Safety of Spironolactone Use in Ambulatory Heart Failure Patients

R.J. Lopes et al: *Clin Cardiol* 2008;31:509–513

To the editor,

We reviewed with great interest the article on safety of spironolactone use in heart failure patients by Lopes et al.¹ As the authors point out, there is scarce information on the use and side effects of spironolactone in routine clinical practice. While the Randomized Aldactone Evaluation Study RALES² and several other retrospective studies including the current one, exclude patients with chronic kidney disease (CKD), it is a common comorbidity seen in up to 30% of patients with congestive heart failure (CHF). Chronic kidney disease not only portends a poor prognosis but also increases the risk of hyperkalemia. There is limited literature regarding the true rate of hyperkalemia in patients with CHF and CKD during episodes of CHF exacerbations (CHFe). We hypothesized that hyperkalemia may exponentially increase during episodes of CHFe with combinations of spironolactone and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB).

To find the true rates of hyperkalemia under such conditions in patients outside of clinical trials and identify patient characteristics that predict hyperkalemia, we conducted a retrospective cohort study that included patients admitted to a tertiary teaching hospital, with a discharge diagnosis of CHF between January 2004 to December 2006. Patients who had systolic heart failure (ejection fraction [EF] <40%), with nondialysis dependent CKD on ACEI or ARB and spironolactone were selected. Chronic kidney disease was defined as serum creatinine >1.5 mg/dL or estimated glomerular filtration rate (eGFR) <60 mL/min for more than 3 months prior to admission. Demographic and laboratory data was extracted from the hospital's electronic database. Patients with hyperkalemia (defined as serum potassium >5.5 mEq/dL) on admission were compared to those without hyperkalemia. A total of 1074 patients were admitted during the study period with CHFe. A total of 99 patients met study inclusion criteria. Pertinent patient characteristics and associated medications are listed in Table 1. Overall 31 patients (31%) developed hyperkalemia. Ten patients developed potassium >6 mEq/dL. None of them resulted in life threatening arrhythmia. As compared to patients who did not develop hyperkalemia, those who did were more likely to be diabetic (Figure 1). No significant differences were noted in their age, sex, EF, medications,

or mean serum creatinine. Based on our sample size, we had 80% power to detect 15% differences among variables in each group. Of those who developed hyperkalemia, 7 patients (22%) developed recurrent hyperkalemia over 30 follow-up visits for CHFe.

Renal dysfunction is an important element in the pathophysiology of patients hospitalized with heart failure. We believe patients with CKD on spironolactone and ACEI or ARB are at increased risk of developing hyperkalemia. Our study confirms this hypothesis. Concomitant use of

Table 1. Patient Characteristics

Patient Characteristics	All Patients % (n = 99)	Hyperkalemic % (n = 31)	Normokalemic % (n = 68)
Age ^a	75 (11)	76	73
Sex (male)	71	77	68
Diabetes ^b	63	77	56
Medications			
ACEI	86	90	84
ARB	15	10	18
Loop diuretics	87	87	87
Thiazides	7	6	7
β-Blockers	78	74	79
Calcium channel blockers	6	3	7
NSAIDS	83	84	82
β Agonists	17	20	16
Insulin	23	26	22
Potassium supplements	25	26	25
Serum Creatinine			
1.1–1.9	57	42	66
2–3.0	34	52	27
≥3	7	7	7
Ejection Fraction			
<20	23	19	25
20–30	36	42	34
>30	39	39	40

^aMean ± SD. ^bP ≤ 0.05

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDS, nonsteroidal antiinflammatory drugs; SD, standard deviation.

The results of our study were presented at the American Society of Nephrology annual meeting held November 2008 in Philadelphia, PA.

Figure 1. Hyperkalemia with and without history of diabetes.

potassium supplements and nonsteroidal antiinflammatory drugs (NSAIDs) may have further contributed to hyperkalemia. However, even after excluding patients on potassium supplements ($n = 26$), incidence of hyperkalemia remained high (38%). Although the use of NSAIDs was not significantly different among the groups, it may have contributed to hyperkalemia via a disproportionate decline in renal function. Diabetes was significantly more common in hyperkalemic patients and may have contributed to it by hyporenemic hypoaldosteronism. Our study is limited by small sample size and the retrospective nature. Based

on current clinical evidence, our study population should have never been on such a combination of medications. This highlights once again the difficult translation of controlled trials into clinical practice. Although the authors chose to answer this by selecting appropriate patients, it would be interesting to note the frequency of use of spironolactone and similar complications in patients with CKD in their impressive database. Such information will not only help identify the frequency of inappropriate medication use and related complications, but may help change practice patterns.

Praveen Kandula, MD, MPH, FACP

Ravish Shah, MD

Division of General Internal Medicine

Southern Illinois University

Springfield, IL

References

1. Lopes RJ, Lourenço AP, Mascarenhas J, Azevedo A, Bettencourt P. Safety of spironolactone use in ambulatory heart failure patients. *Clin Cardiol*. 2008;31(11):509–513.
2. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341(10):709–717.