Eplerenone (Inspra), a new aldosterone antagonist for the treatment of systemic hypertension and heart failure

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Eplerenone is the second oral aldosterone antagonist available in the USA for the treatment of essential hypertension and heart failure. Treatment has been associated with reductions in blood pressure and improved survival (15% reduction in total mortality) for patients with heart failure who are in stable condition after a myocardial infarction. Due to the selectivity of eplerenone for the aldosterone receptor, adverse effects such as gynecomastia and vaginal bleeding seem to be less likely in patients who take eplerenone than in those who take spironolactone. The most severe side effect of spironolactone, hyperkalemia, was also observed with eplerenone. While eplerenone is more selective, with the potential for fewer side effects, its overall efficacy has not been proven to be superior to that of spironolactone in clinical trials. The American College of Cardiology recommends trying spironolactone first and then switching to eplerenone if patients develop gynecomastia, menstrual irregularities, or impotence.

Eplerenone (Inspra) is the second aldosterone antagonist available in the USA. It received Food and Drug Administration approval on September 27, 2002, and October 7, 2003, for the treatment of hypertension and heart failure, respectively. Aldosterone, a hormone of the renin-angiotensin-aldosterone system, has been linked to hypertension, cardiac hypertrophy, and cardiac and vascular fibrosis. Despite treatment with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, suppression of aldosterone is incomplete due to non–angiotensin II regulators of aldosterone production, such as serum potassium. Until recently, the only approved aldosterone antagonist for the treatment of hypertension and heart failure was spironolactone. Spironolactone, although effective for these conditions, has progestational and antiandrogenic adverse effects due to its nonspecific binding to various steroid receptors.

Hypertension affects approximately 50 million people in the USA and 1 billion people worldwide (1). Achieving goal blood pressures (BP) with antihypertensive medications has been associated with a 35% to 40% reduction in stroke incidence, a 20% to 25% reduction in myocardial infarction incidence, and a >50% reduction in heart failure incidence (1). It is estimated that current control rates are still far below the Healthy People 2010 goal of 50% (1). Most patients require 2 or more antihypertensive medications with different mechanisms of action to reach the goal BP values of the Joint National Committee VII.

Nearly 5 million patients in the USA have heart failure, and 500,000 new cases are diagnosed each year. Five hundred million dollars is spent annually on the treatment of heart failure (2). According to the *American College of Cardiology/American Heart Association Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult*, the addition of aldosterone antagonists should be considered for patients with recent or current symptoms at rest despite the use of angiotensin-converting enzyme inhibitors, diuretics, beta-blockers, and/or digoxin. It has been proposed that aldosterone adversely affects the function and structure of the heart; utilizing aldosterone antagonists in addition to standard drug therapy for heart failure in clinical trials reduced mortality and hospitalization rates (2).

INDICATION(S)

Eplerenone is currently indicated in the USA for the treatment of hypertension, either alone or in combination with other agents, and for the first-line treatment of heart failure secondary to myocardial infarction (3).

PHARMACOLOGY/PHARMACOKINETICS

Eplerenone selectively binds to the mineralocorticoid receptor, thereby blocking the binding of aldosterone and thus inhibiting sodium reabsorption and other deleterious aldosterone-mediated mechanisms (3).

Eplerenone is metabolized via the cytochrome P450 (CYP) 3A4 pathway. No active metabolites are known to exist. The elimination half-life is 4 to 6 hours. Steady state is achieved within 2 days. Blood levels are potentiated and increased with concomitant use of inhibitors of the CYP3A4 pathway (e.g., ketoconazole, saquinavir, erythromycin). The pharmacokinetics of eplerenone did not differ between men and women or between whites and blacks. Steady-state area under the curve and maximum concentration are increased with renal and hepatic insufficiency. Hemodialysis does not remove eplerenone.

CLINICAL TRIALS

Most published clinical trials evaluated the efficacy of eplerenone for the treatment of hypertension. One group of researchers, utilizing the same patient population, conducted many of the trials (referenced below). The data were manipulated to reach the

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desired outcomes for each clinical trial. No clinical trials directly compared eplerenone and spironolactone for either indication. Even though a few trials did have a spironolactone arm, this arm was compared only with placebo.

