughout the study, measurements of serum potassium were performed before each dialysis session in both groups. All patients had a haemodialysis solution with 3 mmol/l of potassium, which is part of our routine procedure. Serum aldosterone levels of patients treated with spironolactone were determined after 2 weeks (run-in) and 6 weeks (spironolactone 25 mg three times/week). As spironolactone was administered three times a week and has a much shorter half-life than canrenone, its main metabolite, we measured the plasma level of canrenone after 6 weeks in the spironolactone-treated patients. This measurement was done before the dialysis session and the next administration of spironolactone. Prior to the observation period, dietary advice was provided to all haemodialysis patients, and a basic dietary survey was answered at each dialysis session throughout the study. Daily dietary potassium intake was then estimated by dietitians unaware of patient' group attribution. Interdialytic dietary potassium intake was ranked from 5 to 1 (high, always > 2700 mg/day; high–medium, not constantly > 2700 mg/day; medium, always 2000–2700 mg/day, medium–low, between 2700 and < 2000 mg/day; and low, always < 2500 mg/day). ECGs were performed on a weekly basis in the spironolactone-treated group.

Serum aldosterone measurements

Blood was collected from supine patients and serum was frozen at –20°C. Before assay, samples were slowly thawed at room temperature and aldosterone was measured by direct solid-phase radioimmunoassay, using a commercially available kit (Diagnostic Products Corporation, Los Angeles, CA), according to the supplier's instructions. The intra-assay precision (CV) was between 2.7 and 8.3% and the interassay precision between 3.6 and 10.4%, with a limit of detection of 0.04 nmol/l. Cross-reactivity of the antibody with spironolactone was estimated to be 0.06%. Expected values for normal supine patients are 0.03–0.44 nmol/l [13].

Plasma canrenone measurements

Frozen plasma samples were analysed by reversed-phase high-performance liquid chromatography (HPLC) after solid phase extraction by a bioanalytical company (Biokinet GmbH, Vienna, Austria). HPLC was performed on a reverse phase C18 column with an eluent of methanol/acronitrile/water and UV detection at 280 nm [14].

Statistical analysis

We compared serum potassium in the spironolactone and control groups, adjusting for study period, and taking into account correlations among repeated observations in the same patient by means of generalized estimating equations. All tests of statistical significance for continuous (Student's *t*-test) and categorical (χ^2 test) were two-tailed. Non-parametric tests were used for non-normally distributed data. Calculations were performed using SPSS, version 10.0 (Chicago, IL) and STATA, version 7, Stata Corp (College Station, TX).
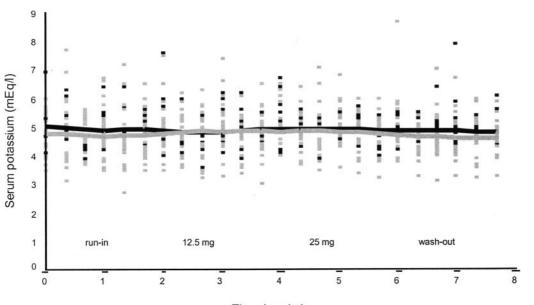
Results

Patient characteristics

Baseline demographic and clinical characteristics of our patients are listed in Table 1 and did not differ between the two groups (spironolactone and control) except for a trend toward a longer duration of renal replacement therapy for the spironolactone group. In particular, use of ion-exchange resins was similar in both groups, as well as the use of medications known to have hyperkalaemic properties.

Serum potassium, dietary potassium and aldosterone levels

Serum potassium did not change in the spironolactone group during the whole study period (Figure 1). Mean baseline, 12.5 mg period, 25 mg period and wash-out period serum potassium levels were respectively

Table 1. Characteristics of study patients

	Spironolactone group ($n = 14$)	Control group ($n = 21$)	
Age (years)	54 ± 14	59 ± 17	NS
Renal replacement therapy (months) (median + IQR)	67 (8–183)	24 (11–100)	NS
Diabetes	2	5	NS
Residual renal function	2	6	NS
ACEIs/ARBs	8	11	NS
β-Blockers	5	6	NS
HCO_3 (mmol/l)	22.9 ± 1.9	23.5 ± 2.8	NS
Kt/V	1.27 (0.2)	1.22 (0.22)	NS
Ion-exchange resin	8	8	NS

5 ± 0.4, 4.9 ± 0.4, 4.9 ± 0.3 and 4.9 ± 0.4 mmol/l in the spironolactone group, and 4.8 ± 0.8, 4.9 ± 0.7, 4.9 ± 0.7 and 4.6 ± 0.7 mmol/l in the control group. In a multivariate analysis adjusted for baseline kalaemia, spironolactone treatment was associated with a modest reduction in serum potassium (-0.2 mmol/ml, $P = 0.016$). Dietary potassium intake was (on a scale from 5 to 1) similar for the two groups throughout the study [25 mg spironolactone period, 2.6 ± 1.2 (spironolactone) vs 2.2 ± 0.9 (control), NS] and did not correlate with serum potassium. The mean plasma canrenone level in the 14 patients treated with spironolactone 25 mg three times/week was 13 ± 5.3 ng/ml. Use of ion-exchange resin was comparable between the two groups during the study period. Basal serum aldosterone levels were not significantly modified by the administration of spironolactone in the 14 treated patients [before, median 0.35 nmol/l; interquartile range (IQR) 0.11–2.83 nmol/l vs after, median 0.22 nmol/l; IQR 0.12–0.60 nmol/l, NS]. There was no correlation between serum aldosterone and potassium levels.

