CLINICIAN UPDATE

Aldosterone Blockade in Patients With Systolic Left Ventricular Dysfunction

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The patient, W.L., is a 62-year-old white man with a history of hypertension, hypercholesterolemia, and an anterior Q-wave myocardial infarction 3 years ago. He has had 2 admissions for heart failure in the past 6 months. He was last discharged 2 months ago on aspirin 325 mg daily, simvastatin 40 mg daily, enalapril 10 mg BID, metoprolol XL 100 mg daily, digoxin 0.25 mg daily, and furosemide 120 mg BID. Over the past month, he has noted some increasing dyspnea on exertion and occasional episodes of paroxysmal nocturnal dyspnea but has not had any increase in peripheral edema or body weight. His left ventricular ejection fraction on discharge from the hospital 2 months ago was 26%, with evidence of a large anterior akinetic area but without evidence of inducible myocardial ischemia on dobutamine echocardiography. His laboratory data today included a hematocrit of 41%, serum creatinine 1.1 mg%, potassium 4.1 meq/L, fasting blood sugar 108 mg%, LDL cholesterol 92 mg/dL, HDL cholesterol 45 mg/dL, triglycerides 188 mg/dL, serum digoxin level 1.2, and brain natriuretic peptide (BNP) (Biosite) 508. ECG revealed evidence of an old anterior myocardial infarction, and chest x-ray showed cardiomegaly with some increase in pulmonary vascularity. At this time, would you suggest any change in his medical regimen?

Angiotensin-converting enzyme (ACE) inhibition and β-blockade have been shown effective in improving survival in patients with systolic left ventricular dysfunction (SLVD) resulting from both ischemic and nonischemic cardiomyopathy; they are indicated in all patients with heart failure (HF) caused by SLVD unless contraindicated or not tolerated. Although they improve the symptoms of HF, loop diuretics and digoxin have not been shown to reduce mortality rate. There is, however, increasing evidence that aldosterone blockade is effective in reducing mortality and morbidity rates in patients with HF caused by SLVD that is associated with both ischemic and nonischemic etiologies.[1,2] Aldosterone-blocking agents have also been shown to be effective in controlling blood pressure in patients with essential hypertension and reducing left ventricular mass, myocardial fibrosis, microalbuminuria, and vascular compliance.[3,4] Their effects on morbidity and/or mortality in patients with essential hypertension, and whether they provide a reduction in clinical events independent of blood pressure–lowering effects, are as yet unknown. Before we further discuss patient W.L., the evidence relating to the role of aldosterone blockade in patients with SLVD will be briefly reviewed.

Effect of Aldosterone Blockade in Patients With Chronic HF Caused by SLVD

The Randomized Aldactone Evaluation Study (RALES)[1] evaluated the role of the aldosterone blocker spironolactone in patients with New York Heart Association class III to IV HF, a history of NYHA class IV HF resulting from either ischemic or nonischemic etiology during the previous 6 months, and a left ventricular ejection fraction ≤40%. Patients with renal dysfunction (creatinine >2.5 mL/dL) and those with serum potassium >5.0 meq/L were excluded. In this study of >1600 patients followed up for a mean of 2 years, spironolactone at a mean dose of 26 mg daily given on top of standard therapy, which included an ACE inhibitor and diuretic with or

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without digoxin and a β-blocker, was associated with a 30% reduction in all-cause mortality ($P<0.001$) and a 35% reduction ($P<0.001$) in hospitalization for HF. The reduction in all-cause mortality was the result of both a 36% reduction ($P<0.001$) in death from progressive HF and a 29% reduction ($P=0.02$) in sudden cardiac death. The major adverse effect of spironolactone was an increase in gynecomastia and breast pain in males. There was also an absolute increase of 1% in serious hyperkalemia (K^+ ≥6.0 meq/L) in patients randomized to spironolactone compared with placebo (P=NS). The beneficial effects of spironolactone on mortality rate were relatively uniform across a number of predefined subgroups.

