Spironolactone in the Treatment of Congestive Heart Failure

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OBJECTIVE: To evaluate evidence supporting the use of spironolactone in managing congestive heart failure.

DATA SOURCES: Literature accessed through MEDLINE (January 1966–December 1999) and cross-referencing of selected articles. Search terms included spironolactone and heart failure.

DATA SYNTHESIS: Heart failure is a leading cause of morbidity and mortality. Through aldosterone antagonism, spironolactone may be an effective pharmacotherapeutic addition to patients not responding to standard drug therapy for heart failure.

RESULTS: Clinical trials have demonstrated that, in patients with heart failure, spironolactone improves laboratory indices, quality of life, and morbidity. Recently, spironolactone has been demonstrated to improve the survival of patients with New York Heart Association (NYHA) III or IV heart failure.

CONCLUSIONS: Spironolactone use should be considered in patients with NYHA Class III or IV heart failure.

KEY WORDS: spironolactone, heart failure, aldosterone.

Ann Pharmacother 2000;34:1336-40.

REQUEST

What evidence supports the use of spironolactone in managing congestive heart failure?

RESPONSE

Background

The pathogenesis of heart failure involves several significant neurohormonal components. Failure of the myocardial tissue to adequately propel blood throughout the body results in increased release of compensatory neurohormones, including two products resulting from the activation of the renin–angiotensin system: angiotensin II and aldosterone. Although increased release of aldosterone may improve cardiac function in the short term, persistently elevated aldosterone concentrations are thought to cause or contribute to many of the adverse changes in heart failure, including water retention,[1] electrolyte abnormalities,[1] myocardial fibrosis,[2] decreased baroreceptor responses,[3] decreased large artery compliance,[4] and increased arrhythmogenicity.[5]

Angiotensin-converting enzyme (ACE) inhibitors, agents proven to decrease the mortality of patients with heart failure,[6] lower serum aldosterone concentrations by decreasing the production of angiotensin II. However, small trials[7,8] evaluating aldosterone concentrations during ACE-inhibitor therapy have shown a lack of sustained suppression. Initial reductions of aldosterone concentrations from baseline measured after four to six weeks of ACE-inhibitor therapy dissipated after three to 12 months of therapy even though angiotensin II concentrations remained suppressed. Explanations for this observation include enhanced sensitivity to angiotensin II, increased release of adrenocorticotropic hormone, and/or a compensatory physiologic reaction, possibly related to the electrolyte shifts resulting from the initial lack of aldosterone. The inability of ACE inhibition to provide lasting suppression of aldosterone concentrations has led to speculation that a role may exist for the use of a direct aldosterone antagonist, such as spironolactone, in the treatment of patients with heart failure.

Clinical Trials

A review of the diuretic effects of spironolactone in heart failure has appeared elsewhere.[9] Historically, the role of spironolactone in heart failure has been to provide synergistic diuresis in patients who are refractory to combined ACE-inhibitor and loop diuretic therapy.[10,11] One early report[10] described three patients with marked congestive heart failure whose symptoms worsened despite treatment with digoxin, a loop diuretic, and an ACE inhibitor. Each patient's regimen was supplemented with spironolactone 50 or 100 mg/d and, after one to four weeks, resulted in improved diuresis, weight loss, and resolution of pulmonary and peripheral edema. The authors attributed these results to the diuretic effects of spironolactone.

An early clinical trial[11] involved 21 patients with New York Heart Association (NYHA) Class III or IV heart failure with marked edema that was unresponsive to loop di-

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uretics. Patients initially received a five-day regimen of an ACE inhibitor at the highest tolerated dosage plus bumetanide 5 mg twice daily. Five patients experienced diuresis quickly, achieving a 25% reduction in excess body weight relative to prior measurements. The other 16 patients had spironolactone 100 mg/d added to their regimen. Within seven days of this therapy, improved diuresis occurred in all but three patients. The mean daily weight loss increased from 0.08 to 0.61 kg. The authors concluded that adding spironolactone appears beneficial in patients unresponsive to loop diuretic and ACE-inhibitor therapy and speculated that increased suppression of the renin–angiotensin–aldosterone pathway may have been responsible for the improved diuresis.

