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The Adequacy of Laboratory Monitoring in Patients Treated With Spironolactone for Congestive Heart Failure

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OBJECTIVES This study was designed to determine the adequacy of monitoring patients receiving spironolactone as well as spironolactone's relationship to hyperkalemia.

BACKGROUND After the Randomized Aldactone Evaluation Study (RALES) demonstrated a 30% mortality benefit for treating severe heart failure patients with spironolactone, acceptance of this drug was overwhelming. Hyperkalemia and worsening renal function were rare in RALES, but laboratory monitoring was frequent. In clinical practice, the incidence of hyperkalemia and worsening renal function and adequacy of follow-up is unknown.

METHODS We reviewed the monitoring of congestive heart failure (CHF) patients with spironolactone initiation after publication of RALES. All potassium and creatinine determinations at baseline and within three months following therapy initiation were assessed. Increased potassium was defined as any [K] $\geq$5.5 mEq/l and severe hyperkalemia as any [K] $\geq$6.0.

RESULTS A total of 840 patients had new prescriptions for spironolactone. Of these, 91% had baseline laboratory values, and 34% did not have any serum potassium or creatinine determined within three months. Patients seen in the cardiology clinic were more likely to have appropriate follow-up ($p \leq 0.001$). Of 551 patients with follow-up laboratory values determined, 15% developed hyperkalemia and 6% developed severe hyperkalemia. Fifty-one patients (9%) developed renal dysfunction, of whom 25 developed hyperkalemia within three months. Hyperkalemia developed in 48 of 138 (35%) patients with baseline creatinine $\geq$1.5 mg/dl and 12 of 19 (63%) with baseline creatinine $\geq$2.5 mg/dl.

CONCLUSIONS Many patients treated with spironolactone for CHF do not receive needed follow-up of potassium or creatinine concentrations, although hyperkalemia and renal dysfunction are common. Elevated baseline creatinine predicts patients at high risk. Physician education of the risks of spironolactone and the need for follow-up is essential. (J Am Coll Cardiol 2005; 46:845–9) © 2005 by the American College of Cardiology Foundation

In 1999, the Randomized Aldactone Evaluation Study (RALES) demonstrated a 30% decrease in mortality for treating congestive heart failure (CHF) patients with spironolactone (1). The benefit was seen in patients already receiving background therapy with angiotensin-converting enzyme (ACE) inhibitors. Previously used in heart failure to promote diuresis, spironolactone was readily accepted as an inexpensive agent to treat severe systolic dysfunction (2,3). However, the potassium-sparing effects of spironolactone pose a great risk for retaining potassium and subsequent fatal arrhythmias, especially in patients taking other medications affecting the renin-angiotensin-aldosterone system. Indeed, Juurlink et al. (4) observed that following publication of the RALES trial there was a marked increase in prescriptions for spironolactone, as well as rates of hyperkalemia-associated mortality and morbidity greater than those observed before the RALES trial.

There are many reasons that could explain more safety problems with spironolactone use in clinical practice than in controlled trials. For example, inappropriate patient selection based on systolic function, New York Heart Association heart failure classification, background medication, and underlying renal disease has been reported in a previous retrospective study (5). We hypothesized that inadequate monitoring of serum potassium concentrations and renal function might also contribute to an increased incidence of hyperkalemia after initiation of spironolactone. We reviewed the monitoring patterns for hyperkalemia and renal dysfunction in CHF patients receiving spironolactone after publication of the RALES trial.

METHODS

Design. This was a retrospective study using the Veterans Affairs Information System Technology and Architecture (VISTA) database. We reviewed in-patient and outpatient electronic records for patients with CHF who received outpatient prescriptions for spironolactone at the following Maryland VA hospitals or clinics: Baltimore, Fort Howard, Cambridge, Perry Point, and Glen Burnie.

Identification of data. We extracted patient information and records from VISTA or through the Computerized Patient Record System (CPRS) interface program. Health care providers at the VA hospital centers use VISTA and CPRS to access and update medical records for patients. The information in the database is available to health care

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CHF = congestive heart failure
CPRS = Computerized Patient Record System
RALES = Randomized Aldactone Evaluation Study
VISTA = Veterans Affairs Information System Technology and Architecture

providers when prescribing spironolactone. Any prescriptions written at the VA medical center are entered into the database before being dispensed from the pharmacy.

We identified a cohort with an in-patient or outpatient diagnosis of heart failure (International Classification of Diseases 428.*x*) in VISTA. Consecutive patients who received their initial prescription for spironolactone between September 2, 1999, and April 1, 2004, were included. The data collection for follow-up laboratory data was through July 7, 2004, to allow evaluation of a three-month follow-up period. A total of 898 patients fit these criteria.