On the basis of this study, spironolactone has been recommended for the treatment of severe HF caused by SLVD in both the United States and European guidelines. The adoption of these recommendations into clinical practice has, however, been variable because the recommendation was based on a single trial, and only 10% to 11% of patients in that study were on a β-blocker.[1] Further information on the role of aldosterone blockade in patients with HF caused by SLVD has become available from the Eplerenone Post–acute myocardial infarction Heart failure Efficacy and SUrvival Study (EPHESUS).[2]

Effect of Aldosterone Blockade in Patients With SLVD After Acute Myocardial Infarction

EPHESUS[2] randomized >6600 patients with evidence of an acute myocardial infarction (AMI), a left ventricular ejection fraction ≤40%, and evidence of HF (except patients with diabetes mellitus, who were required to have only evidence of SLVD) to the selective aldosterone blocker eplerenone or placebo 3 to 14 days after infarction. Patients with a serum creatinine ≥2.5 mg/dL and those with evidence of serum potassium ≥5.0 meq/L were excluded. Study medication was administered a mean of 7.3 days after infarction, beginning at a dose of 25 mg daily for 1 month and then uptitrated to 50 mg daily unless there was evidence of hyperkalemia. Patients randomized to eplerenone at a mean dose of 43 mg daily over a mean follow-up of 16 months had a 15% reduction in total mortality ($P=0.008$) (co-primary end point), a 17% reduction in cardiovascular mortality ($P=0.005$), and a 13% reduction in cardiovascular mortality/cardiovascular hospitalizations ($P=0.002$), including hospitalization for myocardial infarction, stroke, HF, and ventricular arrhythmias (co-primary end point). The major cause of cardiovascular death in this study was sudden cardiac death, which was reduced by 21% ($P=0.003$) in patients randomized to eplerenone. The major cause of cardiovascular hospitalizations was HF. Fifteen percent fewer patients ($P=0.03$) were hospitalized for HF in patients randomized to eplerenone and had 23% fewer episodes of hospitalization for HF ($P=0.002$). Of particular interest was the finding that eplerenone was effective in reducing all-cause mortality as well as cardiovascular mortality/cardiovascular hospitalization in patients on an ACE inhibitor or an angiotensin receptor–blocking agent (ARB) and a β-blocker. Furthermore, eplerenone had a beneficial effect in patients on optimal therapy post-infarction, which included an aspirin, statin, reperfusion within 14 days of myocardial infarction, an ACE inhibitor or ARB, and a β-blocker.

In contrast to the experience in RALES,[1] there was no excess of gynecomastia, breast pain, or impotence in males, attesting to the selectivity of eplerenone for the mineralocorticoid receptor in comparison to spironolactone, which also binds to androgen and progesterone receptors. There was a 1.6% absolute increase in serious hyperkalemia (K^+ ≥6.0 meq/L) in patients randomized to eplerenone ($P=0.002$). There was, however, a 4.7% absolute decrease in the incidence of hypokalemia (K^+ ≤3.5 meq/L) in patients randomized to eplerenone compared with placebo ($P\leq0.001$). Although results of the EPHESUS trial have been reported,[2] it should be emphasized that these results are under review by the US Food and Drug Administration, and eplerenone is not yet indicated for the treatment of SLVD after AMI.

Effect of Aldosterone Blockade on Potassium Homeostasis

Since the publication of RALES,[1] there have been several reports of hyperkalemia associated with the use of spironolactone in patients with HF caused by SLVD.[5–10] Many of these reported episodes of hyperkalemia were associated with hospitalization, renal dysfunction, need for renal dialysis, and in some instances death. Such reports have caused concern, and many clinicians are reluctant to attempt aldosterone blockade. A review of these reports, however, suggests that the majority of episodes of serious hyperkalemia (K^+ ≥6.0 meq/L) associated with aldosterone blockade were at doses above those recommended in RALES[1] and occurred in patients excluded from RALES. Furthermore, serum potassium was often not monitored as recommended in RALES, and the dose of aldosterone blockade was not adjusted according to the level of serum potassium.

In RALES,[1] spironolactone was administered at a dose of 25 mg daily. It was recommended that serum potassium monitoring occur 1 week after initiating therapy, at 1 month, and thereafter every 3 months. An increase in serum potassium ≥5.5 meq/L at any time prompted a review of concomitant medications associated with hyperkalemia, such as potassium supplements or nonsteroidal antiinflammatory agents, and a reduction of the dose of study medication to 25 mg every other day. If, after 4 weeks of therapy, there was no evidence of a serum potassium ≥5.5 meq/L but symptomatic evidence of progressive HF, the dose of study medication could be increased to 50 mg daily. The mean dose of spironolactone in RALES was 26 mg daily; approximately 70% of patients were on 25 mg daily, 15% on 25 mg every other day, and 15% on 50 mg daily. The finding of a serum potassium ≥6.0 meq/L at any time prompted the temporary discontinuation of study med-

