

Pilot randomised double-blind controlled trial of high-dose spironolactone in critically ill patients receiving a frusemide infusion

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Hypernatraemia is relatively common in intensive care patients,¹ and is associated with increased morbidity and mortality.² Associated clinical problems include altered mental state, seizures, coma and death.³ A potential cause of hypernatraemia in the ICU is the administration of loop diuretics such as frusemide to treat conditions including pulmonary oedema and generalised fluid overload states.⁴ Critical care clinicians often aim to achieve a negative fluid balance in patients to improve their physiological status or clinical outcomes,⁵⁻⁷ and frusemide is generally preferred for this purpose. Hypokalaemia is also common in critically ill patients. Low serum potassium levels may be exacerbated by loop diuretics and frequently necessitate potassium supplementation.⁸

Spironolactone is a competitive aldosterone receptor antagonist that causes natriuresis and promotes potassium conservation by the kidney.⁹ It is an established therapy for congestive cardiac failure,¹⁰⁻¹² cirrhosis with ascites,¹³⁻¹⁵ primary hyperaldosteronism (Conn's syndrome),⁹ and female hirsutism.¹⁶ However, the most common use of spironolactone is to offset potassium wasting caused by commonly used diuretics, such as loop diuretics and thiazides. Its long-term use in the outpatient setting has clear benefits to some patients, but it has also emerged that close monitoring of electrolytes, particularly serum potassium levels, is necessary.^{9,17}

The effects of spironolactone on the serum electrolyte profile may be quite beneficial in critically ill patients, particularly those prone to derangements in sodium and potassium balance associated with loop diuretics. We hypothesised that the administration of spironolactone would prevent or attenuate hypernatraemia in patients receiving frusemide infusions by increasing natriuresis. We conducted a randomised double-blind placebo-controlled clinical pilot study to test this hypothesis.

Methods

The study protocol was approved by the Austin Hospital Institutional Ethics Committee and the Victorian Civil and Administrative Tribunal (VCAT). Written informed consent was obtained from each patient's surrogate decision maker,

ABSTRACT

Background: Hypernatraemia may develop during intravenous infusion of frusemide. Spironolactone is an aldosterone antagonist that promotes natriuresis and may attenuate such hypernatraemia, but its effect in this setting has not been previously studied.

Objective: To assess whether the administration of spironolactone to ventilated patients receiving a frusemide infusion attenuates the increase in serum sodium concentration.

Design and setting: Randomised, double-blind, placebo-controlled trial (January 2005 to December 2006).

Patients: 20 patients with a serum creatinine concentration < 300 µmol/L who were undergoing mechanical ventilation in the intensive care unit and had begun a frusemide infusion as treatment for fluid overload within the previous 24 hours.

Methods: Patients were randomly allocated to receive either spironolactone (100 mg three times daily) or placebo by nasogastric tube for the duration of the frusemide infusion. Daily serum levels of urea and creatinine, 24-hour urine sodium and potassium levels, fluid balance and 24-hour blood levels of aldosterone, human atrial natriuretic peptide and plasma renin activity were measured throughout the period of frusemide infusion.

Results: Change in serum sodium concentration over 48 hours from baseline was 3.0 mmol/L for placebo versus -1.0 mmol/L for the spironolactone group ($P=0.08$). Change in serum potassium concentration did not differ between the groups (0.125 mmol/L over 48 hours). There were no significant differences in total urinary sodium or potassium excretion. Serum creatinine, urea, urine volume, fluid balance, potassium requirements and hormone levels were similar in both groups.

Conclusions: In this pilot study, the administration of high-dose spironolactone to ventilated critically ill patients receiving frusemide by infusion had no significant effects on serum sodium level, natriuresis or potassium balance when compared with placebo.

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and VCAT also gave permission for patients to participate in the study.

Patients were included if they were over 18 years of age, were mechanically ventilated, and had been commenced on frusemide by continuous intravenous infusion by the treating intensive care physician for fluid overload within the previous 24 hours. Exclusion criteria were pregnancy, hypersensitivity to spironolactone, hyperkalaemia (serum K concentration >6.0 mmol/L), significant renal failure (serum creatinine concentration >300 μ mol/L), renal replacement therapy, and inability to receive nasogastric medication.

