A 68-year-old Native American housewife who lived on an Indian reservation in Nevada had been under the care of a family practice physician for congestive heart failure (CHF). She had had an acute myocardial infarction (MI) 4 years ago. Left ventricular failure was first noted 18 months ago, and the patient was kept in a compensated state on multidrug therapy until 10 weeks ago when her CHF did not respond to her current regimen. Her medications included digoxin 0.125 mg daily, furosemide 40 mg twice a day, enalapril 20 mg every morning, carvedilol 25 mg twice a day, atorvastatin 20 mg every night at bedtime, ezetimibe 10 mg every night at bedtime, and a salt-poor diet. Physical examination revealed the following: fine moist rales were heard in the right base, there was an S3, S4, a grade 2/4 mitral and a grade 1/4 aortic systolic murmur. The point of maximal impulse was diffuse at the fifth intercostal space on the anterior axillary line. An electrocardiogram revealed an old anteroseptal MI, a brief run of ventricular premature beats, and the average heart rate was 76/min; the blood pressure was 135/70 mm Hg. Serum electrolyte levels were within the normal range, and the blood sugar and urea nitrogen levels were normal. A consultation with a cardiologist based at a medical school was obtained via the Internet. After a thorough review of the patient’s medical history, the addition of eplerenone 25 mg twice a day was recommended, and serum electrolyte levels were to be followed up. Improvement was gradual but definite, and after 4 weeks the patient was asymptomatic, with no hepatojugular reflex and no arrhythmias. The family physician continued weekly and later monthly contact with the university-based cardiologist.

QUESTIONS

1. Eplerenone, a new selective aldosterone receptor antagonist (SARA), was introduced to obviate the adverse effects of spironolactone. Eplerenone has which of the following functions?
   a. binds to mineral corticoid receptors
   b. replaces spironolactone therapy
   c. an adjunct in the treatment of hypertension (HTN) and CHF
   d. all of the above

2. Aldosterone, a mineral corticoid produced by the renin-aldosterone-angiotensin system (RAAS), has which of the following effects?
   a. acts on the epithelia of the kidney, colon, and sweat glands to maintain electrolyte homeostasis
   b. promotes potassium excretion
   c. acts at nonepithelial sites (eg, heart, brain, blood vessels), contributing to left ventricular hypertrophy, vascular inflammation, and fibrosis
   d. b, c

3. Spironolactone, an aldosterone receptor antagonist (ARA), is used in the treatment of primary aldosteronism; which of the following are additional therapeutic indications for spironolactone?
   a. as a diuretic for the edema in hepatic cirrhosis and CHF
   b. to block sodium retention in the renal tubules
   c. potassium sparing
   d. all of the above
4. Increased levels of aldosterone have been associated with which of the following?
   a. bradycardias
   b. myocardial and vascular (renal) hypertrophy and fibrosis
   c. baroreceptor dysfunction, impaired arterial compliance
   d. activation of the sympathetic nervous system
   e. all of the above

5. In some cases, endocrine imbalance has been observed with the routine use of spironolactone.
   a. true
   b. false

6. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) attenuate the adverse cardiovascular (CV) effects of angiotensin, but have little effect on plasma aldosterone levels of activity. This phenomenon is known as which of the following?
   a. ACEI failure
   b. intractable HTN
   c. aldosterone synthesis escape
   d. aldosterone resistance

7. Which of the following are the primary mediators of essential HTN?
   a. the RAAS
   b. angiotensin II (AII)
   c. thyroid-stimulating hormone
   d. urinary catecholamines

