Original Article

Is spironolactone safe for dialysis patients?

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Abstract

Background. Spironolactone is useful in heart failure, but is not given to dialysis patients for fear of hyperkalaemia. This study evaluated the safety of spironolactone administration in haemodialysis patients.

Methods. Fifteen haemodialysis outpatients with mean serum potassium <5.6 mEq/l over the preceding 4 months were treated with spironolactone 25 mg daily for 28 days. Serum potassium was measured before every haemodialysis during the study. Aldosterone and renin were measured at the beginning and end of the study. Patients were monitored for side effects. Data were examined with a paired t-test, with patients serving as their own controls and P < 0.05 considered significant. A sample size of 14 was required to achieve a power of 0.8 and a P = 0.05 to detect a potassium difference of 0.5 ± 0.6 mEq/l. All patients were analysed as intention-to-treat.

Results. The mean potassium level was 4.6 ± 0.6 mEq/l at baseline and 4.9 ± 0.9 mEq/l at study completion (P = 0.14). Thirteen patients completed the trial with no potassium levels >6.0 mEq/l. Four patients had potassium levels between 5.5 and 6.0 mEq/l. One patient was withdrawn at day 20 after developing hyperkalaemia (7.6 mEq/l). Another patient was withdrawn at day 25 after missing a dialysis treatment. There were no differences in either baseline or 28 day aldosterone or renin levels (16.8 ± 28.8 vs 11.7 ± 6.1 ng/dl and 3.5 ± 3.9 vs 3.5 ± 3.5 ng/ml/h, respectively). Infrequent side effects included dry mouth, nosebleed, pruritis, gynecomastia and diarrhoea. No significant leukopenia or anaemia was noted.

Conclusions. Spironolactone may be considered as a treatment option for selected chronic haemodialysis patients with heart disease.

Keywords: hyperkalaemia; aldosterone; spironolactone

Introduction

Patients with end-stage renal failure (ESRF) on haemodialysis die of heart disease at 20–40 times the rate of the general population [1]. According to the United States Renal Data System, cardiovascular disease accounts for >44% of this mortality [2]. Heart disease is almost universal in dialysis patients, who are over-represented in coronary artery disease, hypertension and left ventricular failure [3]. Increasing use of percutaneous and surgical options for heart disease has not altered the grim prognosis for dialysis patients [4–6].

Animal and human data implicate the renin–angiotensin–aldosterone system (RAAS) in the pathophysiology of congestive heart failure [7–9]. In addition to promoting salt retention, aldosterone mediates cardiac remodelling and myocardial collagen deposition [10–12]. Spironolactone, a competitive inhibitor of aldosterone, was administered to patients with chronic cardiomyopathy in the Randomized Aldactone Evaluation Study (RALES) trial [13,14]. Patients with severe left ventricular dysfunction had 30–35% reduction in the risk of death, cardiac death and hospitalization [14].

Hyperkalaemia is a known side effect of spironolactone. The RALES investigators excluded patients with significant renal failure from enrolment, based on a preliminary trial of a subset of patients receiving between 12.5 and 75 mg spironolactone daily. Among patients already selected for a serum creatinine ≤2.0 mg/dl, values >1.6 mg/dl were associated with a higher incidence of hyperkalaemia, as was the use of angiotensin-converting enzyme (ACE) inhibitors and higher dosages of spironolactone. The incidence of serum potassium ≥5.5 mmol/l in patients taking 25 mg spironolactone daily was 13% and the mean increase seen at 12 weeks was 0.37 mmol/l [13].
Clinicians have traditionally avoided giving inhibitors of the RAAS to renal failure patients to avoid precipitating hyperkalaemia and have extended this precaution to ESRF patients. The modest antihypertensive and diuretic effects of spironolactone have never justified formal investigation of this concern. Hyperkalaemia might be a less significant issue for dialysis patients because potassium levels are regulated by dialysis treatments, rather than by renal tubular function. ACE inhibitors have proven to be well-tolerated and useful in ESRF, despite similar concerns.

The current study, in which spironolactone is administered to a chronic haemodialysis population under close laboratory surveillance, tests the hypothesis that spironolactone can be administered safely to ESRF patients without development of significant hyperkalaemia.

**Subjects and methods**

Patients at a single outpatient haemodialysis unit affiliated with a teaching hospital were studied after obtaining written informed consent, the project having been approved by the Institutional Review Board of Allegheny General Hospital.