We defined background medications to include prescriptions providing medications up to 30 days before or after prescribing spironolactone. We determined cardiovascular medication prescriptions, including ACE inhibitors, angiotensin receptor blockers, beta-adrenergic antagonists, loop diuretics, potassium supplements, and cardiac glycosides.

We obtained ejection fraction data from echocardiogram or multiple gated acquisition scan reports. For values reported in closed-end ranges, we calculated a mean ejection fraction. For values reported as open-end ranges, we used defined lower or upper limits in our calculations.

The database provided in-patient and outpatient lab data that could be used to analyze monitoring patterns. The most recent serum potassium and creatinine values, up to one year before prescribing spironolactone, defined baseline values. Peak serum creatinine and potassium concentrations were obtained for the first three months after spironolactone was dispensed. Identical to the RALES trial, serum potassium concentrations ≥5.5 mEq/l defined hyperkalemia, and levels ≥6.0 mEq/l defined severe hyperkalemia. Rising serum creatinine concentrations from baseline to a value ≥2.5 mg/dl defined renal dysfunction. We reviewed in-patient and outpatient electronic charts for patients without follow-up laboratory data in the three months after initiating therapy.

The University of Maryland Medical Center Institutional Review Board and the Veterans Affairs Research and Development Committee reviewed and approved this project.

Statistical analysis. The data are expressed as mean ± SD. A two-tailed Student *t* test was used to compare continuous variables. Chi-square analysis was used to compare discrete variables. The package used was SPSS for Windows, version 11.5 (SPSS Inc., Chicago, Illinois).

RESULTS

We identified 898 patients with a diagnosis of CHF and a new prescription for spironolactone. Thirty-four patients were excluded from the monitoring analysis because they discontinued care at the study institutions during the three-month follow-up period. Twenty-four patients were excluded because of death within three months of starting spironolactone. A total of 840 patients were included in the monitoring analysis.

We found that 556 patients (66%) had serum potassium and creatinine values monitored within three months following initiation of spironolactone (Fig. 1). Five of these patients had values obtained outside of the VA system, with results noted by the prescribing VA physician. Thus, data from 551 patients were available for determination of hyperkalemia frequency. Of the 840 patients, 284 (34%) did not have any follow-up laboratory data. Of the 284 patients, the prescribing physician did not order follow-up laboratory data for 149, 41 failed to follow up for scheduled laboratory draws, and 94 had prescriptions filled at VA while also under the care of outside physicians. There is no evidence that the prescribing VA physician was aware of any laboratory values obtained elsewhere.

Patients with serum potassium concentrations measured within three months of initiating spironolactone were more likely to be receiving the following cardiovascular medications: ACE inhibitors or angiotensin receptor blockers, beta-adrenergic receptor blockers, and digoxin (all $p < 0.05$). These patients were younger (69 ± 11 years vs. 71 ± 11 years, $p < 0.05$) and had lower baseline serum potassium concentrations (4.3 ± 0.5 mEq/l vs. 4.4 ± 0.5 mEq/l, $p < 0.05$) (Table 1).

Of 551 patients with follow-up data, 83 patients (15%) developed hyperkalemia ([K] ≥5.5 mEq/l); 31 (6%) were classified as severe hyperkalemia ([K] ≥6.0 mEq/l). Patients that developed hyperkalemia had higher baseline potassium (4.7 ± 0.7 mEq/l vs. 4.3 ± 0.5 mEq/l, $p < 0.001$) and

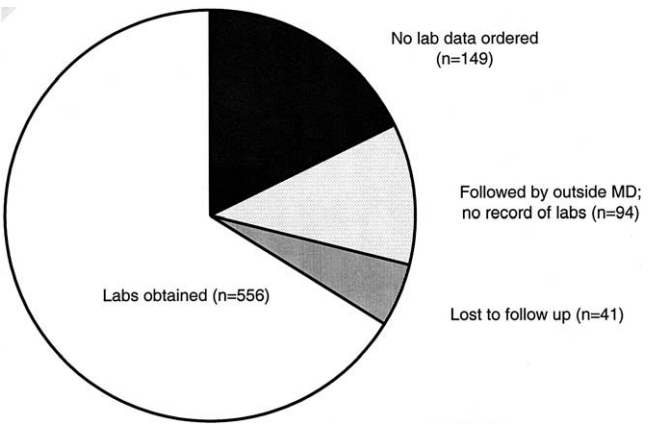

Figure 1. The laboratory monitoring follow-up of patients with heart failure started with spironolactone. One-third of the patients did not have serum potassium checked within three months of drug initiation.