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Clinical Investigations

Use and Side-Effect Profile of Spironolactone in a Private Cardiologist's Practice

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Summary

Background: The beneficial effects of spironolactone on the treatment of cardiovascular diseases are well known, but translating these benefits into private practice can be difficult because of the drug's side-effect profile.

Hypothesis: When patients are monitored over the long term, spironolactone can be used safely with an acceptable side-effect profile.

Methods: We retrospectively studied 762 patients taking spironolactone over a 7-year period in a cardiologist's referral-based practice and monitored them for side effects from the medication.

Results: Data were available on 762 patients. The average age of our patients when started on the medication was 67.2 ± 0.5 years. Of these, 585 (76.8%) patients were treated for heart failure and 155 (20.3%) for hypertension. An average dose of 38.4 ± 1.4 mg of spironolactone was used for treatment of all conditions. Of the 762 patients, 81 (10.6%) experienced side effects while using the medication; 40 had hyperkalemia (5.3%), 14 had gynecomastia (1.8%), and 15 had gastritis (2%). Of the patients with hyperkalemia, average creatinine clearance decreased from 64.6 ± 5.8 ml/min at therapy start to 50.3 ± 5.5 ml/min at the time of onset of side effects.

Conclusion: Spironolactone can be used with an acceptable side-effect profile as long as patients are monitored long-term while receiving the medication.

Key words: spironolactone, eplerenone, hyperkalemia, congestive heart failure, mineralocorticoid, gynecomastia, gastritis, creatinine clearance

Introduction

Since the Randomized Aldactone Evaluation Study (RALES)[1] in 1998 demonstrated a decrease in mortality with the use of spironolactone for patients with congestive heart failure (CHF), there has been much research and interest in the use of the drug for treating heart failure. However, while spironolactone is a familiar drug to many physicians, its use requires additional monitoring, as multiple side effects including hyperkalemia, gynecomastia, and gastritis may occur with use of the drug. Since the release of the trial results, there have been reports of difficulty using spironolactone because of high rates of these side effects.[2, 3] These reports highlight the difficulty in implementing the results from a large, well controlled, multicenter trial to clinical practice.[4] Thus, while RALES was important for demonstrating the survival benefits of spironolactone, translating spironolactone's efficacy and usefulness into clinical practice requires understanding of its clinical side-effect profile and the importance of long-term monitoring.

Materials and Methods

All charts of patients who had taken any form of spironolactone (spironolactone, Aldactone®, [Pfizer, Inc., New York, N.Y., USA], Aldactazide®, [Pfizer, Inc.]) at any time during their treatment were reviewed. This search brought up a total of 762 patients who saw a single private cardiologist between August 31, 1996, and May 23, 2003. The majority of patients were referrals to a cardiologist, managed by both a cardiologist and a primary care physician. Spironolactone was used to treat hypertension, CHF, hyperaldosteronism, superior vena

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cava syndrome, venous insufficiency, and hypomagnesemia. For patients with multiple diagnoses, the primary reason for initiation of spironolactone treatment determined their grouping; of those with CHF, approximately 10% were in New York Heart Association (NYHA) class IV, and the remaining patients were split between classes II and III. Our goal for clinical management has been to keep patients' serum potassium levels between 4 and 5 mmol/l. During therapy, patients had multiple measurements of potassium and creatinine performed by both the primary doctor and the treating cardiologist. Hyperkalemia was defined as any potassium level > 5.0 mmol/l; gynecomastia was defined as breast enlargement and/or tenderness; gastritis was defined as recurring stomach pain after the patient was started on spironolactone. Dosing information was the last available dose at time of data retrieval. Patients without dosing information available from chart review were excluded from that portion of the analysis.