Evidence now exists supporting the thought that spironolactone can be beneficial in the treatment of heart failure in ways other than its diuretic effect.[12-14] In a trial[12] monitoring clinical symptoms, 35 patients with NYHA Class IV heart failure receiving thiazide and/or loop diuretics were randomized to receive captopril alone or with spironolactone 20–40 mg three times daily. After four weeks of therapy, the spironolactone/captopril group experienced significantly greater improvement (from 4.3 to 8.1) in mean dyspnea–fatigue rating score (0 = lowest; 12 = highest possible score) than patients in the captopril monotherapy group (from 4.2 to 6.0; $p < 0.01$). The scores improved prior to the achievement of spironolactone-induced diuresis, thus affirming the thought that spironolactone could contribute to the treatment of heart failure patients apart from its diuretic effects.

MacFayden et al.[13] assessed the impact of spironolactone on heart rate variability, a reflection of the capacity of the myocardium to support the varying metabolic demands of daily living. Thirty-one patients with heart failure already receiving an ACE inhibitor and diuretic were randomized to receive spironolactone 50 mg/d or placebo. The spironolactone dosage was titrated, depending on tolerability, to dosages up to 100 mg/d. Heart-rate variability was assessed after eight weeks in 24 of these patients by measurement of their electrocardiogram R–R interval lengths. The change from baseline in standard deviation of normal-to-normal intervals was 9.1 msec within the spironolactone group compared with –1.2 msec within the placebo group ($p < 0.05$). Other heart-rate variability parameters were also increased. The concentrations of serum procollagen type III amino terminal peptide, an indicator of myocardial fibrosis, were also measured. Fibrosis of myocardial tissue, a process facilitated by aldosterone,[2] has been found in patients having arrhythmias of no apparent etiology.[15] Spironolactone, due to its aldosterone antagonistic properties, could theoretically reduce the incidence of cardiac dysrhythmias by impairing the myocardial fibrosis process. In this investigation, although reductions in serum procollagen type III amino terminal peptide concentrations were observed, the difference was not significant.[13]

The antiarrhythmic effects of spironolactone were studied in a trial[14] that randomized 42 NYHA Class II or III heart-failure patients, already receiving a loop diuretic and an ACE inhibitor, to additionally receive either spironolactone 50 mg/d or placebo. Based on patient tolerance, spironolactone dosages were as high as 100 mg/d. At eight-week assessments, patients receiving spironolactone ($n = 28$) had significantly greater reductions ($p < 0.05$) from baseline in premature ventricular contractions compared with placebo patients (>20% vs. ~10% reduction; $p < 0.05$). The impact spironolactone had on transient ventricular tachycardias could not be fully determined since their occurrence rate was too low for statistical evaluation. The initial results of this study suggested that spironolactone might have suppressed arrhythmias by elevating serum magnesium and intracellular potassium concentrations. In an attempt to confirm this finding, further assessments were conducted in six patients from each group. Myocardial ^{123}I-metaiodobenzylguanidine uptake, a measure of catecholamine uptake by myocardial cells, was increased within the spironolactone patients (from 1.31 to 1.47); it was decreased (from 1.42 to 1.35) within the placebo group ($p < 0.01$). Catecholamines appear to be broken down once inside the myocardial tissue[14]; thus, spironolactone may indirectly reduce circulating catecholamine concentrations, decreasing the potential for cardiac arrhythmias.

