Eplerenone
Cardiovascular Protection

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Abstract—Data from animal studies and clinical trials indicate that aldosterone causes cardiovascular and renal injury through mineralocorticoid receptor–dependent mechanisms. However, although aldosterone receptor antagonism reduces mortality in patients with congestive heart failure, the progesterational and antiandrogenic side effects of the nonspecific aldosterone receptor antagonist, spironolactone, have limited its usefulness in the treatment of hypertension. This review provides an overview of the pharmacology, efficacy, and safety of a new, more selective aldosterone receptor antagonist, eplerenone, in the context of emerging concepts of the role of aldosterone in cardiovascular toxicity. (Circulation. 2003;107:2512-2518.)

Key Words: aldosterone receptors cardiovascular disease hypertension pharmacology

The renin-angiotensin-aldosterone system (RAAS) plays an integral role in cardiovascular homeostasis through its effects on vascular tone and volume. Activation of the RAAS is associated with an increased risk of ischemic cardiovascular events, independent of effects on blood pressure, whereas interruption of the RAAS by angiotensin-converting enzyme (ACE) inhibition or angiotensin type 1 receptor (AT1R) blockade reduces cardiovascular mortality and slows the progression of renal disease. Drugs that interrupt the RAAS reduce the risk of cardiovascular events, preventing the effects of angiotensin (Ang) II on cellular growth and proliferation on vascular superoxide radical formation, and on thrombotic pathways. Ang II also stimulates the synthesis of the mineralocorticoid aldosterone, and emerging data indicate that aldosterone plays an independent role in vascular toxicity and fibrosis. For example, molecular studies suggest that aldosterone may be produced locally in vascular tissue. Aldosterone causes myocardial and aortic fibrosis and nephrosclerosis in animal models, whereas aldosterone receptor antagonism reverses these processes.

In humans, elevated plasma aldosterone concentrations are associated with endothelial dysfunction, myocardial infarction, left ventricular hypertrophy, and death. Although ACE inhibition and AT1 receptor antagonism initially reduce aldosterone concentrations, circulating concentrations of this hormone return to baseline levels with chronic therapy. Coadministration of the aldosterone receptor antagonist, spironolactone, enhances the beneficial effect of ACE inhibition on mortality in patients with congestive heart failure. However, although administration of spironolactone reduces mortality in patients with congestive heart failure, the gastrointestinal and antiandrogenic side effects of this nonspecific aldosterone receptor antagonist have limited its usefulness in the treatment of hypertension predominantly to the treatment of patients with primary hyperaldosteronism. The Food and Drug Administration (FDA) has approved a new, more selective aldosterone receptor antagonist, eplerenone, for the treatment of hypertension. This review provides an overview of the pharmacology, efficacy, and safety of eplerenone in the context of emerging concepts of the role of aldosterone in cardiovascular toxicity.

Classical Aldosterone Physiology

Fifty years ago, Simpson and Tait described the adrenal hormone aldosterone. According to classical mechanisms, aldosterone is secreted by the zona glomerulosa of the adrenal gland in response to stimuli such as Ang II, potassium, and adrenocorticotropic hormone (ACTH). Circulating aldosterone regulates the transport of sodium and potassium by epithelial cells by binding to the inactive cytoplasmic mineralocorticoid receptor (MR) (Figure 1). While the MR binds cortisol with equal affinity, tissue specificity for aldosterone is conferred by the local expression of the enzyme 11β-hydroxysteroid dehydrogenase (11βHSD) type 2, which converts cortisol and corticosterone into the inactive cortisone and 11-dehydrocorticosterone. The binding of aldosterone to the MR results in dissociation of the ligand-activated MR from a multiprotein complex containing molecular chaperones, translocation into the nucleus, and binding to hormone response elements in the regulatory region of target gene promoters. In the distal nephron of the kidney, induction of serum and glucocorticoid inducible kinase-1 (sgk-1) gene...
Vascular Effects of Aldosterone: A Paradigm Shift