Hypertension trials

A multicenter, double-blind, randomized, active-controlled, titration-to-effect trial comparing eplerenone to amlodipine showed noninferiority to amlodipine by assessing mean change in seated systolic BP. Patients ≥50 years of age with hypertension (systolic BP 150–165 mm Hg/diastolic BP ≤95 mm Hg) received either eplerenone (n = 134) or amlodipine (n = 135) as follows: The initial doses were eplerenone 50 mg daily or amlodipine 2.5 mg daily. If systolic BP was >140 mm Hg at 2 weeks, doses were increased to eplerenone 100 mg daily or amlodipine 5 mg daily. If systolic BP was >140 mm Hg at 6 weeks, doses were increased to eplerenone 200 mg daily or amlodipine 10 mg daily. Patients were excluded if they had any of the following: serum potassium ≥5 mEq/L, serum creatinine >1.7 mg/dL (men) or >1.5 mg/dL (women), or diagnosis of significant heart, liver, or kidney disease. After 24 weeks, mean doses of eplerenone and amlodipine were 155 mg and 7.4 mg, respectively. No statistically significant difference in reduction of systolic BP (95% confidence interval, –2.8 to 3.5) or reduction of pulse pressure (16 mm Hg for eplerenone vs 13 mm Hg for amlodipine, $P = 0.07$) was observed. A significantly larger decrease in diastolic BP was observed with amlodipine (95% confidence interval, –4.4 to –0.5, $P = 0.014$). Patients taking amlodipine had slightly more side effects (70% incidence vs 64% for eplerenone); the difference was due mainly to peripheral edema in some patients taking amlodipine ($P < 0.05$). The most commonly reported adverse event for eplerenone was headache (16.4%). Severe hyperkalemia was noted in 3% of the eplerenone-treated group and 1.5% of the amlodipine group. Neither group reported gynecomastia, breast tenderness, or menstrual irregularities (4).

The trial was well designed, the target sample size for each group was met, and appropriate methods were used to measure systolic BP. This trial would have revealed more beneficial results if it had been designed to compare spironolactone to eplerenone, was not limited to prove noninferiority only, and included morbidity and mortality information.

An 8-week multicenter, double-blind, placebo lead-in, parallel-group, dose-ranging study, conducted in adults (aged 21–80 years) with diastolic BP between 95 and 114 mm Hg, evaluated adjusted mean changes in diastolic BP from baseline. Patients received eplerenone 50 mg daily (n = 54), 100 mg daily (n = 49), 400 mg daily (n = 56), 25 mg twice daily (n = 55), 50 mg twice daily (n = 54), or 200 mg twice daily (n = 48); placebo (n = 53); or spironolactone 50 mg twice daily (n = 48). Patient exclusion criteria included the following: malignant hypertension; current use of other medications that influenced BP; current use of nonsteroidal antiinflammatory drugs; myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, angina pectoris, or intermittent claudication in the past 6 months; valve disease; cardiomyopathy/heart failure; stroke/transient ischemic attack; insulin-dependent diabetes mellitus; hepatic disease; serum creatinine >1.5 mg/dL; serum potassium >5 mEq/L; alcohol/drug abuse; sensitivity to steroids; or working a night shift. After 8 weeks, reductions in mean systolic BP/diastolic BP from baseline were observed for all doses of eplerenone ($P < 0.05$). No significant differences in reduction were noted between daily and twice-daily regimens. Dose-related decreases in all measurements were observed for eplerenone. The overall incidence of adverse events was 46%, with headache being reported most frequently. Significant changes in serum potassium levels from baseline were observed in the groups that received eplerenone 400 mg daily or 25 mg, 50 mg, or 100 mg twice daily and in the spironolactone group ($P < 0.05$). There were no reports of menstrual abnormalities, impotence, or gynecomastia. One spironolactone-treated patient experienced intermenstrual bleeding (5). The use of a spironolactone control was beneficial in allowing for observation of positive and negative outcomes among the treatment groups; however, eplerenone was never directly compared with spironolactone. Both were compared with placebo only.