Although improvements in cardiac rhythms and biochemical measurements are of interest, standard therapies should also improve patients' quality of life and mortality rates. The recently published Randomized Aldactone Evaluation Study (RALES)[16] was the first large-scale, randomized, double-blind, placebo-controlled trial conducted to assess the impact of low-dose spironolactone therapy on hospitalization and mortality rates in patients with heart failure. The researchers enrolled 1663 patients with primarily NYHA Class III (70.5% of patients) or IV (29%) heart failure who were already being treated with a loop diuretic (100% of patients) and/or an ACE inhibitor (~95%). The majority of patients were also receiving digoxin (~73%); about 10% of the patients were receiving a β-blocker. The average age of the patients was 65 years; 73% of the patients were men and 87% were white. The mean ejection fraction of the subjects was 25%, and heart failure was due to ischemic causes in 55% of the patients. Patients were permitted to receive vasodilator therapy in addition to ACE inhibitors or as alternative therapy when ACE inhibitors were not tolerated. Patients with renal insufficiency (serum creatinine >2.5 mg/dL) or elevated potassium concentrations (>5 mEq/L) were not permitted into the trial.

Eligible patients were randomized to additionally receive daily placebo ($n = 841$) or spironolactone 25 mg ($n = 822$). The groups were similar with regard to demographics, heart disease severity, and the use of traditional cardiac medications (ACE inhibitors, loop diuretics, digoxin, β-blockers, aspirin). The investigators had previously[17] determined that a 25-mg daily dose of spironolactone was well tolerated and likely to be effective. The dosages of spironolactone were reduced to 25 mg every other day in patients who became hyperkalemic with the initial dose if

modification of concurrent medications could not alleviate this electrolyte disorder. Eight weeks into the trial, the dosage was increased to 50 mg/d, if tolerated, in patients who were experiencing a worsening of their heart failure but had not developed hyperkalemia. The average daily dose ultimately used in the investigation was approximately 25 mg. All-cause mortality was the primary end point; secondary end points included mortality of cardiac cause, hospitalization, and changes in NYHA functional class. The trial was terminated prematurely (average 24-mo length of follow-up) due to the magnitude of improvement observed in the patients receiving spironolactone.[16]

The incidence of overall death was decreased within the spironolactone group compared with the placebo group (34.5% vs. 45.9%, respectively). The authors reported that this was a 30% reduction in the risk of overall deaths (relative risk [RR] 0.70; 95% CI 0.60 to 0.82; $p < 0.001$) and an 11.4% absolute reduction in the incidence of death. Spironolactone reduced the incidence of cardiac death from 37.3% to 27.5%, representing a 31% reduction (RR 0.69; 95% CI 0.58 to 0.82; $p < 0.001$). Spironolactone was also associated with significant decreases in the incidences of sudden death (13.1% vs. 10.0%; $p < 0.02$) and death from worsening heart failure (22.5% vs. 15.5%; $p = 0.001$). In addition to mortality benefit, spironolactone was associated with a significant decrease (30%) in the risk of cardiac-related hospitalizations compared with placebo (515 vs. 753 hospitalizations, respectively; RR 0.70; 95% CI 0.59 to 0.82; $p < 0.001$) compared with placebo. This primarily reflected the significant decrease in hospitalizations for worsening heart failure (413 vs. 663, respectively; RR 0.65; 95% CI 0.54 to 0.77; $p < 0.001$).[16]

Forty-one percent of patients receiving spironolactone improved their NYHA classification compared with only 33% of those receiving placebo ($p < 0.001$). Subgroup analysis indicated that age (≥ vs. <67 y), gender, ejection fraction (≥ vs. <26%), or cause of heart failure (ischemic vs. nonischemic) did not impact the effects of spironolactone therapy. However, spironolactone did not significantly benefit patients with heart failure who were not concurrently receiving either digoxin or ACE-inhibitor therapy, although a beneficial trend was present. The absence of β-blocker therapy did not preclude patients from receiving any benefit from spironolactone; however, the concurrent use of β-blocker therapy did further magnify the favorable effects of spironolactone.[16]