Cardiology records were obtained and manually reviewed for the 40 patients with hyperkalemia. Serum potassium levels were confirmed by medical records, and an explanation for the hyperkalemia was recorded. Both serum creatinine and weight were recorded at time of onset of hyperkalemia and at or near the beginning of therapy. The Cockroft-Gault equation[5] was used to determine the creatinine clearances in this group of patients. Statistical analysis was completed using a paired Student's *t*-test for the 34 patients with hyperkalemia with available creatinine clearances at both beginning of therapy and onset of side effects. A heteroscedastic *t*-test was used for the difference between age at onset of hyperkalemia and age when starting medication. Means are expressed as the mean ± standard error of the mean.

Results

An overview of the patient population is shown in Table I. Data were available for a total of 762 patients (47% male, 53% female) in our study. The average age of patients when they were started on the medication was 67.2 ± 0.5 years. The majority (76.8%) were treated for CHF; 20.3% were treated for hypertension, and 2.9% were classified as "other," which included hyperaldosteronism, superior vena cava syndrome, venous insufficiency, and hypomagnesemia. Dosing information was available in 734 patients. Overall, we used an average dose of 38.4 ± 1.4 mg of spironolactone daily for all conditions. For the treatment of CHF we used a dose of 32.2 ± 1.3 mg, while the treatment of hypertension required a higher dose of 58.3 ± 2.9 mg overall.

Of the 762 patients studied, 81 (10.6%) experienced a side effect while using the medication, 40 (5.3%) had hyperkalemia, 14 (1.8%) had gynecomastia, and 15 (2%) had gastritis. Gastritis usually occurred within 2 weeks of the start of treatment with spironolactone. A total of 12 patients reported "other" side effects, which included decreased libido, hair loss, hypotension, metallic taste, or a therapeutic trial (as a screen for primary aldosteronism, spironolactone was given to determine whether it lowered blood pressure) that required withdrawal of the medication (Table II).

Confounding illnesses and medications in addition to spironolactone treatment are shown in Table III. Overall, 29.7% of patients had diabetes, 71.3% were being treated with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker, about 65% were receiving diuretics (nonpotassium sparing) while being treated with spironolactone, and 33% still required potassium supplementation though they continued treatment with the drug.

Of the 40 patients who developed hyperkalemia, 38% had diabetes, 78% received an ACE inhibitor or an angiotensin receptor blocker, and 11 (28%) received potassium supplementation (Table III). The patients who developed hyperkalemia tended to be older: 73 ± 1.6 years versus the mean starting age in this study of 67.2 ± 0.5 years; this was statistically significant (p = 0.0001). The patients also had worsening renal function at the time they experienced side effects compared with start of therapy (Table IV). Starting serum creatinine averaged at 1.4 ± 0.1 mg/dl while the average serum creatinine at onset of side effects was 1.9 ± 0.2 mg/dl. Given the older age of these patients, the calculated baseline creatinine clearance for those who developed hyperkalemia was 64.6 ± 5.8 ml/min compared with 50.3 ± 5.5 ml/min at onset of side effects, with a statistically significant difference (p = 0.001). Data for the overall creatinine clearance of the 762 patients were not available.

TABLE I Baseline characteristics of study population

Population overview	No. of patients	%	No. of patients with dose information	Mean dose (mg) of spironolactone
Total patients	762	100	734	38.4 ± 1.4
Male	357	47	345	35.1 ± 1.8
Female	405	53	389	41.2 ± 1.9
Mean age at spironolactone start	67.2 ± 0.5			
Diagnosis				
CHF	585	77	563	32.2 ± 1.3
HT	155	20	150	58.3 ± 2.9
Other	22	3	N.A.	N.A.

Abbreviations: CHF = congestive heart failure, HT = hypertension, N.A. = not applicable.