Aldosterone not only contributes to salt and water homeostasis but also exerts direct vascular effects. Just as Ang II is produced locally in vascular tissue, experimental studies provide evidence for local, extra-adrenal production of aldosterone, and for extra-renal actions of aldosterone. Aldosterone can be synthesized by endothelial cells and vascular smooth muscle cells (VSMCs), and locally in tissues such as the brain, blood vessels, and myocardium. Synthesis at extra-adrenal sites appears to be regulated by the same stimuli that regulate adrenal synthesis. Moreover, MR have been identified not only in the epithelial cells of the kidney, colon, and salivary and sweat glands, but also in the brain, heart, and blood vessels. These findings have led many investigators to propose an autocrine or paracrine role for aldosterone. However, studies have provided conflicting evidence as to the importance of local aldosterone production in the human heart.

Aldosterone and Cardiovascular Injury in Animal Models

Contemporary studies further indicate that aldosterone causes cardiovascular injury, independent of effects on blood pressure. Aldosterone promotes vascular inflammation and fibrosis in experimental animal models. For example, during high salt intake, prolonged aldosterone administration causes myocardial fibrosis and ventricular hypertrophy in rats. Concurrent angiotensin-converting enzyme (ACE) inhibition blocks the development of ventricular hypertrophy but not the myocardial fibrosis, suggesting that the fibrotic effects of aldosterone occur in the absence of Ang II. Aldosterone receptor antagonism with either spironolactone or eplerenone prevents aortic and myocardial fibrosis in rat models of primary and secondary hypertension, even in the absence of blood pressure effects. Aldosterone also causes renal fibrosis. In the rat remnant kidney model, aldosterone infusion reverses the protective effects of ACE inhibition and AT1 receptor antagonism. Aldosterone receptor antagonism decreases glomerular damage (thrombosis, sclerosis, and mesangiolysis) and arteriopathy in stroke-prone, spontaneously hypertensive rats and in a renin-dependent radiation model of renal damage, independently of effects on blood pressure.

The mechanism(s) through which aldosterone causes cardiac and vascular fibrosis are the subject of ongoing investigation. Sodium appears to be prerequisite in animal models of aldosterone-induced cardiac fibrosis. Aldosterone may act in part by increasing AT1 receptor binding in vascular tissue. For instance, aldosterone increases AT1 receptor binding in rat VSMC and vessels in a time- and concentration-dependent manner. In the rat heart, aldosterone increases, whereas spironolactone decreases, AT1 receptor density and mRNA accumulation. Aldosterone also exerts direct profibrotic effects. The accumulation of extracellular matrix and resulting fibrosis depends on the balance between the synthesis and the degradation of matrix molecules, such as collagen and proteoglycans. Aldosterone stimulates collagen production by cardiac fibroblasts in some but not all studies.

Studies in the rat indicate that aldosterone/salt treatment induces coronary inflammation, characterized by monocyte and macrophage infiltration and by increased expression of the inflammatory markers cyclooxygenase-2, osteopontin, macrophage chemotactant protein-1, and intracellular adhesion molecule-1. Eplerenone partially decreases blood pressure and attenuates the inflammatory changes in this model. Funder and coworkers have also reported that administration of deoxycorticosterone and salt induces perivascular inflammation in the heart, as well as necrosis and apoptosis. Interestingly, neither aldosterone nor deoxycorticosterone increases expression of transforming growth factor-β1 in the heart in these models. Similarly, aldosterone induces renal PAI-1 expression and fibrosis through a TGF-β-independent pathway.