Adverse Effects

Although the evidence presented here suggests that using spironolactone in heart failure is likely beneficial, patients' ability to tolerate this agent is an important issue to consider. A primary concern with using this drug in patients with heart failure is the potential for inducing hyperkalemia. Published reports,[14,16-18] have described hyperkalemia occurring in patients receiving spironolactone even in the absence of renal disease or other risk factors for hyperkalemia. Spironolactone dosages ≥50 mg/d cause hyperkalemia severe enough to require dose reduction or discontinuation more often than do dosages ≤25 mg/d. A greater risk of hyperkalemia is associated with using spironolactone in patients with baseline serum creatinine concentrations >1.6 mg/dL, or potassium concentrations ≥4.2 mEq/L, or in patients receiving higher dosages of ACE inhibitors.[17] In RALES,[16] spironolactone induced a median increase of 0.3 mEq/L in potassium concentrations, which was statistically significant ($p < 0.001$) but clinically unremarkable. Some patients who developed hyperkalemia subsequently achieved acceptable potassium concentrations after decreasing their spironolactone dose,[14] but others, especially those with preexisting renal disease, required discontinuation of the agent.[14,18]

Gynecomastia and breast pain (combined incidence: 10% spironolactone vs. 1% placebo) were the only significant adverse events ($p < 0.001$) associated with spironolactone use reported in RALES.[16] These effects were not reported in the other trials reviewed above; however, the duration of these trials was much shorter. Although digoxin, by virtue of its steroid-like structure, is also known to induce gynecomastia, its use in RALES was equally distributed among placebo and spironolactone patients.

Dehydration has been reported[10,11] when spironolactone was used in conjunction with high-dose loop diuretics. Complete recovery occurred with fluid replacement and/or drug discontinuation. Renal dysfunction has developed when spironolactone was coadministered with ACE inhibitors, particularly with daily spironolactone dosages of ≥50 mg.[10,11,17,18] Renal function returned to baseline upon withdrawing and/or adjusting the dosages of both medications.[10,11]

Practical Issues

Two practical issues need to be further delineated with respect to the use of spironolactone in patients with heart failure. The first is to identify patients who would benefit from spironolactone therapy. RALES[16] primarily investigated patients with NYHA Class III or IV heart failure. At present, it is not known whether these findings can be extrapolated to patients with less severe forms of heart failure. It may be reasonable to surmise that patients with higher serum aldosterone concentrations may benefit more from aldosterone antagonism, and it has been shown[11] that higher plasma aldosterone concentrations correlate with a weaker response to loop diuretics and ACE inhibitors. Unfortunately, cost and other procedural factors limit the routine assessment of plasma aldosterone concentrations. Clinical trials[11,12] have shown that commonly available urinary Na^+:K^+ concentration ratios are inversely proportional to serum aldosterone concentrations, and a urinary Na^+:K^+ ratio <1.0 may be a useful marker for initiating spironolactone therapy in patients with heart failure.[11]

Once a patient who can benefit from spironolactone therapy has been identified, the second issue is to define when spironolactone should be initiated in relation to other medications proven to be beneficial in heart failure. Given the abundance of clinical supportive data, ACE-inhibitor

therapy or, when patients become intolerant to ACE inhibitors, another form of vasodilator therapy (e.g., hydralazine/isosorbide dinitrate or angiotensin II receptor blocker) should be considered first-line therapy. Diuretics are indicated in patients with congestion. Once these therapies have been initiated and the dosages have been titrated to appropriate levels, clinicians should consider adding other pharmacologic modalities, including spironolactone.

The routine use of β-blocker therapy has most recently become established in the therapy of heart failure.[19] Whether or not spironolactone should be added prior to β-blocker therapy or vice versa in patients eligible to receive β-blocker therapy is not definitively known at present. The results of RALES[16] indicated that spironolactone significantly benefited patients regardless of the presence of β-blocker therapy; however, the benefit associated with spironolactone was more pronounced in patients receiving concurrent β-blocker therapy. This suggests that the ultimate goal of therapy for heart failure should be to initiate both medications; however, it should be noted that β-blocker therapy is not advocated in patients who are clinically unstable or have severe symptoms (i.e., NYHA Class IV).[19]

In RALES,[16] although a favorable trend was observed, spironolactone did not significantly benefit patients who were not receiving concurrent digoxin. Digoxin has been demonstrated[19] to reduce morbidity of heart failure and its use is encouraged, especially in symptomatic patients. Digoxin, however, has not been demonstrated to improve survival of patients with heart failure; it therefore is often avoided due to concerns for possible toxicity.[20] An issue that requires further investigation is whether patients receiving spironolactone should receive concurrent digoxin to maximize the beneficial attributes of spironolactone.