ANSWERS
1. d. all of the above

A new selective aldosterone antagonist, eplerenone (Inspra, Pfizer, Inc, New York, NY) has been approved as an alternative to spironolactone in treating HTN, cardiac edema, and hepatic edema and for cardiac and renovascular protection. Long-term spironolactone therapy has been limited because of its adverse effects, that is, impotence, gynecomastia, hirsutism. Eplerenone is an avid binder to mineral corticoid receptors (while avoiding other steroid receptor sites), has no significant adverse effects to limit its use, and promises to be an important breakthrough in the chronic treatment of CV disorders. Eplerenone, approved in 2002, reduces mortality and hospitalization rates in patients with left ventricular dysfunction and heart failure following an acute MI. Eplerenone limits the maladaptive postinfarction responses that reduce left ventricular remodeling and reactive fibrosis. In the Eplerenone Neurohumoral Efficacy and Survival Study (EPHESUS), more than 6000 postmyocardial patients, who were receiving β-blockers, diuretics, and ACEIs (or ARBs) were randomized to add-on therapy with eplerenone (25-50 mg/d) or placebo for 18 months. The group receiving eplerenone had a lower hospitalization rate and fewer deaths. Currently, phase III trials with eplerenone in the management of HTN and CHF should help determine if the phase II data (see above) can be extended and applied to larger populations of patients and if there are additional benefits with longer use.

As an antihypertensive agent, eplerenone caused reductions in blood pressure similar to those caused by spironolactone but maintained 24-hour antihypertensive control with daily dosing. Eplerenone had none of the antiandrogenic or progestational adverse effects that occurred with spironolactone. Reductions in systolic and diastolic blood pressures were greater with eplerenone than with an ARB (losartan). Another trial comparing eplerenone to an ACEI, eplerenone reduced left ventricular mass and urinary excretion of albumin at levels similar to, albeit slightly less than, an ACEI. In other trials, the combined use of eplerenone and an ACEI produced greater reductions in left ventricular mass and urinary albumin excretion than was evident in other drugs. Eplerenone, with a half-life of 3.5 hours, does not produce active metabolites, and peak plasma levels occur within 2 hours of oral administration. The effects of eplerenone on renal sodium and potassium handling are similar to the effects of spironolactone; both are metabolized and eliminated in the urine and bile. The tolerance to, safety of, and efficacy of eplerenone were tested in phase II and III clinical trials. Daily doses of 50 mg, 100 mg, and 400 mg of eplerenone were safe, effective, and well tolerated. The antihypertensive effect was noted after 4 weeks of therapy.

2. a. acts on the epithelia of the kidney, colon, and sweat glands to maintain electrolyte homeostasis
   c. acts at nonepithelial sites (eg, heart, brain, blood vessels), contributing to left ventricular hypertrophy, vascular inflammation, and fibrosis

Aldosterone is a mineral corticoid hormone synthesized in the adrenal glomerulus. It is the final product of the RAAS and acts on the epithelia of the kidney, colon, and sweat glands to maintain electrolyte homeostasis, specifically to promote retention of sodium and excretion of potassium. Initially, aldosterone was thought to act only at epithelial sites, but it was subse-
quently shown to influence nonepithelial sites, such as the brain, heart, and blood vessels. Excess aldosterone induces vascular and cardiac fibrosis, ventricular hypertrophy, impairs baroreceptor and endothelial function, potentiates the effects of norepinephrine, and enhances vascular inflammation that leads to CV disease and its sequelae. The physiological function of aldosterone was considered limited to conservation of sodium, potassium, and water. Currently, aldosterone plays a critical role in the pathogenesis of renal and CV disease by raising blood pressure via fluid/electrolyte balance, activation of the sympathetic nervous system, and direct cellular actions, independent of AII. In essential HTN, aldosterone increases the incidence of myocardial hypertrophy, heart failure, and other CV events.

3. d. all of the above

Aldosterone exerts effects beyond renal handling of sodium, potassium, and magnesium; for example, aldosterone induces myocardial/perivascular fibrosis, reduces myocardial levels of norepinephrine, and increases plasminogen activator inhibitor levels. The result has been the expansion of ARA (spironolactone) and SARA eplerenone use in CV disease, specifically heart failure and HTN. Spironolactone has been the traditional treatment for primary aldosteronism. It is typically used in the treatment of edema, due to hepatic cirrhosis and CHF, both of which are associated with excessive aldosterone secretion. Spironolactone blocks the sodium-retaining action of aldosterone on the renal tubules, reverses the excretion of potassium and increases sodium excretion. Spironolactone reduces mortality significantly in class IV CHF (New York Heart Association Classification), when combined with standard heart failure therapy. Because of its dramatic cardiorenal benefits, spironolactone is now standard protocol for this population. Until recently, spironolactone was the only current clinical agent to directly and nonselectively block the actions of aldosterone. In low doses, unrelated to its diuretic or hemodynamic effects, spironolactone when combined with standard heart failure therapy significantly reduces mortality in moderate to severe heart failure.