Several studies have provided evidence for rapid nongenomic effects of aldosterone. For example, aldosterone increases Na/H antiporter activity in VSMCs through a membrane, rather than nuclear receptor. The nongenomic effects of aldosterone are rapid (<5 minutes), transcription independent, and not blocked by classical aldosterone antagonists, including spironolactone or its active metabolite, canrenone. The role of the MR in fibrosis has been confounded by a recent report that conditional expression of an antisense mRNA of the MR in cardiomyocytes causes reversible cardiac fibrosis in mice and that this effect is increased by concurrent spironolactone administration. Although this
provocative report has raised many new questions about the pathophysiological role of the cardiac MR, it must be emphasized that in intact animals, the proinflammatory and fibrotic effects of aldosterone in the heart, vasculature, and kidney are reversed by MR antagonism.

Aldosterone and Cardiovascular Injury in Humans

Studies suggest that aldosterone also contributes to cardiovascular toxicity in humans, independent of the effects of Ang II. Clinical studies indicate a correlation between aldosterone concentrations and cardiovascular and renal morbidity and mortality. Patients with primary hyperaldosteronism exhibit endothelial dysfunction, a predictor of future cardiovascular events, compared with patients with essential hypertension. Increased plasma aldosterone concentrations are associated with decreased arterial compliance in hypertensive individuals. Conversely, aldosterone receptor antagonism improves endothelium-dependent vasodilation in patients with congestive heart failure.

During chronic interruption of the RAAS with ACE inhibition, aldosterone concentrations return toward baseline or "escape," potentiating the effects of this class of drugs. In the Randomized Aldactone Evaluation Study (RALES), addition of spironolactone reduced mortality by 30% in patients with New York Heart Association (NYHA) class 3 or 4 heart failure who were already treated with an ACE inhibitor, diuretics and digoxin (Figure 2). The specific mechanism(s) underlying the beneficial effect of aldosterone receptor antagonism with spironolactone in RALES are not known. Spironolactone may prevent sudden death by increasing serum potassium or by altering myocardial norepinephrine uptake. At least one study has shown that coadministration of spironolactone reduces ventricular arrhythmias in patients with congestive heart failure. In addition, a substudy of RALES implicates a potential link between the antifibrotic effects of spironolactone and the mortality benefit. Thus, spironolactone significantly decreased circulating concentrations of the aminoterminal portion of the procollagen type II precursor, a marker of collagen turnover, and the decrease in PIINP predicted an improvement in mortality.

Pharmacology of Eplerenone

Eplerenone, like spironolactone, is a competitive antagonist of the aldosterone receptor. Eplerenone, chemically described as Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, y-lactone, methyl ester (7a,11a,17a), was derived from spironolactone by the introduction of a 9a,11a-epoxy bridge and by substitution of the 17a-thioacetyl group with a carbomethoxy group (Figure 3). Although eplerenone exhibits 10- to 20-fold lower affinity for the aldosterone receptor in vitro compared with spironolactone, studies in humans suggest that eplerenone is 50% to 75% as potent as spironolactone. The substitution of the 17a-thioacetyl group confers eplerenone with significantly increased selectivity for the aldosterone receptor over other steroid receptors. For example, in rats the IC50 of eplerenone for the aldosterone receptor was 360 nmol/L, whereas the IC50s for the androgen, progesterone, and estrogen receptors were >10 000 nmol/L.

Mean peak concentrations are reached ~1.5 hours after oral administration of eplerenone in humans (data on file, NDA 21-437, GD Searle LLC). Absorption is not affected by food. Absolute oral bioavailability is not known. Eplerenone is cleared primarily via metabolism by CYP4503A4 to inactive metabolites, with an elimination half-life of 4 to 6 hours. By comparison, spironolactone is converted to the active metabolites, canrenoate and canrenone, which have half-lives between 17 and 22 hours. The apparent plasma clearance of eplerenone is 10 L/h. The apparent volume of distribution is 43 to 90 L. About 50% of eplerenone is bound to plasma proteins, primarily alpha 1-acid glycoproteins.