When spironolactone therapy is going to be initiated, it has been recommended[17] that patients receiving concurrent ACE-inhibitor therapy should first receive spironolactone 25 mg/d if the serum potassium concentration is within normal limits. The spironolactone dosage should be decreased if hyperkalemia or renal dysfunction develops. In addition, clinicians should consider titrating the dosage up to 50 mg/d, if tolerated, in patients whose heart failure is progressing despite the initiation of spironolactone. Patients receiving spironolactone, especially in conjunction with ACE inhibitors, should have their serum potassium and creatinine concentrations monitored after seven days of treatment and then frequently (weekly–monthly) for the first few months, and routinely (every 3–6 mo) thereafter. The drug should be avoided in patients with renal insufficiency or high baseline serum potassium concentrations. Patients with serum baseline potassium concentrations >5.0 mEq/L were excluded from RALES.[16] Potassium supplements or potassium-retaining or -containing medications should be used cautiously, if at all, in patients receiving spironolactone, especially if ACE inhibitors or angiotensin II receptor blockers, medications also known to increase serum potassium concentrations, are being used concurrently.

Summary

A compilation of results from clinical trials imply that appropriately dosed spironolactone is a well-tolerated agent that improves the laboratory indices, quality of life, and morbidity of patients with heart failure. More recently, spironolactone also has been demonstrated to improve the survival of patients with more serious degrees of heart failure. These data, along with current knowledge of the mechanisms of action of spironolactone and the pathophysiology of heart failure, indicate that spironolactone can benefit patients with NYHA Class III or IV heart failure.

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EXTRACTO

OBJETIVO: Evaluar la evidencia que apoya el uso de espironolactona en el manejo de fallo cardíaco congestivo.

FUENTES DE INFORMACIÓN: Literatura accesada a través de MEDLINE (enero de 1966 a diciembre 1999) y referencia cruzada de articulos selectos. Espironolacona y fallo cardíaco fueron incluídos como términos de búsqueda.

SÍNTESIS: Fallo cardíaco es una causa principal de morbilidad y mortalidad. Espironolactona, a través de su antagonismo de aldosterona, puede ser una adición farmacoterapéutica efectiva para pacientes que no han respondido a la terapia farmacológica estándar de fallo cardíaco.

RESULTADOS: Estudios clínicos han demostrado que espironolactona mejora los parámetros de laboratorio, la calidad de vida, y morbilidad en pacientes con fallo cardíaco. Recientemente se demostró que el uso de espironolactona mejora la supervivencia de pacientes con fallo cardíaco clase III ó IV de la Asociación del Corazón de New York (NYHA, por sus siglas en inglés).

CONCLUSIÓNES: El uso de espironolactona debiera ser considerado en pacientes con fallo cardíaco clase III ó IV de la NYHA.

Juan Francisco Feliú

RÉSUMÉ

OBJECTIF: Évaluer la littérature concernant l'utilisation de la spironolactone dans le traitement de l'insuffisance cardiaque.

DEVIS EXPERIMENTAL: Une recherche via MEDLINE a été effectuée au cours de la période de janvier 1966 à décembre 1999. Les termes spironolactone et insuffisance cardiaque ont été utilisés.

RÉSUMÉ: L'insuffisance cardiaque représente une cause importante de mortalité et de morbidité. La spironolactone peut être ajoutée dans le traitement pharmacologique de l'insuffisance cardiaque chez les patients ne répondant pas au traitement conventionnel.

RÉSULTATS: Les études cliniques ont démontré que chez les patients présentant une insuffisance cardiaque, la spironolactone améliore la qualité de vie, les tests de laboratoire, et la morbidité. Récemment, une étude a démontré que la spironolactone améliorait la survie des patients avec insuffisance cardiaque de la NYHA classe III ou IV.

CONCLUSIONS: La spironolactone devrait être utilisée chez les patients en insuffisance cardiaque de la NYHA classe III ou IV.

Louise Mallet