A 12-week multicenter, double-blind, randomized, placebo-controlled, parallel-arm, intention-to-treat trial evaluated the mean changes in diastolic BP between placebo and eplerenone. Patients with systolic BP <180 mm Hg, diastolic BP 95 to 110 mm Hg, or 24-hour mean diastolic BP ≥85 mm Hg received eplerenone 25 mg, 50 mg, 100 mg, or 200 mg once daily or placebo (n = 90 for each dose range and placebo). Patients with recent myocardial infarction or unstable angina, heart failure, hepatic/renal disease, secondary hypertension, uncontrolled diabetes mellitus, serum creatinine >1.7 mg/dL for men or >1.5 mg/dL for women, or baseline serum potassium >5 mEq/L were excluded. After 12 weeks, significant reductions in diastolic BP were observed in the 50 mg, 100 mg, and 200 mg eplerenone groups. Significant reductions in systolic BP were observed for all doses of eplerenone. The eplerenone groups had dose-related increases in serum potassium or elevated serum potassium levels compared with the placebo group. The most common reported adverse events in patients receiving eplerenone was headache (11.6%); however, the frequency was not significantly higher than in those receiving placebo. One patient each in the eplerenone 100 mg and placebo group experienced impotence (6). Limitations to the study were that 3 of the 5 arms failed to reach their target sample size, and statistical analysis was performed by using one-sided tests.

Eplerenone monotherapy in black and white adult populations was compared with placebo and losartan in a randomized, double-blind, placebo- and active-controlled, placebo run-in, parallel group trial. The study population was stratified at a 2:1 ratio of black to white patients. The primary endpoint was the mean change in diastolic BP from baseline to final visit. Patients were eligible for inclusion if their systolic BP was <180 mm Hg and diastolic BP was between 95 and 109 mm Hg without medication. Patients receiving 1 or 2 antihypertensive medications were eligible if their BP was <140/90 mm Hg. Eplerenone treatment was initiated at a dose of 50 mg, titrated to 100 mg/day, and increased if necessary to a maximum of 200 mg/day; losartan treatment were initiated at 50 mg and titrated to 100 mg/day if BP was ≥140/90 mm Hg at weeks 4, 8, or 12. Eplerenone demonstrated a significantly greater reduction in mean BP from baseline than placebo or losartan for all patients combined ($P < 0.001$) and for black patients ($P \leq 0.001$). Mean changes in white patients' BP were

significantly greater for the eplerenone arm than for the placebo arm (P = 0.001) but were not significantly different than those for the losartan arm. No patients in the eplerenone arm experienced impotence, gynecomastia, or breast tenderness; however, 2 patients reported menstrual disorders and 2 reported decreased libido. The observed change in serum potassium level was significantly greater for the eplerenone arm than for the other arms, with a change of +0.09 ± 0.03 mEq/L (P < 0.001 for eplerenone vs placebo, P = 0.003 for eplerenone vs losartan). More patients within the placebo and losartan arms than the eplerenone arm discontinued treatment because of treatment failure (P = 0.0001 for eplerenone vs placebo, P < 0.001 for eplerenone vs losartan). Upper respiratory system disorders were the most frequently reported adverse events for both the eplerenone and losartan arms. Two patients in the eplerenone group reported menstrual disorders, and 2 reported decreased libido (7).

Even though this trial included both black and white patients, most of the trial population (63%) was black, which may limit application of the results to all races and may also have influenced the improved efficacy seen in the "all patients" group. The researchers failed to list their target sample sizes for each arm. Patients were withdrawn if their systolic BP was >150 mm Hg or diastolic BP was >96 mm Hg after treatment initiation, thus excluding patients whose need for BP reduction was greatest.

