



Eplerenone: A Novel Selective Aldosterone Blocker for Hypertension

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Aldosterone is a mineralocorticoid steroid hormone that contributes to the development of hypertension, myocardial hypertrophy, and cardiovascular morbidity. It is a product of the renin-angiotensin-aldosterone system (RAAS) and has the potential to cause edema through sodium and water retention. Aldosterone exhibits its actions at the heart, vasculature, and kidney, and these effects are likely to significantly promote cardiovascular disease.¹ Although angiotensin-converting enzyme (ACE)-inhibitors and angiotensin-receptor blockers (ARBs) target the RAAS, these agents do not suppress aldosterone production adequately.

Spironolactone is a competitive aldosterone receptor antagonist that inhibits the action of aldosterone. The Randomized Aldactone Evaluation Study (RALES) trial,² discussed later, has revealed significant benefits in terms of mortality in patients with severe congestive heart failure. However, spironolactone is associated with progestational and antiandrogenic side effects, such as gynecomastia and impotence, as a result of its binding to other steroid receptors.³ The need for a more selective aldosterone receptor antagonist has emerged.

Eplerenone (InspraTM, GD Searle, Division of Pharmacia) is the first agent in a new class of drugs known as the selective aldosterone-receptor antagonists (SARAs).^{3,4} Because this aldosterone blocker has little affinity to androgen and

progesterone receptors, it produces fewer steroid-like effects (such as gynecomastia in men) than spironolactone does. Compared with spironolactone, eplerenone has a 15- to 20-fold lower affinity for the mineralocorticoid receptor; however, because of specific binding to aldosterone, fewer adverse events occur.⁵ Eplerenone is similar to spironolactone in structure, but it differs in its replacement of the 17 α -thioacetyl group of spironolactone by a carbomethoxy group, which provides selectivity for the mineralocorticoid receptor over other steroid receptors.^{1,6}

PHARMACOKINETICS

The pharmacokinetic parameters of eplerenone are demonstrated from a single dose of a 100-mg trial in humans.¹ Its bioavailability is greater than that of spironolactone, probably because its protein binding is less.^{3,5} Unlike spironolactone, eplerenone does not appear to have an active metabolite.^{1,5} Its half-life is 3.5 to five hours.⁵ The drug is a substrate of the CYP3A4 isoenzyme, but its effect on the cytochrome P-450 (CYP-450) is not clinically relevant.^{5,6} It is excreted in urine (66%) and in feces (32%).

STUDIES IN HYPERTENSION

The mainstay of the treatment of hypertension is the use of anti-neurohormonal agents, such as beta blockers, ACE-inhibitors, and ARBs, along with the newer strategy of an additional anti-aldosterone agent. Studies show that the best effective dose of eplerenone for the treatment of hypertension is 100 mg taken orally once daily.^{7,8} The optimal dosage has not been yet defined.⁵

The Burgess Study⁹

In a 12-month, double-blind, titration-to-effect study, Burgess et al. compared eplerenone with the ACE-inhibitor enalapril in 499 patients with mild to mod-

erate hypertension, defined as diastolic blood pressure (BP) between 95 and 110 mm Hg. If diastolic BP remained at or above 90 mm Hg, the drugs were titrated to incremental increases of eplerenone 100 mg and 200 mg daily or enalapril 20 mg and 40 mg daily.

Both drugs reduced BP at week 24 and at 12 months in a comparable fashion. In patients with microalbuminuria at baseline, a greater reduction in the urine albumin:creatinine ratio (UACR) was observed with eplerenone than with enalapril at week 24 (-61.5% vs. -25.7%, $P = .01$). In general, eplerenone was as effective as enalapril in controlling blood pressure and was associated with fewer side effects, such as cough.

The White Study¹⁰

In another double-blind, titration-to-effect trial, White et al. compared the effect of eplerenone on BP, vascular compliance, and microalbuminuria in 269 older subjects with the calcium-channel blocker amlodipine over 24 weeks. Patients with systolic hypertension and/or a widened pulse pressure received eplerenone 50 mg or amlodipine 2.5 mg daily. The doses were titrated to eplerenone 100 and 200 mg daily or to amlodipine 5 and 10 mg daily at two and six weeks to reduce systolic BP to 140 mm Hg or less. As a result, eplerenone brought about BP reductions comparable to those of amlodipine (-20.5 vs. -20.1 mm Hg, $P = .83$). Patients taking eplerenone experienced less peripheral edema (3.7% vs. 25.2%, $P < .001$) and showed a greater improvement in microalbuminuria (-52.3% vs. -10.4%, $P = .002$) than did patients taking amlodipine.

