Clinical Investigations

Safety of Spironolactone Use in Ambulatory Heart Failure Patients

Address for correspondence:
Ricardo J. Lopes, MD
Department of Cardiology
Hospital São João
4200-319 Porto, Portugal
rjlclopes@hotmail.com;
rjlclopes@yahoo.com.br

Ricardo J. Lopes, MD, Ana Patricia Lourenço, MD,* Joana Mascarenhas, MD, Ana Azevedo, MD, PhD,*,† Paulo Bettencourt, MD, PhD*

Department of Cardiology; *Department of Interal Medicine, Hospital São João; †The Service of Epidemiology, University of Porto, Porto, Portugal

ABSTRACT

Background: Since the Randomized Aldactone Evaluation Study (RALES), the use of spironolactone is recommended in systolic heart failure (HF) patients that have been in New York Heart Association (NYHA) class III or IV. There is limited information on the use, side effects, and withdrawal rate of spironolactone in routine clinical practice.

Hypothesis: Side effects related to spironolactone use are more common than reported in clinical trials.

Methods: Patients who had moderate to severe left ventricular systolic dysfunction (LVSD) under optimized medical therapy were included. We introduced spironolactone in those with serum potassium (K+) $\leq$5 meq/L, and serum creatinine (Cr) $\leq$2.5 mg/dL. Spironolactone was withdrawn if serum K+$\geq$5.5 meq/L, serum Cr increased more than 30%–50% of the baseline value, and/or if the patient had gynecomastia.

Results: We selected 134 patients followed in an HF clinic. In our sample, 56.7% of the patients (76 out of 134) were currently or had formerly been on spironolactone therapy. The rate of spironolactone withdrawal was 25% (19 out of 76). Reasons for suspension were hyperkalemia (17.1%), renal function deterioration (14.5%), gynecomastia (5.3% of males), and other reasons (1.3%).

Conclusion: Spironolactone side effects are common and are mostly related to effects on the angiotensin-aldosterone axis. Our results reinforce the need to closely monitor serum K+ and Cr levels in patients treated with spironolactone, as its side effects are more common than reported in clinical trials.

Key words: spironolactone, heart failure, hyperkalemia, renal function deterioration

Introduction

Since the Randomized Aldactone Evaluation Study (RALES),[1] the use of spironolactone is consensual in heart failure (HF) patients with left ventricular ejection fraction (EF) <35% and are, or had been, in New York Heart Association (NYHA) class III or IV. Furthermore, the demonstration that eplerenone reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular systolic dysfunction (LVSD) with EF <40%, and either HF or diabetes,[2] reinforced the use of aldosterone receptor-blocker in HF patients. With the wide use of spironolactone there have been reports of serious side effects, such as hyperkalemia and renal failure.[3–8] Fatal hyperkalemia[4–6] and renal failure[5] requiring dialysis have also been reported. These observations and the scarce information on the use, side effects, and withdrawal rates of spironolactone in routine clinical practice led some authors to discuss the adequacy of spironolactone use in HF patients.[9]

In this study, we aimed to quantify the occurrence of side effects related to spironolactone use in a group of HF patients with moderate to severe LVSD, on optimized medical therapy, and who were followed in an HF clinic since 2000. We hypothesized that side effects related to spironolactone use are more common than reported in clinical trials.

Methods

We conducted a retrospective, cohort study that included patients followed in an HF clinic since the year 2000. All patients had moderate (EF<35%) to severe (EF<25%) LVSD documented by echocardiography. An HF diagnosis was made according to the European Society of Cardiology criteria.[10]

Data on demographics, LVSD severity, HF aetiology, NYHA class, diabetes occurrence, baseline serum creatinine (Cr), potassium (K+), and cardiovascular drug therapy were obtained from medical records. Criteria considered appropriate to spironolactone use were: moderate or severe LVSD, serum K+ $\leq$5 meq/L, and serum Cr $\leq$2.5 mg/dL. The therapeutic protocol for spironolactone use was: the initial dose was 12.5 mg qd, and after 4 wk of therapy was increased to 25 mg qd if K+ <5.5 meq/L, and renal function was stable. The maximum dose tolerated was registered. Renal function and kalemia were monitored according to RALES recommendations: 1 wk after initiating therapy, after 1 mo, and at least every 3–6 mo thereafter. Spironolactone was withdrawn if serum K+ $\geq$5.5 meq/L, serum Cr increased more than 30%–50% of the baseline value, and/or the patient had gynecomastia.