Study design

Twenty patients who were mechanically ventilated and receiving frusemide by continuous intravenous infusion were enrolled between January 2005 and December 2006. The frusemide infusion was managed by the treating medical and nursing staff in accordance with clinical fluid balance goals. Half the patients were randomly assigned to receive spironolactone (100 mg three times daily) via enteral feeding tube, and half received a matched placebo, continued for the same duration as the frusemide infusion. The study drug and matching placebo were prepared and packaged by hospital pharmacy staff. The spironolactone dose was chosen as it is at the upper range of dosing recommendations,⁹ represents a sufficiently high dose to expect a detectable biological effect, and is recognised to be safe.¹⁰ Enteral administration was necessary as no commercial intravenous preparations are available. Absorption of spironolactone from the gastrointestinal tract is complete and rapid, with bioavailability approaching 100% when it is given with food.¹⁸

ICU nursing staff administered supplemental potassium (intravenous and/or enteral potassium chloride) to maintain a serum potassium concentration greater than 4.0 mmol/L, in accordance with usual practice.

Data collection

Baseline data included age, sex, weight, APACHE III scores on ICU admission and for the duration of ICU stay. In addition, blood biochemistry parameters over the course of clinical management were recorded. After randomisation, daily measurements of serum electrolytes were obtained. Twenty-four-hour urine samples were assessed to determine concentration and total daily excretion of sodium, potassium, urea and creatinine. Daily fluid balance and total daily frusemide dose were measured. Serum levels of aldosterone, human atrial natriuretic peptide (h-ANP) and angiotensin II (AT II), and plasma renin activity were measured before commencement of the study drug and at the end of Day 1.

Given the fluid overload state necessitating diuretics in all participants, fluids were administered only if required for nutrition and drug therapy. All participants received enteral nutrition (Isosource 1 Calorie/mL, Novartis Nutrition Corporation, Minneapolis, Minn, USA), and drug infusions were provided in 5% dextrose unless incompatible. Hypotonic fluids were given if clinically important hypernatraemia (serum Na concentration >150 mmol/L) developed during the frusemide infusion. All patients received standard intensive care monitoring and therapy as prescribed by the treating intensive care physician. Other aspects of management in the ICU were not affected by participation in the study.

Outcome measures

The primary outcome measure was the change in serum sodium level occurring over the duration of frusemide therapy. Secondary endpoints included changes in urinary electrolyte profile and hormonal regulation of sodium and potassium balance (aldosterone, h-ANP and plasma renin activity), daily fluid balance, frusemide dose, potassium replacement requirements, and changes in arterial oxygenation.

Statistical analysis

From previous observations in ICU patients receiving frusemide infusions, we hypothesised that a likely increase in serum sodium concentration without intervention would be 5 mmol/L from the beginning of treatment to the highest level recorded during treatment. Assuming a standard deviation of 3 mmol/L, we calculated that 10 patients would be needed in each group to have $>80\%$ power to detect attenuation in the sodium increment down to 1 mmol/L, also with a standard deviation of 3 mmol/L at an α of 0.05.

Statistical analysis was performed using SPSS 12.0 (SPSS, Chicago, Ill, USA). Differences between the two groups were assessed using the Mann-Whitney U test, with a P value <0.05 taken to indicate statistical significance.

Results

Baseline characteristics of patients allocated to each group were similar, with no important differences in age, length of ICU stay or renal impairment. Casemix in each group was also similar, reflecting many common conditions treated in general ICUs (Table 1).

Initial biochemical and hormonal concentrations did not differ significantly between the groups. Frusemide by continuous infusion was administered to all patients for at least 2 days, with two patients in each group receiving it for longer.

The greatest change in serum sodium concentration from baseline was a median of 5 mmol/L for the placebo group

Table 1. Baseline characteristics of study participants, by treatment group

Characteristic	Placebo*	Spironolactone*
Sex (no. of patients)		
Male	6	7
Female	4	3
Median age (years)	67 (52–76)	67.5 (55–79)
Median weight (kg)	63 (53–82)	70 (63–77)
Median APACHE III	23.5 (16.8–25.8)	21 (14.5–27.5)
Median ICU LOS (days)	4 (3–5)	3 (2–3)
Admission serum creatinine concentration > 200 µmol/L	3	3
Admission diagnosis (no.)		
Severe sepsis/septic shock	6	4
Cardiogenic shock	1	2
COPD/respiratory failure	0	2
Malignancy with multiple organ dysfunction	2	1
Acute pancreatitis	1	0
Diabetic ketoacidosis	0	1