ication, which could be reinstituted after adjusting concomitant medication and the return of serum potassium to <5.5 meq/L. In EPHESUS,[2] eplerenone was initiated at 25 mg daily for 1 month and then increased to 50 mg daily (a dose approximately equivalent to 25 mg a day of spironolactone) with a similar recommendation for monitoring of serum potassium and adjustment of study medication according to serum potassium measurements. This strategy, both in RALES[1] and EPHESUS,[2] was not associated with the adverse events noted in clinical practice with spironolactone. It should, however, be pointed out that there have been occasional episodes of serious hyperkalemia associated with the use of spironolactone even when the RALES recommendations are followed.[1] This may relate in part to the recommendation to exclude patients with a serum creatinine >2.5 mg/dL. Such a strategy appears inadequate in elderly patients, those with a low body mass index, and those with diabetes mellitus because serum creatinine may underestimate renal dysfunction in these circumstances. On the basis of experience in RALES[1] and EPHESUS,[2] it would be prudent to exclude patients with severe renal dysfunction and a creatinine clearance ≤30 mL/min and to be cautious in those with a creatinine clearance between 30 and 50 mL/min, who should be followed up even more closely than recommended in the RALES recommendations for monitoring of serum potassium and creatinine.

It is important to emphasize that although aldosterone blockade is effective in reducing mortality on top of an ACE inhibitor or ARB and a β-blocker, it is essential to monitor serum potassium. Potassium blood levels may be monitored at any convenient laboratory and do not require a patient visit to the physician. Failure to follow the dosing recommendations in RALES[1] and EPHESUS[2] and to recognize the potential for serious hyperkalemia could result in renal dysfunction and possibly death. If, however, the physician is willing to monitor serum potassium, adjust the dose of aldosterone blocker according to the level of serum potassium, exclude those with severe renal insufficiency, and cautiously monitor those with mild-to-moderate renal insufficiency, it is apparent from the RALES[1] and EPHESUS[2] studies that patients with SLVD will benefit from an improvement in mortality as well as morbidity.

Although aldosterone blockade is associated with an increase in serious hyperkalemia, it also can protect against hypokalemia (K^+ ≤3.5 meq/L). Hypokalemia may be as great or potentially a greater risk than hyperkalemia in patients with HF. In patients with systolic hypertension in the Systolic Hypertension in the Elderly Program (SHEP) trial,[11] blood pressure was controlled with a diuretic with or without a β-blocker and resulted in a significant reduction in cardiovascular events. However, ≈7% of patients in SHEP developed hypokalemia. In these patients, the benefit of blood pressure control on cardiovascular events was negated. In patients with HF caused by SLVD, Cooper et al[12] have found that patients treated with a loop diuretic in the Studies Of Left Ventricular Dysfunction trial had an increase in mortality compared with those not on a diuretic. Although this could reflect the fact that patients on a diuretic had more severe HF than those not on a diuretic, it is important to note that those patients on a potassium-sparing diuretic, mainly spironolactone, had a reduction in mortality both from progressive HF and sudden cardiac death in comparison to those on a diuretic. In EPHESUS,[2] there were almost twice as many episodes of hypokalemia prevented than episodes of hyperkalemia induced by eplerenone.

How Long Should an Aldosterone Blocker Be Administered?

In patients with severe chronic HF caused by SLVD, an aldosterone blocker should be maintained indefinitely, as should an ACE inhibitor and a β-blocker. In patients with SLVD and HF after AMI, the optimum duration of treatment is less certain. One approach might be to maintain an aldosterone blocker indefinitely in those patients with persistent left ventricular systolic dysfunction (left ventricular ejection fraction ≤40%) or signs of HF. In those patients who improve their left ventricular ejection fraction ≥40% and in those who are asymptomatic, it might be reasonable to consider withholding the aldosterone blocker after a period of 1 to 2 years. A final recommendation must await a more detailed analysis of the EPHESUS trial[2] (in which the mean follow-up was 16 months; range, 0 to 33 months).

Which Aldosterone Blocker?

In patients with severe HF caused by SLVD, it would be reasonable to consider spironolactone according to the dosing regimen recommended in RALES.[1] Those male patients who develop gynecomastia, breast pain, or impotence and those females who develop menstrual irregularities or other spironolactone-related side effects should be given a trial of eplerenone 25 to 50 mg daily, when available, to maintain aldosterone blockade.