Data storage and analysis were performed using SPSS version 13.0 (SPSS Inc, Chicago, Ill., USA). Continuous

Received: June 3, 2007
Accepted with revision: August 21, 2007

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20284

TABLE 1: Patients baseline characteristics

Characteristics	Total (n = 134)	Spironolactone (a) (n = 76)	No spironolactone (b) (n = 58)	p-value a versus b
Age (y)	66.0±13.0	65.7±12.2	66.7±13.2	0.678
Sex (male/female)	93/41	57/19	36/22	0.156
Severe LVSD (%)	68.4	75.0	58.6	0.068
NYHA class (%)				0.153
I	31.3	24.6	39.6	
II	58.3	61.5	54.2	
III	10.4	13.8	6.3	
IV	0	0	0	
Ever in class NYHA III/IV (%)	31.6	40.8	19.0	0.012
Ischemic HF etiology (%)	51.5	54.7	47.4	0.512
Diabetes (%)	27.2	23.7	32.8	0.332
Serum K+ (meq/L)	4.60±0.52	4.51±0.49	4.74±0.54	0.039
Serum Cr (mg/dL)	1.26±0.52	1.18±0.27	1.36±0.73	0.841
Medications (%)				
Diuretic	95.6	98.7	93.1	0.219
ACEI	91.2	92.1	89.7	0.852
ARB	11.8	12.1	11.8	1.000
β-blocker	91.9	90.8	93.1	0.868
β-blocker dose (mg of carvedilol)	32.7±18.6	33.5±19.4	32.1±17.9	0.728
ACEI dose (mg of lisinopril)	14.2±7.8	13.8±8.3	15.0±7.0	0.238

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; Cr = creatinine; HF = heart failure; K+ = potassium; LVSD = left ventricular systolic dysfunction; NYHA = New York Heart Association.

variables are presented as mean±standard deviation, and categoric variables are presented as frequencies. Comparisons between groups of patients (spironolactone versus no spironolactone and spironolactone withdrawl versus spironolactone maintenance) were made using the *t* test for continuous variables (Mann-Whitney U test was used when the continuous variable was non-normally distributed), and chi-square test was used for categoric variables. Statistical significance was accepted when p-value <0.05.

Results

We selected 134 patients with moderate to severe LVSD. Their baseline characteristics are described in Table 1.

In our sample, 56.7% of patients (76 out of 134) were currently or had formerly been on spironolactone therapy. The mean spironolactone dose was 18.8±12.5 mg. The only statistically significant differences between patients on spironolactone and patients not on spironolactone were baseline serum K+, which was lower in the spironolactone group; and the proportion of patients who had ever been in NYHA class III or IV, which was higher in the spironolactone group. There was also a tendency for patients on spironolactone therapy to have more severe LVSD (75% versus 58.6%) and higher NYHA class; however, these differences did not reach statistical significance. All other baseline characteristics were similar between these 2 groups (Table 1).

The rate of spironolactone withdrawal was 25% (19 out of 76). Causes for suspension were hyperkalemia and renal function deterioration in 8 patients (10.5%), hyperkalemia in 5 patients (6.6%), renal function deterioration in 2 patients (2.6%), gynecomastia in 2 male patients (3.5%), gynecomastia

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20284

TABLE 2: Comparisons of baseline characteristics of patients who withdrew and maintained spironolactone therapy

Characteristics	Spironolactone withdrawal (n = 19)	Spironolactone maintenance (n = 57)	p-value
Age (y)	67.3±10.6	65.9±12.7	0.670
Sex (male/female)	16/3	41/16	0.444
Severe LVSD (%)	73.7	75.4	1.000
NYHA class (%)			0.690
I	11.1	29.8	
II	61.1	61.7	
III	27.8	8.5	
IV	0	0	
Once in class III/IV NYHA (%)	42.1	40.4	1.000
Ischemic HF etiology (%)	47.4	56.1	0.690
Diabetes (%)	15.8	26.3	0.533
Serum K+ (meq/L)	4.41±0.52	4.37±0.33	0.801
Serum Cr (mg/dL)	1.15±0.26	1.15±0.23	0.987
Cr Cl (mL/min)	63.8±24.0	65.0±30.3	0.886
Medications (%)			
Diuretic	100	98.2	1.000
ACEI	94.7	91.2	1.000
ARB	5.3	14.0	0.436
β-blocker	94.7	89.5	0.819
Spironolactone dose (mg)	16.5±6.0	19.6±14.1	0.579
β-blocker dose (mg)	32.1±17.5	30.1±20.2	0.789
ACEI dose (mg)	15.3±6.3	13.3±8.8	0.172

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; Cr = creatinine; Cr Cl = creatinine clearance; HF = heart failure; K+ = potassium; LVSD = left ventricular systolic dysfunction; NYHA = New York Heart Association.

and renal function deterioration in 1 patient (1.3%), and other reasons in 1 patient (1.3%). In summary, 17.1% of patients had hyperkalemia, 14.5% of the patients had renal function deterioration, and 5.3% of males had gynecomastia. Baseline characteristics of patients who withdrew from spironolactone and those who maintained spironolactone therapy were similar. Namely, there were no differences regarding NYHA class III, diabetes, renal function, or drug therapy (Table 2).