The Weinberger Study¹¹

Weinberger et al. hypothesized that 186 hypertensive patients with low plasma renin levels might be salt-sensitive or volume-sensitive and would re-

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spond better to aldosterone blockers than to ACE-inhibitors or ARBs. This 16-week, randomized, double-blind study compared the efficacy of eplerenone and the ARB losartan in patients with low renin levels. Eplerenone 100 mg or losartan 50 mg daily was used initially; if no adequate response was achieved after four weeks, the dose was further titrated to eplerenone 200 mg or losartan 100 mg daily. If BP remained uncontrolled at week eight, hydrochlorothiazide (HCTZ) was added.

The change in systolic BP was significantly greater in the eplerenone group than in the losartan group (-15.8 vs. -10.1 mm Hg, $P = .017$). Fewer patients taking eplerenone needed add-on therapy with HCTZ.

The Pratt Study¹²

To further explore the effect of eplerenone versus losartan, Pratt et al. conducted a 16-week, double-blind, randomized, placebo-controlled study comparing the efficacy of both medications in 348 black and 203 white patients with mild to moderate hypertension (diastolic BP, 95 to 110 mm Hg). As expected, baseline renin levels were lower in the black patients than in the white patients. Eplerenone was superior to losartan in lowering systolic BP in black patients (-13.5 vs. -5.3 mm Hg, $P < .001$) but not in white patients (-12.3 vs. -8.5 mm Hg, $P = .13$). Both drugs were also effective in reducing microalbuminuria.

The Krum Study¹³

A double-blind, placebo-controlled trial by Krum et al. investigated the effects of adding eplerenone to the regimen of 341 hypertensive patients whose BP was not controlled by ACE-inhibitors or ARBs. The initial dose of eplerenone was 50 mg once daily and was increased to 100 mg if required.

After eight weeks, the reduction in BP was significant in both combination groups compared with the monotherapy groups ($P \leq .05$). Adding eplerenone or placebo to ACE-inhibitors caused a reduction of -13.4 vs. -7.5 mm Hg, respectively, in systolic BP. In a similar fashion, when eplerenone or placebo was added to the ARBs, patients experienced a decrease of -16.0 mm Hg or -9.2 mm Hg, respectively, in systolic BP. As a result, eplerenone might be useful as add-on therapy in hypertensive patients when BP cannot be controlled with ACE-inhibitors or ARBs alone.

The Pitt Study¹⁴

Pitt and associates studied the efficacy of eplerenone, the ACE-inhibitor enalapril, and the combination of both agents in a double-blind, randomized, forced-titration trial. One hundred fifty-three patients with hypertension and left ventricular hypertrophy received target doses of eplerenone 200 mg daily, enalapril 40 mg daily, or eplerenone 200 mg with enalapril 10 mg; target doses were reached after four weeks of forced titration. If hypertension remained uncontrolled, HCTZ 12.5 or 25 mg or amlodipine 10 mg was added.

At the end of nine months, all groups experienced similar reductions in BP. In addition, eplerenone alone was as effective as enalapril alone in bringing about regression of left ventricular hypertrophy. The combination of these two agents caused significantly greater reduction in left ventricular mass than did eplerenone monotherapy (-27.2 vs. -14.5 g, $P = .007$), but the reduction was not significantly greater when enalapril was used alone (-27.2 vs. -19.7 g, $P = .107$).

All three treatments also resulted in decreased microalbuminuria. The combination regimen was superior to both monotherapy regimens (both $P < .001$). The trial results suggest that in addition to its ability to reduce BP, eplerenone confers cardiovascular benefits.

The Epstein Study¹⁵ and Other Trials

Several other trials, discussed earlier,^{9,10,12,14} as well as a study by Epstein et al.,¹⁵ evaluated the role of eplerenone in reducing microalbuminuria. This randomized, double-blind trial compared the renal and antihypertensive effects of eplerenone, the ACE-inhibitor enalapril, and a combination of both agents over 24 weeks. Two hundred fifteen diabetic hypertensive patients with proteinuria received eplerenone 200 mg, enalapril 40 mg, or eplerenone 200 mg with enalapril 10 mg daily, with target doses reached by forced titration.

If BP remained uncontrolled, HCTZ 12.5 mg was added and the dose was increased, up to 25 mg if necessary. Combination therapy was more effective in reducing the UACR than was eplerenone alone (-74% vs. -62%, $P = .018$), and eplerenone was superior to enalapril (-62% vs. -45%, $P = .015$). The reduction of microalbuminuria was independent of

the level of the decrease in BP; this suggests that eplerenone might offer renal protection in hypertensive patients with type 2 diabetes.