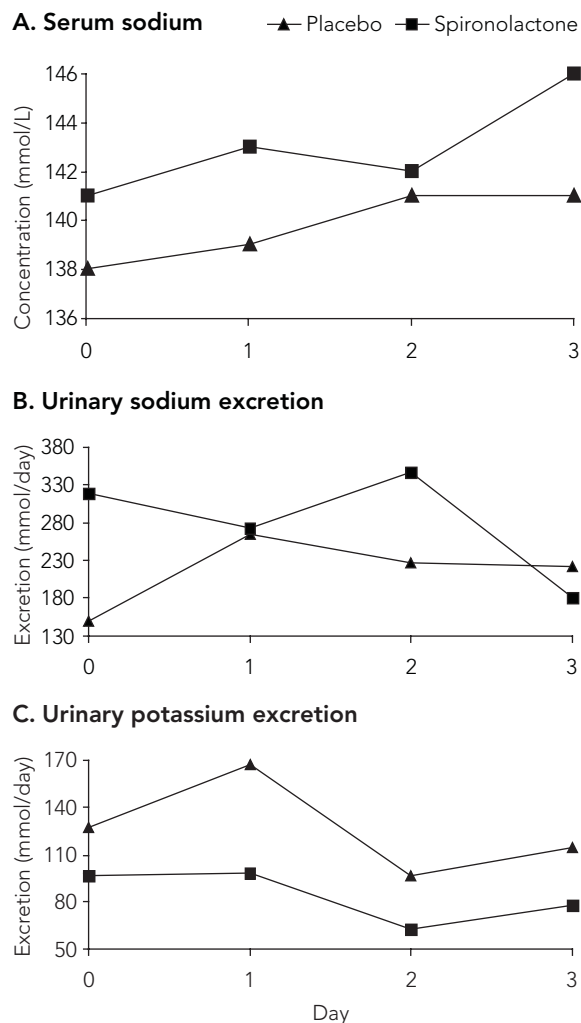
LOS = length of stay. COPD = chronic obstructive pulmonary disease.

* Values in parentheses are the interquartile range.

versus -1 mmol/L for the spironolactone group ($P=0.18$). Other changes in blood and urinary biochemistry results are summarised in Table 2. The change in serum sodium concentration from baseline to the average over Days 1 and 2 was 3.0 mmol/L for the placebo group versus -1.0 mmol/L for the spironolactone group ($P=0.08$) (Figure 1A). The change from baseline serum potassium concentration was minimal for both groups, with a maximum deviation of less than 2.1 mmol/L. The median increase in serum potassium concentration from baseline to the average over Days 1 and 2 was 0.125 mmol/L in each group ($P=0.53$).

The change in total urinary sodium excretion from baseline to the average over Days 1 and 2 tended to be lower in the placebo group than in the spironolactone group (49.25 mmol/day v 118.5 mmol/day; $P=0.92$) (Table 2, Figure 1B). Similar amounts of potassium were excreted over Day 1 and Day 2. The median change in potassium excretion (averaged over 2 days) from baseline was 22.22 mmol/day in the placebo group versus 19.65 mmol/day in the treatment group ($P=0.23$) (Table 2, Figure 1C). No significantly different changes in renal function or hormone levels were evident (Table 2).

There was no difference in changes to daily potassium replacement from baseline between the two groups ($P=0.48$), with median requirements of 25 mmol/day and 20 mmol/day for the placebo and spironolactone groups,

Figure 1. Serum sodium concentration and urinary excretion of electrolytes, by treatment group

respectively ($P=0.35$). No significant differences were observed in urine volume, overall fluid balance, frusemide dosing or need for potassium replacement (Table 3).

To ensure adequate sensitivity for the detection of small, but potentially important differences between the two groups, all appropriate data were also log transformed and subjected to parametric analysis; no significant differences were found.

Discussion

We conducted a randomised placebo-controlled double-blind pilot study of the effects of administration of spironolactone on sodium balance in mechanically ventilated intensive care patients receiving a frusemide infusion for fluid overload.

Table 2. Median changes (Δ) in biochemical parameters from baseline, averaged over 48 hours of therapy

	Placebo*	Spironolactone*	<i>P</i>
Δ Serum electrolyte concentration (mmol/L)			
Sodium	3.0	-1.0	0.08
Potassium	0.125	0.125	0.53
Δ Urinary electrolyte excretion (mmol/day)			
Sodium	49.25 (-128.9 to 113.5)	118.5 (-49 to 195.1)	0.92
Potassium	22.22 (-23.5 to 72.4)	19.65 (-65.5 to 34.0)	0.23
Δ Serum creatinine concentration (μ mol/L)	22.75 (-4.38 to 39.13)	4.75 (4.13 to 6.88)	0.44
Δ Blood urea concentration (mmol/L)	2.2 (0.86 to 5.71)	1.25 (0.65 to 2.83)	0.35
Δ Hormone levels			
Plasma renin activity (ng/mL/h)	-6.1 (-7.0 to 0.2)	-0.3 (-0.6 to 8.5)	0.09
Angiotensin II (pg/mL)	2.5 (-42 to 0.1)	-0.8 (-1.9 to 81.5)	0.17
Human atrial natriuretic peptide (pg/mL)	-17 (-5 to 86)	-8 (-15 to 8)	0.11
Plasma aldosterone (pg/mL)	-44 (-116 to -1)	-20.5 (-77.75 to -11.5)	0.54

* Values in parentheses are the interquartile range.