In post-AMI patients, evidence-based medicine would suggest administering eplerenone according to the dosing regimen in EPHESUS.[2] When cost is a major factor and relatively short-term use of aldosterone blockade is anticipated, one might consider administering spironolactone according to the dosing regimen in RALES.[1] One should, however, be cautious in applying 25 mg of spironolactone to patients with an AMI without further evidence from a larger number of patients. Initial experience by Hayashi et al[13] using intravenous canrenoate, a metabolite of spironolactone, on day 1 post-infarction after percutaneous reperfusion followed by 25 mg of spironolactone daily for 1 month suggests that this regimen is effective in preventing ventricular remodeling and collagen formation. The effects of this dosing regimen on morbidity and mortality are uncertain. Although both spironolactone and eplerenone block the effect

of aldosterone at the mineralocorticoid receptor, there are insufficient data at this time to be confident about their relative effectiveness and risk/benefit ratio. For example, because of its metabolite potassium canrenoate, spironolactone has a relatively longer half-life than eplerenone. It can be postulated that the longer half-life of spironolactone could result in a higher incidence of hyperkalemia in comparison to eplerenone. Similarly, the effects of spironolactone on androgen and prostagen receptors might have beneficial or detrimental effects on the cardiovascular system other than those seen in EPHESUS.[2] Clearly, further prospective direct trials comparing spironolactone to eplerenone will be necessary to determine if there are any differences in their risk/benefit ratio. In the interim, it would be prudent to use the drug regimen and indications proven by the pivotal prospective randomized studies.[1,2]

Which Patients Should Be Treated With an Aldosterone Blocker?

Aldosterone blockade is effective in patients with severe chronic HF caused by SLVD associated with both ischemic and nonischemic cardiomyopathy.[1] It has also been found effective in patients with HF caused by SLVD after AMI. Although evidence suggests that ventricular remodeling, endothelial function, heart rate variability, baroreceptor function, and myocardial collagen formation are improved by aldosterone blockade in patients with mild-to-moderate HF caused by SLVD (NYHA class II through III),[14,15,16] there is no prospective evidence from randomized studies as to the effect of aldosterone blockade on mortality or morbidity in these patients. It might, however, be reasonable to extrapolate from the results of aldosterone blockade in those patients with severe chronic HF studied in RALES,[1] and those with less severe HF studied in EPHESUS after infarction, to those with mild-to-moderate chronic HF. Until further data are available, it would not be reasonable to extrapolate the findings in RALES[1] and EPHESUS[2] to those patients with HF caused by preserved systolic function and those with asymptomatic SLVD without further prospective randomized studies powered to evaluate clinical events.

Mechanism of Action of Aldosterone Blockade

Aldosterone-blocking agents are known to increase diuresis and natriuresis and to lower blood pressure in patients with essential hypertension while sparing potassium. Although these "classic" effects of aldosterone blockade may account for its effects in controlling blood pressure, over the past several years, other nonrenal effects of aldosterone blockade have been demonstrated that may in large part be responsible for its beneficial effects in patients with SLVD after AMI and in chronic HF. These mechanisms have been recently reviewed[17–27] and include: an effect on vascular inflammation, vascular remodeling and compliance, ventricular hypertrophy and fibrosis, endothelial dysfunction, myocardial norepinephrine uptake, heart rate variability, baroreceptor function, fibrinolysis, and platelet activation.

Future Indications for Aldosterone Blockade

Other potential indications for aldosterone blockade will require further prospective evaluation, including patients with HF with preserved systolic function; those with asymptomatic SLVD; prevention of mortality and morbidity in patients with essential hypertension and left ventricular hypertrophy; prevention of progressive renal dysfunction; prevention of the progression of atherosclerosis, and prevention of ischemic events. Our understanding of the role of aldosterone blockade in patients with cardiovascular disease is still in its early stage. The mechanisms associated with the beneficial effects of aldosterone blockade on mortality and morbidity in patients with SLVD are still incompletely understood. Although predicting the outcome of future randomized studies is difficult, it is reasonable to postulate that the beneficial effects of aldosterone blockade in the RALES[1] and EPHESUS[2] studies in patients with SLVD treated with standard therapy including an ACE inhibitor and a β-blocker likely will extend beyond these indications.

Patient W.L.

On the basis of the above discussion, it would appear reasonable to recommend that patient W.L., with evidence of an ischemic cardiomyopathy and recent hospitalizations for HF despite "optimal therapy," be given an aldosterone-blocking agent.

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