Serious adverse events experienced by patients with chronic heart failure taking spironolactone

C Berry, J J V McMurray

Abstract
In patients with chronic heart failure, spironolactone added to conventional treatment may lead to serious and, occasionally, fatal hyperkalaemia. In some cases this seems to happen because spironolactone causes diarrhoea. Four cases involving men with New York Heart Association functional class III heart failure are presented. As these cases revealed, close monitoring of blood chemistry is mandatory after starting spironolactone, and patients should be advised to stop spironolactone immediately if diarrhoea develops.

Keywords: spironolactone; heart failure; hyperkalaemia

Treatment with the aldosterone receptor antagonist spironolactone is now indicated in severe (New York Heart Association (NYHA) functional class III/IV) chronic heart failure (CHF).1 We describe four such patients who experienced diarrhoea and renal dysfunction early after starting spironolactone.

Case 1
A 54 year old man with NYHA class III CHF presented with a three day history of confusion. Spironolactone 25 mg daily had been started one month earlier. His other medication included diclofenac sodium 50 mg three times daily, frusemide (furosemide) 80 mg once daily, and enalapril 10 mg twice daily. He had a Glasgow coma scale of 13/15. His blood pressure was 131/77 mm Hg, the pulse rate was 65 beats per minute, and there was generalised hyperreflexia. An ECG showed broad QRS complexes and peaked T waves. On admission, the patient's serum sodium concentration was 131 mmol/l, potassium 4.4 mmol/l, urea 4.6 mmol/l, and creatinine 75 µmol/l. The patient was started on an insulin/glucose infusion. Two hours later his condition deteriorated and he suffered a fatal cardiac arrest.

Case 2
A 77 year old man with NYHA class III CHF, atrial fibrillation, and gout was started on spironolactone 25 mg daily. His other treatment included frusemide 80 mg twice daily, trandolapril 4 mg once daily, bendrofluazide 5 mg once daily, allopurinol 300 mg once daily, and warfarin. Before treatment with spironolactone, his plasma sodium concentration was 137 mmol/l, potassium 3.8 mmol/l, urea 9.9 mmol/l, and creatinine 137 µmol/l. He developed diarrhoea within a few days of starting spironolactone. This was stopped immediately and his diarrhoea resolved. Spironolactone 25 mg was restarted. At this time his plasma sodium concentration was 142 mmol/l, potassium 3.9 mmol/l, urea 19 mmol/l, and creatinine 199 µmol/l. His diarrhoea recurred and the dose of spironolactone was reduced to 5 mg daily. Although the diarrhoea then settled, his renal function continued to deteriorate. After one month on the reduced dose of spironolactone, his plasma urea and creatinine concentrations were 27.8 mmol/l and 250 µmol/l, respectively. A 90% ostial stenosis of his right renal artery was found and balloon angioplasty with stent insertion was performed. His renal function failed to improve (potassium 4.8 mmol/l, urea 55.6 mmol/l, creatinine 488 µmol/l) and he had a fatal cardiac arrest one month later.

Case 3
A 61 year old man with NYHA class III CHF was started on spironolactone 25 mg daily. His other medication included enalapril 10 mg twice daily, bumetanide 2 mg daily, aspirin 75 mg daily, and digoxin 250 µg daily. His blood pressure was 88/76 mm Hg and his blood chemistry showed: sodium 138 mmol/l, potassium 5.3 mmol/l, urea 18.9 mmol/l, and creatinine 168 µmol/l. Before initiation of spironolactone these values had been: sodium 137 mmol/l, potassium 8.2 mmol/l, urea 43 mmol/l, and creatinine 771 µmol/l. The patient was started on an insulin/glucose infusion. Two hours later his condition deteriorated and he suffered a fatal cardiac arrest.

Case 4
A 77 year old man with NYHA class III CHF was started on spironolactone 25 mg daily. His other medication included frusemide 120 mg

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daily, amlodipine 10 mg daily, and captopril 50 mg three times daily. His blood chemistry results at that time were: sodium 136 mmol/l, potassium 3.4 mmol/l, urea 10.9 mmol/l, and creatinine 130 µmol/l. He had diarrhoea during the following week and spironolactone was stopped. Shortly afterwards, at the patient’s request, spironolactone was restarted in the form of a suspension (10 mg/5 ml daily). His renal function deteriorated. The blood chemistry results three weeks later were: sodium 142 mmol/l, potassium 5.8 mmol/l, urea 22.1 mmol/l, and creatinine 259 µmol/l. The spironolactone was stopped and his renal function is currently under close observation.

**Discussion**

Treatment with spironolactone, in combination with an angiotensin converting enzyme (ACE) inhibitor, is now recommended for patients with severe chronic heart failure.1 This recommendation is based on the RALES (randomized Aldactone evaluation study) trial which randomised 1663 patients to placebo or spironolactone (mean dose 26 mg) receiving conventional treatment, including an ACE inhibitor in 95% of patients.1 In RALES there were 14 (2%) cases of serious hyperkalaemia (> 6.0 mmol/l) in the spironolactone group, compared to 10 (1%) cases in the placebo group. The authors concluded that spironolactone could be safely prescribed in these patients.

We performed a retrospective case record analysis of CHF patients discharged from the cardiology ward during the six months before and after publication of RALES.1 Spironolactone was prescribed in 15 out of 83 (18%) discharged patients pre-RALES, compared to 42 out of 86 (49%) discharged patients after its publication. Hyperkalaemia (potassium > 5.0 mmol/l) occurred in 36% of these patients. We have described four of the more serious of these episodes in detail here.

Heart failure patients may be prone to serious hyperkalaemia when taking the combination of spironolactone and ACE inhibitor, as a result of aldosterone antagonism, diarrhoea,2 pre-renal failure, renovascular disease, diabetes mellitus (which may predispose to hyperkalaemia with spironolactone),3 old age, and interactions with other drugs (for example, non-steroidal anti-inflammatory drugs). Our findings show that real life clinical experience with a drug can differ greatly from that reported in clinical trials.

In our experience, heart failure patients who have been started on spironolactone are at risk of diarrhoea. In the British National Formulary gastrointestinal upset, but not diarrhoea, is reported as a possible adverse effect of spironolactone.

We advise frequent checks of blood chemistry after a patient has been started on spironolactone. A suggested regimen might include blood tests on days 3–5, 10–14, 35–42, and three monthly thereafter. Our own view is that 25 mg daily of spironolactone would be associated with acceptable efficacy while minimising the risk of renal dysfunction, hyperkalaemia, and possibly diarrhoea.

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