Electrocardiograms

The weekly ECGs were analysed by two cardiologists unaware of the presence of spironolactone treatment; no signs of hyperkalaemia were found.

Discussion

In this non-blinded, non-randomized study, 25 mg of spironolactone administered thrice weekly to haemodialysis patients did not increase serum potassium.

Fig. 1. Serum potassium in 14 haemodialysed patients included in the study (black dots) and in 21 controls who declined the study (grey dots). Lines represent non-parametric regression lines. Patients in the spironolactone group received no treatment during weeks 1–2 (run-in) and 7–8 (wash-out), 12.5 mg after each haemodialysis session during weeks 3–4, and 25 mg during weeks 5–6. Control patients received no spironolactone throughout.

These results demonstrate that the cautious administration of spironolactone should not be contraindicated in this population known to have a dramatic increase in cardiovascular mortality.

This study does have some limitations, however. First, the dose used in this study is below the average dose used in the RALES study. Based on the metabolism of spironolactone, we have estimated that similar plasma drug levels in haemodialysis patients should be obtained with 25 mg given three times a week. However, the demonstration of a pharmacological effect using markers such as those used in the RALES dose-finding study (sodium retention test, N-terminal pro-ANF and PRA levels) was not possible in this study because of the renal failure. As no spironolactone or canrenone determination was performed in the RALES study, we do not know whether low-dose spironolactone three times/week in haemodialysis patients provides similar plasma levels as those reached after daily administration. Mean plasma canrenone level, determined at 48 h in our study group, was ∼50% lower than the mean plasma canrenone level obtained at 24 h in normal volunteers receiving a conventional dose of 50 mg spironolactone daily over 5 days [15]. Therefore, we estimate that 25 mg of spironolactone three times/week in haemodialysis patients is equivalent to the average dose used in the RALES study.

Another important limitation is the design of the study. This was a non-blinded, non-randomized study. To include only patients who accepted to receive spironolactone may have introduced some bias favouring a tighter potassium control. To examine this possibility, we enrolled all the patients who declined to receive spironolactone in the control group. The patients included in the study were closely monitored (serum potassium dosage at each dialysis), and most of them were compliant with the low potassium diet. Our dietary survey, however, did not detect major differences in dietary potassium intake between the two groups or in the use of exchange resins. It is unlikely that the participating subjects deliberately restricted their potassium intake. However, we cannot rule out the possibility that low-dose spironolactone would aggravate hyperkalaemia in the case of acutely increased dietary potassium intake, exertional hyperkalaemia, hyperglycaemia or digoxin toxicity. Similarly, more than half of our patients were also treated with ACEIs or angiotensin receptor blockers (ARBs). The low number of patients included in the study prevents us from asserting that low-dose spironolactone administration in haemodialysis patients treated concomitantly with ACEIs or ARBs is completely safe. In addition, most of the patients in the spironolactone-treated group had no residual renal function, and we cannot extrapolate our results to haemodialysis patients with residual diuresis, where renal potassium excretion, albeit reduced, is still present. Finally, due to its molecular weight and its high protein binding [12], plasma levels of spironolactone and its active metabolites should be unchanged by haemodialysis, but more

data on the pharmacokinetics of these compounds during haemodialysis are necessary. Hyperkalaemia induces the activation of both renal and extrarenal homeostatic mechanisms to decrease serum potassium. Long-term extrarenal potassium homeostasis is regulated principally by gastrointestinal excretion in haemodialysis patients. However, low-dose spironolactone does not seem to interfere significantly with colonic adaptation to hyperkalaemia in haemodialysis patients. Our results are in agreement with a previous study investigating the action of aldosterone in anephric haemodialysis patients, where seven patients were challenged with 300 mg of oral spironolactone daily *vs* no medication during 3 days. Spironolactone was found to induce a small and transient rise in potassium levels after an acute potassium load. However, no persistent hyperkalaemia and no change in intestinal potassium excretion were demonstrated [11]. Recently, low-dose spironolactone (25 mg) administered every day for 10 months was not found to elevate serum potassium above 5.5 mmol/l in a patient treated by peritoneal dialysis and suffering from heart failure [16]. This treatment resulted in a significant improvement of his ejection fraction (from 32 to 46%).

Plasma aldosterone levels become elevated with advanced renal failure and participate in the adaptative mechanisms of chronic renal failure. Haemodialysis patients are characterized by high basal levels of plasma aldosterone [13] and, recently, plasma aldosterone concentrations were shown to be related to left ventricular hypertrophy in non-diabetic ESRF patients [15]. In our patients, mean basal serum aldosterone levels were not high, but a wide range of values was observed which might be due to concomitant renin–angiotensin system blockade. Similarly, no significant change in serum aldosterone levels was demonstrated in the spironolactone-treated group, making it unlikely that low doses of spironolactone enhance aldosterone secretion.

We do not know whether 25 mg of spironolactone administered three times weekly would be effective in decreasing cardiovascular mortality in these patients, and it is unreasonable to expect cardiovascular data in a single centre short-term trial. Regarding the high cardiovascular mortality in these patients, the results of this study are encouraging because they open up the possibility of a treatment which has demonstrated its efficacy in patients with normal renal function. However, because of several limitations (non-randomized and non-blinded, administration of kayexelate, tight monitoring of serum potassium levels), this study has to be considered as a pilot study and we cannot conclude that spironolactone administration (25 mg three times/week) will be equally safe under other conditions. Indeed, more clinical trials to study thoroughly the pharmacokinetics of low-dose spironolactone during haemodialysis and to assess the safety of spironolactone in a larger haemodialysed population should be performed before drawning any conclusions regarding the safety of spironolactone in this population.

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