The pharmacokinetics of eplerenone 100 mg/d are similar in males and females. The Cmax and area-under-the-concentration curve (AUC) of eplerenone are increased 22% and 45%, respectively, in subjects >65 years compared with subjects 18 to 45 years old. The Cmax and AUC are 19% and
26% lower, respectively, in blacks compared with whites. The C\textsubscript{max} and AUC are increased in renal insufficiency, and eplerenone is not removed by hemodialysis. The C\textsubscript{max} and AUC of eplerenone are increased 3.6% and 42%, respectively, in patients with Child-Pugh Class B hepatic impairment compared with normal subjects.

**Efficacy**

**Hypertension**

At the time of FDA approval, the efficacy and safety of eplerenone had been evaluated in clinical studies of 3091 patients. In a published, 8-week, double-blind, placebo-controlled trial in 417 patients with mild to moderate hypertension (seated diastolic blood pressure ≥95 mm Hg, <114 mm Hg), eplerenone significantly decreased seated systolic and diastolic blood pressure in a dose-dependent manner over a dose range of 50, 100, and 400 mg/d.\textsuperscript{61} The dose of 400 mg/d eplerenone was equivalent to 50 mg BID spironolactone. There was no effect of eplerenone on heart rate. At the lower doses of 50 mg and 100 mg/d, twice-daily dosing (ie, 25 mg bid and 50 mg bid) reduced seated systolic and diastolic blood pressures to a greater extent than did once-daily dosing. Eplerenone also significantly decreased ambulatory blood pressure. The mean changes in systolic and diastolic blood pressures were comparable with once-daily and twice-daily dosing; however, at a dose of 400 mg BID, reductions in trough systolic blood pressure and trough diastolic blood pressure were greater with twice-daily dosing (200 mg BID) than with once-daily dosing.

Krum et al\textsuperscript{64} reported the hypotensive effect of add-on therapy with eplerenone (50 mg increasing to 100 mg) in patients who were already taking an ACE inhibitor (n=177) or an AT\textsubscript{1} receptor antagonist (n=164). Coadministration of eplerenone significantly reduced seated systolic blood pressure compared with coadministration of placebo in both the ACE-inhibitor and AT\textsubscript{1} receptor antagonist groups. Eplerenone significantly reduced diastolic blood pressure in the AT\textsubscript{1} receptor antagonist–treated group but not in the ACE inhibitor–treated group. There was no effect of add-on therapy with eplerenone on heart rate.

Dose-related increases in active plasma renin and aldosterone are seen 12 to 24 hours after eplerenone administration.\textsuperscript{61,64} The change in PRA and aldosterone during 400 mg/d dosing was equivalent to that observed during spironolactone 50 mg BID; the aldosterone response to 200 mg BID eplerenone was significantly greater. Addition of 50 to 100 mg/d eplerenone to treatment with ACE inhibitor or AT\textsubscript{1} receptor antagonist increased active plasma renin 92.5% and 95.9%, respectively, and serum aldosterone 70.3% and 60.4%, respectively.

Among subjects enrolled in clinical trials of eplerenone for the treatment of hypertension, 14% were black Americans, 22% were 65 years of age or older, and 4% were 75 years of age or older (data on file, GD Searle LLC). Approximately equal numbers of men (54%) and women (46%) were studied. There was no effect of either gender or age on the blood pressure response to therapy. In one study of low-renin hypertensive patients, blood pressure reductions during titration with eplerenone were smaller in blacks than in whites. In both low-renin hypertension and in black patients with mild-to-moderate hypertension, eplerenone up to doses of 200 mg/d was superior to the AT\textsubscript{1} receptor antagonist losartan (50 to 100 mg/d) in lowering blood pressure.\textsuperscript{65} Although hydrochlorothiazide could be added to eplerenone (32.5%) or losartan (55.6%) in the trial in low-renin hypertension, data are not available as to the comparative effects of hydrochlorothiazide and eplerenone on blood pressure in this population. Eplerenone (50 to 200 mg/d) appears to be comparable to amlodipine (2.5 to 10 mg/d) in reducing blood pressure in an older (mean age 67.7 years) population.\textsuperscript{65}