Severe hyperkalemia (≥6 meq/L) occurred in 7 patients (9.2%), but there were no related deaths. None of the patients with deteriorating renal function needed dialysis. Patients who suspended spironolactone therapy were not on K+ supplementation or nonsteroid anti-inflammatory drugs. Most of these patients (75%) were on low doses of spironolactone (12.5 mg qd). The time elapsed until spironolactone discontinuation was variable; ranging between 35 d and 976 d.

Discussion

In our group of patients with mild to moderate HF and moderate to severe LVSD, 56.7% were treated with spironolactone. The rate of spironolactone withdrawal was expressive (25.0%). Hyperkalemia (17.1%) and renal function deterioration (14.5%) were the main causes for suspension. Severe hyperkalemia (≥6 meq/L) occurred in 7 patients (9.2%), but fatalities were reported. None of the patients with renal function deterioration needed dialysis.

In RALES,[1] spironolactone use was associated with reduction in all-cause mortality and hospitalization for HF in patients with left ventricular EF <35% and who were or had been in NYHA class III or IV. Patients with serum Cr >2.5 mg/dL and/or serum K+ >5 meq/L were excluded from the trial. Spironolactone at a mean dose of 26 mg (25–50 mg) daily was given in addition to standard HF therapy. The main side effects observed in this severe HF population were gynecomastia (10%), with severe hyperkalemia (K+ ≥6 meq/L) occurring in 2% of patients.

More recently, the Epleronone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial[2] demonstrated that eplerenone reduces morbidity and mortality among patients with acute myocardial infarction complicated by LVSD, and either HF or diabetes. In contrast to spironolactone, eplerenone use was not associated with gynecomastia (occurring in only 0.5% of patients), but was related to higher rates of severe hyperkalemia (5.5%). However, there was a 4.7% absolute decrease in the incidence of hypokalemia when compared with placebo. In both trials, the use of an aldosterone antagonist was not associated with significant renal function deterioration.

With the wide use of spironolactone, there have been several reports of renal failure and hyperkalemia.[3–8] Some[4–6] of these reports describe side effects leading to hospitalization, dialysis, and in a few cases, death. However, a higher dose of spironolactone than that recommended in RALES was used in most cases. Furthermore, spironolactone was used in a broader group of patients (including asymptomatic patients and patients without a left ventricular systolic function evaluation), and serum K+ and Cr monitoring did not follow the established recommendations.

In our clinic, we started spironolactone (18.8±12.5 mg) in 76 of our HF patients with moderate to severe LVSD under optimized medical therapy. There is no experimental evidence from randomized trials demonstrating the benefit of aldosterone blockade on morbidity and mortality in patients with mild to moderate HF (patients who have never been in NYHA class III or IV), but it seems reasonable to use spironolactone when they have moderate to severe LVSD.[11] With the progressive deterioration of left ventricular systolic function, the activation of renin-angiotensin-aldosterone axis increases in the same proportion. Evidence showing that ventricular remodeling, endothelial function, heart rate variability, baroreceptor function, and myocardial collagen formation are improved by aldosterone blockade reinforces this suggestion.[12–14] Our sample included 59.2% patients treated with spironolactone (45 out of 76) who had never been in NYHA class III or IV. We considered that even in these mild to moderate HF patients, spironolactone therapy would have beneficial effects given their LVSD severity. None of our patients had serum Cr >2.5 mg/dL or serum K+ >5.0 meq/L when they started spironolactone. Renal function and kalemia were monitored according to RALES recommendations.

Although the main recommendations for starting spironolactone and monitoring serum K+ and renal function were followed, the rate of spironolactone withdrawal in our population was high (25.0%), with hyperkalemia occurring in 17.1% (severe hyperkalemia in 9.2% versus 2% in RALES) and renal function deterioration occurring in 14.5% of the patients (not reported in RALES). Gynecomastia occurred less frequently than reported in RALES (5.3% versus 10%). Our patients were on lower spironolactone doses (≤25 mg); frequently 12.5 mg qd (75%).

Pitt B et al.[11] considered that serum Cr may underestimate renal dysfunction, especially in elderly patients and those with low body mass index and diabetes mellitus, suggesting that it would be better to exclude from spironolactone therapy patients with Cr clearance <30 mL/min and be cautious in those with Cr clearance between 30 and 60 mL/min. One possible explanation for our high rate of spironolactone withdrawal is the overestimation of renal function, which seems normal when we look at serum Cr (1.26±0.52 mg/dL), but it is mildly to moderately decreased when estimated by Cr clearance (62.1±28.3 mL/min). We think that our sample was probably too small to detect Cr clearance differences between patients who withdrew and those who maintained spironolactone therapy (Table 2).