Summary

In addition to its action in lowering BP, eplerenone appears to provide protection to the heart and kidneys.⁹⁻¹⁵ Larger studies are clearly needed to confirm these findings and to determine whether the organ-protective effects of eplerenone are produced by reductions in BP or by another mechanism.

STUDIES IN HEART FAILURE

Aldosterone acts negatively on the cardiovascular system by causing myocardial necrosis, vascular injury, endothelial dysfunction, catecholamine release, and cardiac arrhythmias.¹⁶ The inhibition of RAAs is associated not only with a reduction in BP but also with a regression of left ventricular hypertrophy and in reduced target-organ damage.

The RALES Trial²

The RALES investigators noted a decrease in the overall risk of mortality by 30% in 1,663 patients with severe congestive heart failure who were using spironolactone; as a result, the effects of aldosterone-receptor blockers are beneficial in patients with severe heart failure caused by left ventricular dysfunction. However, the effect of aldosterone-receptor blockers on patients with systolic left ventricular dysfunction caused by acute myocardial infarction (AMI) remains unknown. Because eplerenone is a selective aldosterone antagonist, the question remains: will it have similar effects in patients with heart failure? In addition to its effect in reducing BP, eplerenone has shown to be efficacious in moderating neurohormonal markers of heart failure.

The EPHEBUS Trial¹⁷

The *Eplerenone Neurohormonal Efficacy and Survival Study* (EPHEBUS) is a randomized, double-blind, multicenter, placebo-controlled trial that is designed to investigate the efficacy of eplerenone in patients with heart failure as a result of AMI. The rationale for blocking aldosterone after an AMI is to inhibit the RAAS, which is activated in patients with heart failure, resulting in elevated nor-

epinephrine levels and a loss of serum potassium and magnesium. These effects can lead to myocardial damage, ventricular remodeling, and heart failure.

The EPHEBUS trial researchers hypothesized that aldosterone blockade by eplerenone in these patients would improve survival by (1) increasing nor-epinephrine uptake by the myocardium, thereby reducing sudden cardiac death, and (2) maintaining potassium and magnesium levels. These drug actions are to be tested over 2.5 years or until 1,012 deaths occur in 6,200 patients. Eligible participants can be included in the study at any time from the onset to 14 days after an AMI, which is characterized by abnormal cardiac enzymes, electrocardiographic irregularities, and clinical symptoms. Other eligibility factors include a left ventricular ejection fraction less than or equal to 40%, as documented by angiography or echocardiography after the AMI.

Patients receive 25 to 50 mg of eplerenone daily in addition to standard therapy with ACE-inhibitors, diuretics, beta blockers, digoxin, and/or nitrates.^{4,17} The reason for the lower dose—lower than for the treatment of hypertension—is its effectiveness in blocking aldosterone receptors, even though this dose appears to be subdiuretic and subhemodynamic. Besides other benefits of aldosterone blockade, the chronic effect on the kidney may be important in patients receiving loop diuretics for sodium retention.

Overall, the EPHEBUS trial is designed to quantify a wide range of clinical outcomes as well as economic evaluations.¹⁸ The primary endpoints include death from all causes and the rate of occurrence of cardiovascular mortality or morbidity that leads to hospitalization. Secondary endpoints include new onset of atrial fibrillation or flutter, functional class, and quality-of-life assessments.

ADVERSE EVENTS

The aforementioned studies in humans demonstrate a good safety profile for eplerenone,^{9-15,17} with the incidence of adverse reactions similar to those conferred by placebo. Because of the lower affinity of this agent for androgen and progesterone receptors relative to spironolactone, side effects such as

gynecomastia and breast pain rarely occur.¹⁷ In available studies involving hypertensive patients, either gynecomastia was not observed, or it occurred with an incidence similar to that associated with placebo.⁵ Further clinical trials with eplerenone are required to confirm a lower association of endocrine events.

Hyperkalemia is an expected adverse effect that occurs with aldosterone-receptor antagonists, and this effect is dose-related. A downward dose adjustment is indicated if clinical hyperkalemia occurs.⁵

Specific data on the adverse effects of eplerenone have not been published. Except for the lower incidence of antiandrogenic or antiestrogenic effects, general precautions should be similar to those applied to spironolactone.⁵

CONCLUSION

Eplerenone selectively blocks aldosterone receptors, inhibiting its detrimental actions. In the existing clinical trials, eplerenone's effectiveness was found to be comparable to that of spironolactone in reducing BP. Further studies are needed to show the potential benefits of eplerenone in reducing target-organ damage and mortality. More published data from hypertensive trials, as well as results from the EPHEBUS trial, are expected.

The Food and Drug Administration has now approved eplerenone for the treatment of hypertension.¹⁹ Eplerenone should be available on the market sometime in 2003.

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