**Left Ventricular Hypertrophy**

Left ventricular (LV) hypertrophy is associated with increased cardiovascular morbidity and mortality in patients with essential hypertension.\textsuperscript{66} The 4E Study (Eplerenone, Enalapril, and Eplerenone/Enalapril Combination Therapy in Patients with Left Ventricular Hypertrophy) compared the effects of 9-month treatment with eplerenone 200 mg/d (n=64), enalapril 40 mg/d (n=71), or eplerenone 200 mg/d plus enalapril 10 mg/d (n=67) on LV mass, systolic and diastolic blood pressures, and urinary albumin-creatinine ratio (UACR) in patients with mild-to-moderate hypertension and echocardiographic evidence of LVH.\textsuperscript{67} Patients were given concomitant diuretic or amlodipine therapy at 8 weeks if necessary to achieve blood pressure control. The degree of blood pressure reduction was similar among the 3 treatment groups. All three treatments significantly reduced LV mass as assessed by magnetic resonance imaging (MRI); the effect of combination enalapril and eplerenone on LV mass (−27.2 g) was significantly greater than the effect of eplerenone alone (−14.5 g, P=0.007). The change in mass in the enalapril only group was −19.7 g. UACR, a risk factor for cardiovascular events,\textsuperscript{68} was significantly reduced in the combination group (−52.6%) compared with either the eplerenone (−24.9%, P=0.001) or enalapril alone (−37.4%, P=0.038) groups.

Three other as yet unpublished studies have examined the effects of eplerenone on the UACR.\textsuperscript{65} In a study of patients with mild-to-moderate hypertension, eplerenone (50 to 200 mg/d) reduced blood pressure −16.5/−13.3 mm Hg and UACR 61.5%, whereas enalapril (10 to 40 mg) reduced blood pressure −14.8/−14.1 mm Hg (NS versus eplerenone) and UACR 25.7% (P=0.01 versus eplerenone). In a study of older patients with systolic hypertension, eplerenone reduced UACR to a greater extent than did amlodipine (−52.3% versus −10.4%, P=0.002) at comparable hypotensive doses. In patients with type 2 diabetes, eplerenone 50 to 200 mg/d, enalapril 10 to 40 mg/d, and eplerenone + enalapril (10 mg) reduced UACR 62% (P=0.015 versus enalapril), 42%, and 74% (P=0.018 versus eplerenone and P<0.001 versus enalapril), respectively. Although these preliminary data suggest a favorable effect of eplerenone on microalbuminuria, a critical analysis of the data must await publication of these trials.

**Congestive Heart Failure**

The Eplerenone Neurohormonal Efficacy and Survival Trial (EPHESUS) was designed to evaluate the effect of the
addition of eplerenone (25 to 50 mg/d) to standard therapy with ACE inhibitors, AT1 receptor antagonists, β-blockers, digoxin, and diuretics on the primary end points of all-cause mortality and the time to first occurrence of either cardiovascular mortality or morbidity leading to hospitalization in 6200 patients with LV dysfunction (ejection fraction <40%) after a recent (3 to 14 days) myocardial infarction. The recently published results indicate that addition of eplerenone significantly reduced all cause (P = 0.008) and cardiovascular (P = 0.0002) mortality.69 EPESUS promises to provide important information not only about outcome, but also about the neurohormonal effects of eplerenone in this patient population.

Side Effects and Drug–Drug Interactions
The adverse effects of eplerenone stem directly from its mechanism of action. MR antagonism with eplerenone causes a dose-dependent increase in serum potassium concentration from 0.08 mmol/L to 0.36 mmol/L at the 400-mg/d dose.61 By comparison, the median increase in serum potassium observed in the RALES trial, in which spironolactone was given to patients receiving ACE inhibitors as well as loop diuretics, was 0.3 mmol/L.21 Eplerenone should be avoided in patients receiving potassium supplementation (including salt substitutes) or other potassium-sparing diuretics, such as amiloride and triamterene.

