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Spironolactone therapy in older patients—the impact of renal dysfunction

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Abstract

Low dose spironolactone reduces the risk of death from heart failure. We examined the effects of spironolactone on potassium homeostasis in a cohort of elderly patients with congestive heart failure (CHF). Eighteen patients >70 years, mean 80.5 ($\pm$SD 6.3) with New York Heart Association CHF Grade II–IV were enrolled. All patients were commenced on 25 mg spironolactone daily. The dose was reduced to 12.5 mg daily when hyperkalemia (potassium >5.0) occurred. A serum creatinine of >150 μmol/l was defined as indicating renal impairment (RI). Blood pressure, pulse rate, urea, creatinine, Na^+ and K^+ were measured at baseline, day 2–5, day 28 and more often if clinically indicated. Nine of those recruited had RI. Baseline serum potassium was significantly higher in those with RI, mean 4.56 ($\pm$0.30) vs. 4.04 ($\pm$0.30) mmol/l ($P<0.01$). Six patients with RI developed hyperkalemia versus one of those with serum creatinine <150 μmol/l ($P<0.05$). Serum K^+ returned to normal in all patients when the dose of spironolactone was reduced to 12.5 mg daily with one exception in whom the medication was withdrawn. When spironolactone is prescribed to older patients with CHF, hyperkalemia appears more likely in those with RI. Halving the dose to 12.5 mg daily results in normalisation of serum potassium. Older patients commencing spironolactone therapy should have serum potassium monitored frequently, particularly in the presence of RI.

Keywords: Congestive heart failure; Hyperkalemia; Ageing; Renal impairment; Spironolactone

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1. Introduction

It has recently been demonstrated that the aldosterone receptor antagonist spironolactone reduces the risk of both death from congestive heart failure (CHF) and sudden death from cardiac causes (Pitt et al., 1999). Physiological changes associated with increasing age predispose elderly patients to hyperkalemia. These include an age-related reduction in glomerular filtration rate (Lindeman et al., 1985) as well as reduced renin and aldosterone secretion in older persons (Weidmann et al., 1975; Noth et al., 1977). A rise in serum creatinine above 150 μmol/l will not occur due to ageing alone and usually indicates renal impairment (RI).

In this study, we examined the effects of spironolactone on potassium homeostasis in a cohort of elderly patients with congestive cardiac failure and evaluated the impact of RI on these responses.

2. Methods

Patients with New York Heart Association (NYHA) CHF grades II–IV were enrolled. All patients were over 70 years of age at recruitment. Baseline characteristics are shown in Table 1. Patients were excluded if they had a baseline serum potassium level >5.0 mmol/l, if they were taking oral potassium supplements. All conventional medications used in the treatment of heart failure were allowed. RI was defined as having a baseline serum creatinine >150 μmol/l. The biochemical responses of this group were compared with those of patients with baseline serum creatinine <150 μmol/l. Patients whose serum K^+ levels rose to a level >6.0 mmol/l were withdrawn from the study.

Patients were commenced on 25 mg of spironolactone daily which was reduced to 12.5 mg daily if hyperkalemia developed. Baseline clinical measurements of blood pressure, heart rate and NYHA classification were noted and serum potassium, creatinine and urea were measured. These were repeated at day 2–5, day 14, day 28 and more often if clinically indicated. Left ventricular fractional shortening was measured where possible. The primary end-point of the study was the development of hyperkalemia (serum potassium >5.0 mmol/l). Data was analysed using SPSS 8.0. Baseline characteristics were compared using an independent student t-test. A two-sided Fischers Exact test was used in comparing proportions of patients in both the normal and RI groups who developed hyperkalemia.

3. Results

Eighteen patients aged 70–92 years (80.6 ± 6.3) were recruited, nine of whom had RI. All results are presented as mean ± 1 SD. Baseline serum potassium was significantly higher in those with RI mean 4.56 (± 0.30) vs. 4.04 (± 0.30) mmol/l ($P = 0.008$), as was serum creatinine 180.8 (± 12.86) vs. 89.50 (± 27.74) ($P < 0.001$). There were no other significant differences between both groups at baseline

(Table 1). During the study period, there was no significant change in pulse rate, blood pressure, urea or creatinine (Table 2). Six patients with RI developed hyperkalemia compared with only one of those with serum creatinine < 150 μmol/l ($P = 0.02$). Serum potassium returned to the normal range in all patients when the dose of spironolactone was reduced to 12.5 mg daily. One patient with RI was withdrawn from the study having developed hyperkalemia of 6.3 mmol/l at day 14 on 25 mg spironolactone daily. No patients reported other adverse effects, which necessitated withdrawal of spironolactone.

4. Discussion

The addition of 25 mg of spironolactone to the regime of older patients with NYHA Class II–IV CHF is associated with significantly greater incidence of hyperkalemia when the baseline serum creatinine is greater than 150 μmol/l. A reduction in the dosage to 12.5 mg daily resulted in normalisation of the serum potassium.