Eligibility for inclusion was determined upon review of medical records and laboratory data for 4 months immediately preceding enrolment. Adult haemodialysis patients met the criteria for inclusion if chronic dialysis had proceeded for at least 4 months and expected survival was >6 months. Adequate dialysis clearances (monthly urea reduction ratios consistently >65%) were also required. Exclusion criteria included an average serum potassium >5.5 mEq/l over the previous 4 months or any single serum potassium level of >6.0 mEq/l, urea reduction ratios of <65%, a history of failure to take medications reliably or of failure to attend scheduled dialysis treatments, an unstable vascular access, hospital admission within the past 30 days, allergy to spironolactone, history of ventricular arrhythmia and pregnancy or inability to achieve effective contraception.

**Treatment**

Participants received 25 mg oral spironolactone each day for 28 days. Study medication was provided by the hospital pharmacy from a single bulk stock of the drug. Pre-enrolment medications, including ACE inhibitors, were continued throughout the study with no changes other than the addition of the study drug. Six patients took ACE inhibitors during the study.

**Assessments**

Complete blood count (CBC), serum aldosterone and plasma renin activity were obtained at baseline and repeated after completing the study medication on day 28. An additional CBC was drawn after 14 days of spironolactone treatment. Serum potassium was determined prior to initiation of the study drug and before each dialysis session. Potassium values between 5.6 and 6.0 mEq/l were treated with a reduction of the dialysis potassium concentration by 1.0 mEq/l, unless the dialysate potassium concentration was already 1.0 mEq/l, in which case the patient continued in the study with the dialysate unchanged. Any serum potassium value >6.0 mEq/l or any failure to attend a scheduled haemodialysis treatment necessitated withdrawal from the study and discontinuation of spironolactone.

The primary outcome assessment was the presence or absence of hyperkalaemia (defined as serum potassium >6.0 mEq/l). Secondary endpoints included effects upon blood counts, renin and aldosterone levels and adverse events. Dialysis nurses assessed the patients before each dialysis session and the investigators assessed each patient at least once per week for any adverse events, which were considered serious adverse events if additional therapy or hospitalization was required.

**Statistical analysis**

Serum potassium concentrations of all patients in the dialysis unit were analysed during an 11 month period prior to the study. A Gaussian distribution of serum potassium levels was noted with most values between 4.5 and 5.5 mEq/l. The mean value was 4.9 ± 0.6 mEq/l. Hyperkalaemia (serum potassium >6.0 mEq/l) occurred 77 times over 940 patient-months, an incidence of 8.2%. Based on these data, 14 patients would be required to detect a 0.5 mEq/l increase in serum potassium with a power of 80% at P = 0.05. Five comparisons were made using the paired t-test to determine if potassium levels increased during the study period.

**Results**

Fifteen patients were enrolled and 14 patients completed the study. Patient demographics were typical of the overall population of the dialysis unit (Table 1). Pre-enrolment medications were continued throughout the study.

**Primary assessment**

Mean serum potassium levels were 4.6 ± 0.6 mEq/l at baseline and 4.7 ± 0.6 mEq/l at study completion (P = 0.19) (Figure 1). Spironolactone therapy was successfully undertaken for the full 28 day course in 13 of 15 subjects (86.7%). Nine patients completed the trial with all serum potassium levels < 5.6 mEq/l.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 (33–87)a</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>10/5</td>
</tr>
<tr>
<td>Race (black/white)</td>
<td>11/4</td>
</tr>
<tr>
<td>Patients taking ACE inhibitors</td>
<td>6</td>
</tr>
<tr>
<td>Baseline potassium levels (mEq/l)b</td>
<td>4.8 ± 0.5</td>
</tr>
<tr>
<td>Mean urea reduction ratio (%)</td>
<td>75 ± 7</td>
</tr>
</tbody>
</table>

aValue reported as mean and range.
bValue reported as mean ± SD of all patients for a 4 month period pre-study.
requiring no adjustments in the haemodialysis prescription. Four patients had serum potassium levels between 5.6 and 6.0 mEq/l. Dialysate potassium was decreased by 1.0 mEq/l in two of these patients. The remaining two patients were already prescribed dialysate potassium of 1.0 mEq/l, the lowest available in the dialysis unit, and continued to take spironolactone without adjustment in dialysis prescription. None of these four patients subsequently had any serum potassium levels > 5.5 mEq/l.

Spironolactone was discontinued after ≥20 days of treatment in two subjects. One of these patients missed a dialysis treatment on day 25 and was removed from the study. His serum potassium level was 7.5 mEq/l on day 27, after 5 days without dialysis, and resolved with resumption of haemodialysis. A second patient developed hyperkalaemia (7.6 mEq/l) on day 20 of treatment and the study drug was discontinued according to the study protocol (Figure 2). Serum potassium values of all patients were included in the statistical analysis until the time that study medication was stopped.

Secondary assessments

Serum renin and aldosterone values showed no significant differences between baseline and post-treatment values (16.8 ± 28.8 vs 11.7 ± 6.1 ng/dl and 3.5 ± 3.9 vs 3.5 ± 3.5 ng/ml/h, respectively). CBCs and platelet counts were unchanged.