Another possible explanation for our results is a saturation, or near-saturation, of the renin-angiotensin-aldosterone axis. Most of our patients were on angiotensin-converting enzyme inhibitors (ACEI) (92.1% versus 95% in RALES) or angiotensin-receptor blocker (ARB) (12.1%) therapy and were on a high dose of ACEI (13.8±8.3 mg of lisinopril). β-blockers are known to increase the risk of hyperkalemia[11] and, in contrast to RALES, most of our patients were on β-blocker therapy (90.8% versus 10%). This fact may have also contributed to the high rate of spironolactone withdrawal that we reported.

This study had some limitations. First, we described side effects of patients on spironolactone therapy, but we did not compare them with their frequency in the remaining patients not on this drug. Although we do not think it would be probable, the side effects verified in our patients could be a characteristic of our population and not only due to spironolactone therapy. Side effects in this sample compared with side effects reported in RALES were abusive in that we did not know whether the remaining characteristics were similar. It is interesting to note that we reported an expressively higher rate of side effects than RALES. Second, not all of the patients had formal indication to start spironolactone, but we assumed that for their ventricular dysfunction they should also benefit from its introduction. Additionally, we did not think that this broader indication was the reason for such a high rate of side effects.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20284

Conclusion

Side effects related to spironolactone use were common and mostly associated with effects on the renin-angiotensin-aldosterone axis. Underestimation of renal dysfunction, use of other drugs blocking the renin-angiotensin-aldosterone axis, and the elevated rate of β-blocker use are possible explanations for the high rate of hyperkalemia and renal dysfunction in our study. Creatinine clearence should be used to estimate renal function. Our results reinforced the need to closely monitor serum K+ and Cr levels in HF patients treated with spironolactone, because side effects are more common than reported in clinical trials.

References

1. Pitt B MD, Zannad F MD, Remme WJ MD, Cody R MD, Castaigne A MD, et al.: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341(10):709–717
2. Pitt B MD, Zannad F MD, Remme WJ MD, Neaton J PhD, Martinez F MD, et al.: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348(14):1309–1321
3. Tamirisa KP MD, Aaronson KD MD, MS, Koelling TM MD. Spironolactone-induced renal insufficiency and hyperkalemia in patients with heart failure. *Am Heart J* 2004;148(6):971–978
4. Juurlink DN MD, PhD, Mamdani MM Pharm. D, MPH, Lee DS MD, Kopp A BA, Austin PC PhD, et al.: Rates of Hyperkalemia after publication of the randomized Aldactone evaluation study. *N Engl J Med* 2004;351(6):543–551
5. Schepkens H MD, Vanholder R MD, PhD, Billiouw JM MD, Lameire N MD, PhD: Life-threatening hyperkalemia during combined therapy with angiotensin converting enzyme inhibitors and spironolactone: An analysis of 25 cases. *Am J Med* 2001; 110: 438–441
6. Berry C MD, McMurray JJ MD. Serious adverse events experienced by patients with chronic heart failure taking spironolactone. *Heart* 2001;85:E8
7. Hauben M MD, MPH, Reich L MD, Gerrits CM Pharm.D, PhD. Reports of hyperkalemia after publication of RALES–a pharmacovigilance study. *Pharmacoepidemiol Drug Saf* 2006; 15(11): 775–783
8. Svensson M MD, Gustafsson F MD, Galatius S MD, Hildebrandt PR, MD, Atar D MD. Hyperkalemia and impaired renal function in patients taking spironolactone for congestive heart failure: retrospective study. *BMJ* 2003;327:1141–1142
9. Ko DT MD, Juurlink DN MD, PhD, Mamdani MM Pharm.D, MPH, You JJ MD, Wang JT MSc, et al.: Appropriateness of spironolactone prescribing in heart failure patients: A population-based study. *J Card Fail* 2006;12(3):205–210
10. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, et al.: Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: The Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; 26: 384–416
11. Pitt B MD: Aldosterone blockade in patients with systolic left ventricular dysfunction. *Circulation* 2003;108:1790–1794
12. Farquharson CA MBChB, MRCP, Struthers AD MD, FRCP: Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. *Circulation* 2000;101:1722–1728
13. Yee KM MRCP, Pringle SD MD, FRCP, Struthers AD MD, FRCP, FESC: Circadian variation in the effects of aldosterone blockade on heart rate variability and QT dispersion in congestive heart failure. *J Am Coll Cardiol* 2002;37(7):1800–1807
14. Modena MG MD, FACC, FESC, Aveta P MD, Menozzi A MD, Rossi R MD: Aldosterone inhibition limits collagen synthesis and progressive left ventricular enlargement after anterior myocardial infarction. *Am Heart J* 2001;141(1):41–46

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20284