Table 1
Baseline characteristics of the patients (Mean ± SD)

Characteristic	Normal renal function	RI
Age (years)	81.73 ± 7.20	79.22 ± 5.07
Sex, *no*. (%)		
Male	2 (22)	5 (55)
Female	7 (78)	4 (45)
Blood pressure (mmHg)		
Systolic	117.2 ± 21.32	117.9 ± 21.01
Diastolic	65.5 ± 12.70	66.4 ± 13.32
Heart rate	84.2 ± 14.3	78.3 ± 8.0
New York Heart Association Class, *no*. (%)		
II	1 (11.1)	0 (0)
III	5 (55.5)	6 (66.6)
IV	3 (33.3)	3 (33.3)
Left ventricle # shortening	24.87 ± 5.2	28.17 ± 5.9
Medications	No. (%)	No. (%)
Loop diuretics	9 (100)	9 (100)
ACE inhibitors	6 (66)	4 (44)
Digitalis	5 (55)	6 (66)
Aspirin	6 (66)	5 (55)
Beta blockers	1 (11)	1 (11)
Angiotensin II antagonists	0 (0)	1 (11)
Creatinine (μmol/l)	89.5 ± 27.74	180.8 ± 12.86 ($P < 0.001$)
Urea (mmol/l)	9.4589 ± 7.437	13.8 ± 3.96
K^+ (mmol/l)	4.04 ± 0.30	4.56 ± 0.30 ($P = 0.008$)

Table 2
Changes in clinical and biochemical parameters during the 28 day study period in patients with normal renal function and RI

	Day 1		Day 2–5		Day 14		Day 28	
Parameter	Normal	RI	Normal	RI	Normal	RI	Normal	RI
Na (mmol/l)	137.6 ± 4.9	139.3 ± 3.01	138.4 ± 3.8	137.5 ± 5.8	137.5 ± 4.7	137.4 ± 3.8	138.3 ± 3.5	136.4 ± 3.4
K (mmol/l)	4.0 ± 0.3	4.6 ± 0.3	4.3 ± 0.3	5.1 ± 0.5	4.3 ± 0.4	4.6 ± 0.4	4.5 ± 0.4	4.9 ± 0.2
Urea (mmol/l)	9.5 ± 7.4	13.8 ± 3.9	9.6 ± 5.5	13.5 ± 4.9	8.4 ± 3.6	17.7 ± 6.8	8.1 ± 5.3	15.9 ± 2.1
Cre (mmol)	89.5 ± 27.7	180.8 ± 12.9	84.3 ± 22.1	161.2 ± 33.9	84.7 ± 17.3	178.6 ± 37.1	97.7 ± 28.7	189 ± 26.2
Sys BP (mmHg)	117.2 ± 21.3	117.9 ± 21.0	119.8 ± 15.0	116.8 ± 15.6	112 ± 19.9	125.5 ± 17.3	118.7 ± 29.9	114 ± 10.8
Dias BP (mmHg)	65.5 ± 12.7	66.4 ± 13.3	65.1 ± 0.4	70.8 ± 8.8	64.5 ± 9.5	69.7 ± 8.4	69.4 ± 10.3	64.8 ± 5.6
HR (beats/min)	84.2 ± 14.3	78.3 ± 8.0	74.2 ± 8.1	78.6 ± 8.9	87.6 ± 8.1	75.6 ± 8.61	80.9 ± 6.7	76.2 ± 5.3

All measurements presented as mean ± 1 SD.

Recent evidence suggests that spironolactone in low dosage is beneficial to patients with CHF (Pitt et al., 1999). The mechanism of this benefit is unproven but potentially these include reduced vascular collagen turnover and myocardial fibrosis, improved heart rate variability and reduced early morning rises in heart rate (McFadyen et al., 1997). Since the prevalence of CHF rises with increasing age and older patients are susceptible to hyperkalemia (Biswas and Mulkerrin, 1997) our study was designed to identify if older patients could tolerate this dosage of spironolactone.

While renal function deteriorates with increasing age (Lindeman et al., 1985) a rise in serum creatinine level above 150 μmol/l usually indicates established RI. Our study demonstrates that an early (within 28 days of commencement) rise in serum potassium levels is much more likely to develop in those older patients with elevated baseline serum creatinine levels. Reduction of the dosage of spironolactone to 12.5 mg daily resulted in normalisation of serum potassium in this group. In their study, Pitt et al. reduced the dosage of spironolactone to 25 mg alternate days in patients who could not tolerate the higher dosage and these patients were included in the final analysis of the results, which demonstrate clear-cut benefits from therapy (Pitt et al., 1999). The absence of significant change in serum urea or creatinine levels is not surprising since low dose spironolactone has little apparent diuretic effect (The RALES Investigators, 1996).

When spironolactone is prescribed to older patients with CHF, hyperkalemia appears more likely in those with RI. Halving the dose to 12.5 mg daily results in normalisation of serum K^+. Older patients commencing spironolactone therapy should have their serum K^+ monitored frequently, particularly in the presence of RI.

References

Biswas, K., Mulkerrin, E.C., 1997. Potassium homeostasis in the elderly. Q. J. Med. 90, 487–492.

Lindeman, R.D., Tobin, J.D., Shock, N.W., 1985. Longitudinal studies on the rate of decline of renal function with age. J. Am. Geriatr. Soc. 33, 278–285.

McFadyen, R.J., Barr, C.S., Struthers, A.D., 1997. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc. Res. 35, 30–34.

Noth, R.H., Lassman, M.N., Tan, S.Y., 1977. Age and the renin aldosterone system. Arch. Intern. Med. 137, 1414–1417.

Pitt, B., Zannad, F., Remme, W.J., Cody, R., Castaigene, A., Perez, A., Palensky, J., Wittes, J., 1999. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N. Engl. J. Med. 341, 709–717.

The RALES Investigators, 1996. Effectiveness of spironolactone added to an angiotensin converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure. The Randomised Aldactone Evaluation Study (RALES). Am. J. Cardiol. 53, 457–481.

Weidmann, P., De Myttenaere-Buesztein, S., Maxwell, M.H., De Cima, J., 1975. Effect of ageing on plasma renin and aldosterone in normal man. Kidney Int. 8, 325–333.