The frequency and severity of hyperkalemia during eplerenone are expected to be increased in patients with renal insufficiency, diabetes, and microalbuminuria. Patients with these conditions were excluded from clinical trials of eplerenone in hypertension. However, rates of hyperkalemia, defined as a serum potassium >5.5 mmol/L, as a function of calculated creatinine clearance have been analyzed across all studies and were 2.6%, 5.6%, and 10.4% in patients with baseline creatinine clearances >100 mL/min, 70 to 100 mL/min, and <70 mL/min, respectively (data on file, GD Searle LLC). In a study of patients with type 2 diabetes and microalbuminuria, the frequency of hyperkalemia was 33% in patients receiving eplerenone 200 mg/d and 38% in patients receiving eplerenone and the ACE inhibitor enalapril.

Rates of sex hormone–related side effects appear to be lower during treatment with eplerenone than with treatment with spironolactone. In controlled trials lasting 6 months or longer, the rates of gynaecomastia, mastodynia, or either in men were 0.7%, 1.3%, and 1.6% (data on file, GD Searle LLC). By comparison, the rate of gynaecomastia or mastodynia in men in the RALES trial, in which the mean time of follow-up was 24 months, was 10%,21 and the rate of gynaecomastia in men with essential hypertension treated with spironolactone has been reported as 6.9%.70 In trials of eplerenone, the rate of abnormal vaginal bleeding in females was 0.8% and similar to that seen in subjects given active treatments other than spironolactone.

Additional laboratory adverse events that have been observed in clinical trials of eplerenone include mild dose-dependent increases in cholesterol (from 0.4 mg/dL at 50 mg/d to 11.6 mg/dL at 400 mg/d), triglycerides (7.1 mg/dL at 50 mg/d to 26.6 mg/dL at 400 mg/d) and serum creatinine (0.01 mg/dL at 50 mg/d to 0.03 mg/dL at 400 mg/d) and decreases in serum sodium (from 0.7 mmol/L at 50 mg/d to 1.7 mmol/L at 400 mg/d) (data on file, GD Searle LLC). Approximately 0.66% of patients have developed 3-fold–elevated serum transaminases, but no cases of hepatic failure have been reported. In one study, thyroid-stimulating hormone was reported to be increased in patients given 400 mg/d eplerenone.61 Eplerenone does not affect the QT interval.

Because eplerenone is metabolized primarily by CYP3A4, it should not be given together with potent inhibitors of this enzyme, such as ketoconazole. In pharmacokinetic studies, ketoconazole induced a 5-fold increase in eplerenone AUC, while less potent inhibitors of CYP3A4 (such as verapamil, erythromycin, fluconazole, and saquinavir) increased the eplerenone AUC approximately 2-fold. Grapefruit juice increased eplerenone exposure by 25%, whereas the CYP3A4 inducer St John’s Wort reduced the AUC of eplerenone by 30%.

Conclusion
The mineralocorticoid aldosterone causes cardiovascular injury in animal models and humans. Aldosterone receptor antagonism has been shown to reduce mortality in ACE inhibitor–treated patients with congestive heart failure. The progesterational and antiandrogenic side effects of spironolactone have limited its utility in the treatment of hypertension. Eplerenone is a new selective aldosterone receptor antagonist with decreased progesterational and antiandrogenic side effects compared with spironolactone. Eplerenone effectively reduces blood pressure compared with agents such as spironolactone, enalapril, losartan, and amlodipine. The effect of eplerenone on mortality in hypertensive patients is not known. Like spironolactone, eplerenone increases serum potassium, particularly in patients taking other potassium-sparing drugs such as ACE inhibitors and AT1 receptor antagonists and in patients with renal insufficiency. Eplerenone reduced mortality in patients with left ventricular dysfunction.

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References


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