The Randomized Aldactone Evaluation Study (RALES) trial determined the effects of ARA in patients with class IV CHF. In addition to an ACEI, digitalis, and diuretics, patients were randomized to either spironolactone or placebo groups. The study was terminated early because of the significant benefit of spironolactone on mortality (30% reduction in mortality in the spironolactone-treated group). This trial demonstrated that blocking aldosterone has clinical benefit even when other RAAS blocking agents are used. Both experimental and clinical studies have demonstrated the beneficial effects of spironolactone in blocking aldosterone.

4. b. myocardial and vascular (renal) hypertrophy and fibrosis
c. baroreceptor dysfunction, impaired arterial compliance
d. activation of the sympathetic nervous system

Increased levels of aldosterone are associated with an increase in myocardial and renovascular hypertrophy and fibrosis, baroreceptor dysfunction, impaired arterial compliance, and sympathetic activation. In animal models, aldosterone was involved in the development of vascular injury and malignant nephrosclerosis. In a study comparing degrees of renal insufficiency with levels of aldosterone, patients with more advanced renal failure had the highest levels of plasma aldosterone. The ability of ACEI and ARB therapy to retard the overall progression of renal and CV disease, beyond simple antihypertensive effects, adds support to AII as the principal mediator of these deleterious changes. The role of the RAAS as a major mechanism in the pathogenesis of HTN and renal disease is well established.

5. a. true

The routine and chronic use of spironolactone is limited by its endocrine side effects. Spironolactone has a strong affinity for progesterone and androgen receptors. Its antiandrogenic side effects in men (gynecomastia and erectile dysfunction) and the progesteroneside effects in women (menstrual irregularities, amenorrhea, and postmenopausal bleeding) limit its use for prolonged treatment. In the RALES trial, a significant number of patients discontinued their treatment with spironolactone because of side effects such as breast pain and gynecomastia.

6. c. aldosterone synthesis escape

Despite randomized trials showing the efficacy of ACEI in the treatment of heart failure, morbidity and mortality remain high. ACEIs and ARBs suppress the RAAS and are considered the cornerstone for both HTN and heart failure therapy; however, they have little effect on plasma aldosterone levels or activity. The lack of ACE inhibition or ARB effect on aldosterone permits the continued unabated detrimental effects of this final RAAS hormone, a phenomenon known as “aldosterone synthesis escape.” To counter these dele-
serious effects, ARAs have been developed and employed as complementary treatment to ACEIs and ARBs. Inhibition of the RAAS with ARAs is associated with a decrease in blood pressure, regression of left ventricular hypertrophy, and reduction of target organ damage.

7. a. the RAAS
   b. AII

Hypertension is a major health problem with significant risks for coronary artery, cerebrovascular, peripheral vascular, and renal disease. Many pathological factors have been identified in essential HTN; however the primary mediators are AII and the RAAS.

Summary

The edematous states, specifically those in CHF and cirrhosis of the liver, are associated with excessive aldosterone secretion and represent states of secondary hyperaldosteronemia. Aldosterone promotes sodium retention by the renal tubules. Spironolactone, first introduced 50 years ago (1953), blocks the action of aldosterone on renal transport of electrolytes, thus acting as an effective diuretic, and in addition, has potentiating effects on other diuretics, including the thiazides. Spironolactone has undesirable side effects that have limited its clinical use; the most significant are impotence, gynecomastia, and hirsutism. Eplerenone, a recently introduced selective ARA, decreases morbidity and mortality in patients with CHF following MI and has none of the androgenic or estrogenic side effects of spironolactone. Eplerenone is an effective alternative for spironolactone.

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