Clinical Update

A new treatment option for severe heart failure

Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709-17.

Background

Over the past decade significant advances have been made in the treatment of congestive heart failure (CHF). Despite the reduction in morbidity and mortality conferred by angiotensin-converting-enzyme (ACE) inhibitors and β-blockers, the burden of illness from CHF remains high. Although ACE inhibitors inhibit the renin–angiotensin–aldosterone system, complete suppression of aldosterone production does not occur.[1] Given the deleterious effects of aldosterone, which include salt and water retention, sympathetic activation and vascular fibrosis, aldosterone-receptor blockade with spironolactone may be beneficial in patients with CHF.[2]

Question

Does the addition of spironolactone to a standard treatment regimen for heart failure reduce morbidity and mortality among patients with severe CHF?

Design

In this study 1663 patients with severe CHF (New York Heart Association [NYHA] functional class III or IV) were randomly assigned to receive placebo or spironolactone (starting dose 25 mg) in a double-blind fashion. At the time of study entry almost all patients were taking ACE inhibitors and loop diuretics, and most were taking digoxin. Important exclusion criteria included an elevated creatinine level (> 221 μmol/L) or a potassium level above 5 mmol/L at baseline. Patients were monitored for hyperkalemia and rising creatinine levels 1 week after starting therapy, every 4 weeks for the first 12 weeks, and every 3 to 6 months thereafter. Spironolactone therapy was stopped if the creatinine level reached 354 μmol/L. The primary end point was death from any cause. Secondary end points included admission to hospital because of cardiac causes and change in NYHA functional class. Data were analyzed using the intention-to-treat principle.

Results

The baseline characteristics of the patients were similar in both groups. Over two-thirds were classified as NYHA functional class III. The average daily dose of ACE inhibitor was 15 mg of enalapril or lisinopril, or 63 mg of captopril. Ischemia was the cause of CHF in just over half of the patients. After 2 years of follow-up, the mean daily dose of spironolactone in the treatment arm was 26 mg.

The study was stopped after a mean follow-up of 24 months because the death rate was significantly lower in the spironolactone group than in the placebo group (35% v. 46% respectively; relative risk 0.70, 95% confidence interval [CI] 0.60–0.82; $p < 0.001$). The number of hospital admissions because of cardiac causes was also significantly lower in the spironolactone group than in the placebo group (515 v. 753; relative risk 0.70; 95% CI 0.59–0.82; $p < 0.001$). Fewer patients in the placebo group than in the spironolactone group showed improvement in functional class. Serious hyperkalemia (potassium level above 6.0 mmol/L) occurred in 10 patients in the placebo group and 14 patients in the spironolactone group (difference not significant, $p = 0.42$). Gynecomastia or breast pain was reported in 10% of men taking spironolactone, although few of them (1.2%) stopped taking the drug for this reason.

Commentary

The patients in this study had advanced heart failure, as demonstrated by their high mortality rate. The addition of spironolactone, at doses that have little diuretic effect, resulted in significant reductions in mortality and hospital admissions and improved functional status of patients with CHF. There were surprisingly few episodes of serious hyperkalemia. This is attributable to the use of spironolactone in low dose and strict adherence to exclusion criteria.

Practice implications

The absolute risk reduction of 11% means that only 9 patients with severe CHF need to be treated with low-dose spironolactone for 2 years to prevent 1 death. Patients with pre-existing hyperkalemia or significant renal impairment, however, are ineligible for this treatment. When initiating spironolactone therapy, physicians must monitor potassium and creatinine levels closely. — *Kathryn A. Myers*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

References

1. Struthers AD. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. *J Card Fail* 1996;2:47-54.
2. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol* 1996;78:902-7.