We found that spironolactone had no significant effects on the incidence or severity of hypernatraemia compared with placebo despite administration at a dose of 300 mg/day, which is substantially more than the dose usually used to treat heart failure or ascites. Similarly, the degree of natriuresis and kaliuresis did not differ greatly between the groups. Spironolactone also did not exert any significant effect on potassium balance, renin-angiotensin-aldosterone hormone levels, daily fluid balance, daily frusemide dose or daily potassium replacement requirements.

From previous observations in ICU patients receiving frusemide infusions, we hypothesised that spironolactone administration would reduce the rise in serum sodium concentration resulting from frusemide therapy by 4 mmol/L. Assuming a standard deviation of 3 mmol/L, this pilot trial was designed to have >80% power to detect a significant difference at an α of 0.05. As the first pilot randomised clinical trial of spironolactone in ICU patients receiving a frusemide infusion, we enrolled 10 patients in each group so that safety could be evaluated. As such, the ability to detect subtle changes in serum sodium is potentially limited, and we cannot exclude the possibility that statistically

significant differences in serum electrolytes might emerge from a larger study. However, it seems probable that any impact on serum electrolytes would be too small to be clinically important.

The lack of clinically significant effect was unexpected. Several explanations are possible. The homeostatic mechanisms regulating intravascular volume and serum electrolytes in health may behave unpredictably in critically ill patients. Evidence has been observed previously of dissociated renin and aldosterone secretion,¹⁹ as well as zona glomerulosa dysfunction within the adrenal cortex²⁰ of ICU patients, and this may contribute to the lack of effect in our study. In addition, although the study population did not have severe renal failure, some patients in each group had varying degrees of renal impairment, according to measured levels of serum creatinine. This measure itself may not accurately reflect the degree of renal dysfunction in the rapidly changing pathophysiological state of multiple organ dysfunction in intensive care patients.²¹ Such kidney dysfunction may render the renal tubule less amenable to pharmacological manipulation in a predictable manner, so that the usual effects of spironolactone were not apparent.

Table 3. Fluid balance, change in potassium requirements, and daily frusemide dose averaged over 48 hours of therapy (values are median [interquartile range])

	Placebo	Spironolactone	<i>P</i>
Urine volume (mL)	3160 (2512 to 3928)	2681 (2297 to 4689)	0.58
Fluid balance (mL)	-760 (-1363 to -165)	-1179 (-2227 to -758)	0.36
Change in potassium requirements from baseline (mmol/day)	25 (25 to 48)	20 (5 to 45)	0.35
Total daily frusemide dose (mg/day)	168 (74 to 295)	97 (71 to 288)	0.89

Consistent with this possibility, it has been previously observed that hyper-reninaemic hypoaldosteronism occurs in critically ill patients,²² and that the inhibitory effects of spironolactone on the actions of aldosterone are absent²³ or reduced^{24,25} in animal septic shock models.

Spironolactone is readily and completely absorbed when administered enterally, especially when co-administered with food,¹⁴ so it is reasonable to expect adequate bioavailability. While we cannot exclude poor absorption of the study drug as a contributing factor to our findings, clinical evaluation as part of daily management reviews indicated that enteral feeds were adequately tolerated.

Patients enrolled in our study were observed for a period up to a mean of 4 days (placebo group) and 3 days (spironolactone group). Previous experience with spironolactone use for other indications suggests that serum and urinary electrolytes should be affected at these high doses over this period.²⁶⁻²⁸ We also observed that even patients who received the study drug for longer periods (5–7 days) did not show significant alterations to their electrolyte profile. Although it is possible that longer administration of spironolactone might eventually affect sodium and potassium balance, the impact is probably minor and of limited clinical utility given that few ICU patients require loop diuretic infusions for periods longer than those studied.

Our study has strengths and limitations. It was prospective, double-blind and randomised in design. It dealt with a significant clinical issue and was conducted with simultaneous measurement of the hormonal response to intervention. Nonetheless, it was a small study, and its negative findings may reflect lack of statistical power. However, this limitation is inherent to all pilot phase I equivalent investigations. Although the change in serum sodium concentration may seem to show a positive trend towards an effect of spironolactone that justifies further studies, this finding occurred in isolation, with no evidence of a biological effect on any other measures of activity. As such, it appears more likely to be due to chance.

Conclusions

Spironolactone administration does not appear to be a clinically effective strategy to limit the impact of furosemide infusions on serum sodium concentration in critically ill patients. Other strategies may be more effective, including use of different furosemide doses and careful electrolyte supplementation. Although spironolactone will continue to have a role in the management of aldosterone excess, ascites and congestive cardiac failure, its use in the prevention of hypernatraemia and excessive water diuresis in ICU patients needing furosemide infusions cannot be recommended.

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