TABLE II Total side effects occurring during spironolactone treatment

Side effects	No. of patients	%	No. of patients with dose information	Mean dose (mg) of spironolactone	Mean age at side effects
Total side effects	81	10.6			
Hyperkalemia	40	5.2	38	35.7 ± 5.1	73 ± 1.6 [a]
Gynecomastia	14	1.8	12	38 ± 7.5	64 ± 2.5
Gastritis	15	2.0	11	61.9 ± 34.1	71 ± 2.8
Other	12	1.6			

[a] The age at onset of hyperkalemia was significantly different from that at the start of therapy (p = 0.0001).

TABLE III Confounding medical conditions

	All patients		Hyperkalemia		Gynecomastia		Gastritis	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Diabetes mellitus	226	30	15	38	3	21	4	27
ACE/ARB	543	71	31	78	12	86	8	53
Diuretics	495	65	26	65	9	64	7	47
Potassium supplements	250	33	11	28	6	43	3	20
ACE/ARB, DM	183	24	10	25	3	21	3	20
ACE/ARB, DM, and diuretics	139	18	8	20	2	14	3	20
ACE/ARB, DM, diuretics, and potassium supplements	62	8	1	3	2	14	1	7

Abbreviations: ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, DM = diabetes mellitus.

Discussion

Aldosterone is produced locally in the adrenal gland, brain, and smooth muscle cells of blood vessels and the myocardium.[6] Higher plasma levels of aldosterone have deleterious effects on the cardiovascular system; in CHF, they are known to be positively linked to mortality.[7] Aldosterone has also been found to cause myocardial and aortic fibrosis in animals, induce coronary inflammation and left ventricular hypertrophy, and cause glomerular damage.[8] It is interesting that the use of ACE inhibition to reduce aldosterone levels only works transiently,[9] implying that damage caused by aldosterone continues after ACE inhibition.

Spironolactone and eplerenone are both mineralocorticoid receptor antagonists. Spironolactone has been available for years and is familiar to many physicians. It works by binding to and blocking the mineralocorticoid receptor. Spironolactone has a half-life of 1.6 h, after which it is converted into a secondary metabolite, canrenone, which is also metabolically active and has a half-life of 16.5 h. Because of spironolactone's steroid structure, it can cause gynecomastia, impotence, decreased libido, hirsutism, and menstrual irregularities.[10] In addition, because it blocks one of the body's main mechanisms for lowering potassium, hyperkalemia can also result.

Eplerenone, which is derived from spironolactone, has a 10–20-fold lower affinity for the mineralocorticoid receptor in vitro. Its half-life is 4–6 h, and it is mainly eliminated by the CYP3A4, with no active metabolites after breakdown.[11] A chemical modification of the drug makes it more specific for the mineralocorticoid receptor over other steroid receptors and hence makes its side-effect profile more acceptable than that of spironolactone.[8]

Spironolactone has been proven to be beneficial for patients with heart failure. The RALES trial demonstrated a 30% reduction in mortality for heart failure compared with placebo. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[12] found a 15%

TABLE IV Renal function of the 34 patients with hyperkalemia

Mean serum creatinine at therapy start onset	1.4 ± 0.1 mg/dl
Mean serum creatinine at side effect onset	1.9 ± 0.2 mg/dl
Mean creatinine clearance at therapy start	64.6 ± 5.8 ml/min
Mean creatinine clearance at hyperkalemia onset	50.3 [a] ± 5.5 ml/min

[a] The mean creatinine clearance at time of onset of hyperkalemia was significantly lower than the creatinine clearance at therapy start (p = 0.001).

reduction in mortality compared with placebo in patients with left ventricular dysfunction after myocardial infarction. The EPHESUS trial did not show as large a decrease in mortality, but it did demonstrate gynecomastia at rates similar to placebo and was one of the first to demonstrate a reduction in mortality with the combined use of beta blockers and mineralocorticoid antagonists.[5] Multiple other studies have demonstrated the beneficial effects of spironolactone, including improved nitric oxide-induced vasodilation in the peripheral arteries[13] and improved left ventricular ejection fraction, left ventricular end-systolic volume, and exercise tolerance,[14] as well as a decrease in the frequency of premature ventricular complexes and episodes of ventricular tachycardia in patients with CHF.[15]