No serious side effects were noted during the 28 day study period and no patient required discontinuation of spironolactone for adverse events. Observed side effects included dry mouth (n = 2), nosebleed (n = 1), mild pruritis (n = 1), gynecomastia (n = 1) and transient diarrhea (n = 1). These side effects were mild and transient.

Discussion

Spironolactone administered to stable, chronic haemodialysis patients in low doses resulted in serious hyperkalaemia (serum potassium ≥6.0 mEq/l) in only one of 14 patients who adhered to prescribed haemodialysis treatments. Thirteen patients avoided severe hyperkalaemia (serum potassium ≥6.0 mEq/l) although two required an adjustment in dialysis prescription. One patient required discontinuation of spironolactone due to development of severe hyperkalaemia and another patient developed hyperkalaemia after 5 days without any haemodialysis treatment. There was no significant shift in the weekly average serum potassium
level in the study group (Figure 2). This was not significantly different from the incidence of hyperkalaemia in the study population (8.0%) or the entire dialysis unit (8.2%) during the preceding 11 month period.

Spironolactone was administered safely to haemodialysis patients and was well tolerated with very few adverse events reported. Importantly, none of the adverse events experienced resulted in spironolactone withdrawal.

Hyperkalaemia due to spironolactone is not a trivial concern. Schepkens [15] reported 25 non-dialysing patients with creatinine clearances of 25–35 ml/min having episodes of hyperkalaemia > 6.0 mEq/l while taking both spironolactone and ACE inhibitors. These patients had haemodialysis treatments, intensive care unit admissions and cardiac arrests. Severe but reversible deterioration of renal function had occurred in nearly all cases, often due to superimposed volume depletion. The mean dose of spironolactone was 57 mg and the authors concluded that a daily dose of 25 mg should not be exceeded and that elderly and at-risk patients should be monitored closely. Our study patients were assessed thrice weekly for potassium levels and we did not exceed the RALES trial spironolactone dose of 25 mg.

ESRF patients may be at lower risk than their non-dialysing counterparts with chronic renal disease, because dialyser clearance of potassium is not reduced by spironolactone. Increased extrarenal conservation of potassium in anuric ESRF patients has been seen with high doses of spironolactone, nearly eight times the dose used in the current study [16].

Our low incidence of hyperkalaemia depended in part upon using the same low doses of spironolactone as the RALES trial. Most of the limited experience with spironolactone in ESRF used doses of spironolactone between 300 and 400 mg per day [17,18]. We chose a lower dose because spironolactone exerts significant effects on cardiac morbidity and mortality at doses well below those required for effective anti-hypertensive or diuretic action. Aldosterone blockade prevents the collagenous remodelling of the ventricles seen in rat models of congestive heart failure due to aortic and renovascular banding [10,11] and other studies have shown reduction of circulating collagen precursors, reduced cardiac uptake of norepinephrine and reductions in ventricular ectopy and heart rate variability in humans and animals [8,9]. Spironolactone 25 mg was given to five haemodialysis patients in one study for 3 days. At this low dose, spironolactone decreased diastolic and mean arterial pressures, as well as right heart pressures, pulmonary artery pressures and systemic and pulmonary vascular resistance. The haemodynamic effects of spironolactone suggested increases in venous and arterial compliance, which could help explain the efficacy of spironolactone in heart failure. Serum potassium levels were unchanged [19].

The importance of these results is underscored by the tremendous burden of cardiac morbidity and mortality borne by dialysis patients. Spironolactone is now considered to be a standard of care in the management of heart failure and our results suggest that low-dose spironolactone may be given safely to dialysis patients.

The limitations of the current study include a small population sample. Future studies on larger patient samples are indicated to confirm these data. This small pilot study is not powered to make any conclusions about the additive impact of ACE inhibition and spironolactone, but we did not observe a trend towards increased hyperkalaemia in patients taking both drugs. In addition, rigorous patient selection within our study population may have contributed to the positive results, as our subjects were younger and more compliant than an unselected haemodialysis population. Generalizing the safety of spironolactone to all patients on dialysis may not, therefore, be valid. Patients undergoing peritoneal dialysis were not studied, though they might be expected to have overall less hyperkalaemia than patients on haemodialysis. Prudent selection of stable, compliant patients without predilection for severe hyperkalaemia is still advisable.

In summary, this study demonstrates that spironolactone can be administered safely to stable compliant haemodialysis patients. Additional studies will be required to determine whether reduction in the risks of cardiovascular morbidity and mortality in ESRF patients parallels risk reduction in the general population.

Conflict of interest statement. None declared.

References


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