In what manner the mineralocorticoid receptor antagonists improve survival is yet to be determined. A substudy of the RALES group found that plasma procollagen type III amino-terminal peptide was higher before treatment and that spironolactone reduced these levels, suggesting that the mineralocorticoid receptor antagonists may reduce cardiac fibrosis; the marker was also found to correlate negatively with survival.[16] Other studies have found improvement in norepinephrine uptake, leading to more rapid norepinephrine breakdown and a potential explanation for the decrease in cardiac sudden death (via decreased arrhythmias) seen in RALES.[17]

In patients with reduced glomerular filtration rates, a slight worsening of heart failure or dehydration can result in hyperkalemia while the patient is taking a mineralocorticoid antagonist. One study found hyperkalemia (defined as serum potassium > 5.2 mmol/l) in more than 25% of the patients taking the medication,[2] while another study found severe hyperkalemia in 25 of 262 patients treated with an ACE inhibitor and spironolactone while being seen in the emergency department.[18] The study points out some of the trends our data demonstrated: patients susceptible to hyperkalemia tend to be older and have worse renal function at the time hyperkalemia develops compared with the time when therapy was started; thus, long-term monitoring is required.

The average age of our patients when started on spironolactone (67 years) is similar to patients' ages in both RALES and EPHESUS. Five percent of our patients developed hyperkalemia, 2% developed gynecomastia, and 2% had gastritis, compared with the results RALES and EPHESUS which report a 2 and 5.5% incidence of serious hyperkalemia (defined as a potassium level of ≥ 6 mmol/l) and a 9 and 0.5% incidence of gynecomastia, respectively. These reports did not report gastritis per se, but reported "gastrointestinal disorder" similar to placebo in RALES and higher than placebo in EPHESUS. Gastritis appears to be a frequent complaint in our practice. It is notable that the dose received by patients with gastritis is much higher than the other doses, but this is due more to an anomaly of one patient being on a very high dose of 200 mg b.i.d. in a smaller group of 15 patients. Based on our screening for gastritis, we believe that our measurement of gastritis, though lower than that in RALES or EPHESUS, represents an accurate estimate of stomach pain caused by the use of the drug, which often resulted in the need for discontinuing the medication.

Overall, the dose of spironolactone we used (38.4 vs. 25 mg) was higher than that used in RALES. This is due to several reasons, including the fact that we used the medication to treat hypertension and hyperaldosteronism, and our use of the medication predated publication of the RALES results; at that time exact dosing guidelines were not available.

Our study found a higher incidence of hyperkalemia than that found in RALES. This is not surprising considering that several factors influenced our research: (1) Our definition of hyperkalemia was lower than the RALES criteria. (2) Many patients who developed hyperkalemia were receiving potassium supplementation as a result of the combined use of loop diuretics and management goal serum potassium of between 4 and 5 mmol/l. (3) Many patients were also treated with an ACE inhibitor, which also contributes to decreased glomerular filtration rates. (4) It is more difficult to follow patients in a private setting than in a rigorously controlled randomized trial. (5) It is also a result of the higher dose of spironolactone used in our study. We also found that the patients with hyperkalemia tended to be older, reflecting decreased creatinine clearance with age contributing toward hyperkalemia.

Study Limitations

Limitations include the fact that the majority of our patients were older, and, because of the nature of a retrospective study, analyses of the patients' well-being and serum electrolytes were undertaken at random times after initiation of therapy. It is very possible that hyperkalemia and some other side effects not mentioned by the patients could have been missed. Overall, though, our data provide insight into the side effects resulting from use of spironolactone in private practice over a 7-year period. We continue to support the use of this drug strongly, but caution against its use without careful, long-term monitoring for hyperkalemia and vigilance for factors that may decrease a patient's renal function and result in hyperkalemia.

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