Heart failure trials

The Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS), a 16-month international, multicenter, randomized, double-blind, placebo-controlled study, evaluated the efficacy of eplerenone in reducing morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure. Primary endpoints were time to death from any cause, time to death from cardiovascular causes, or hospitalization for heart failure, acute myocardial infarction, stroke, or ventricular arrhythmia. Patients received eplerenone 25 mg daily or matching placebo for 4 weeks and then the eplerenone dose was increased if necessary to a maximum of 50 mg daily. To be eligible, patients must have experienced an acute myocardial infarction within the prior 3 to 14 days, have left ventricular dysfunction, or have evidence of heart failure. Excluding potassium-sparing diuretics, standard drug therapy was allowed. Death from any cause occurred in 14.4% of patients in the eplerenone arm and 16.7% of those in the placebo arm (relative risk, 0.85; P = 0.0008). Mortality rates at 1 year were 11.8% and 13.6% in the eplerenone and placebo groups, respectively. Death from cardiovascular causes or hospitalization for cardiovascular events occurred in 27% of patients receiving eplerenone and 30% of patients receiving placebo (relative risk, 0.87; P = 0.002). Systolic BP and diastolic BP increased in both groups from baseline throughout the trial; however, the increase was less for the eplerenone group. Subgroup analyses, defined *a priori*, revealed a benefit from eplerenone in patients treated with angiotensin-converting enzyme inhibitors or beta-blockers. Serum concentrations of potassium and creatinine increased in both groups, and the increases were greater in patients who received eplerenone. Serious hyperkalemia was more frequent in the eplerenone-treated patients (5.5%) than in those treated with placebo (3.9%) (P = 0.002) (8).

Table 1. Adverse events reported most frequently with eplerenone

Adverse event	Rate (%) of adverse event
Hyperkalemia (K^+ >5.5 mEq/L)	33% (eplerenone alone) 38% (eplerenone and enalapril)
Hypertriglyceridemia	15%
Hyponatremia	2.3%
Mastodynia	0.8% (men)
Abnormal vaginal bleeding	0.6% (women)
Gynecomastia	0.5% (men)

EPHESUS was a large, well-designed outcome trial in which eplerenone yielded substantial improvement in mortality and morbidity compared with placebo. When compared with results of the RALES trial, however, these results are modest, and the improvement was only half of that observed in the RALES trial. Major differences between the 2 trials, such as differences in the patient populations (patients in RALES were sicker and older) and different baseline treatment regimens (more patients in EPHESUS were on beta-blockers, aspirin, statins, and/or angiotensin-converting enzyme inhibitors) may explain the differences in results.

The 4E-Left Ventricular Hypertrophy Study, a 9-month double-blind, randomized trial, enrolled 202 patients with left ventricular hypertrophy and hypertension. Patients received eplerenone 200 mg daily, enalapril 40 mg daily, or eplerenone 200 mg daily plus enalapril 10 mg daily. After 8 weeks, hydrochlorothiazide 12.5 to 25 mg and/or amlodipine 10 mg was added if diastolic BP was >90 mm Hg. The study's purpose was to compare left ventricular mass regression by magnetic resonance imaging in patients receiving eplerenone alone, enalapril alone, or the combination. Eplerenone significantly reduced left ventricular mass from baseline (–15 ± 3 g; n = 50), like enalapril (–20 ± 3 g; n = 54; P = 0.258), but the combination was more effective than eplerenone alone (–27 ± 3 g; n = 49; P = 0.007). All treatments reduced both systolic and diastolic BP equally. The most common side effect of eplerenone was hyperkalemia (9).

Measuring left ventricular hypertrophy with magnetic resonance imaging is investigational, and the correlation between quantity of regression and clinical effect is controversial. The target sample size of 55 patients per group to adequately power the study for the primary endpoint was not met for any of the groups. The statistical test evaluated only how well the medication reduced left ventricular size and not the potential for left ventricular growth despite adequate treatment.

ADVERSE EFFECTS

The overall adverse effect rate for patients on eplerenone was 47%, and 3% of patients discontinued its use as a result. The most notable/common adverse effects observed in clinical trials are summarized in *Table 1*.

DOSING AND ADMINISTRATION

The recommended starting dose of eplerenone for the treatment of essential hypertension is 50 mg once daily titrated to a maximum of 50 mg twice daily. For the treatment of heart failure,

Table 2. Costs of eplerenone and spironolactone

Drug/dose	Cost per tablet
Eplerenone 25 mg	$2.93
Eplerenone 50 mg	$2.93
Spironolactone 25 mg	$0.26
Spironolactone 50 mg	$0.48
Spironolactone 100 mg	$0.80

the recommended starting dose is 25 mg once daily, titrated over 4 weeks if tolerated to the target dose of 50 mg once daily. No adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Class B) or for the elderly. Patients taking a CYP3A4 inhibitor should receive an initial starting dose of 25 mg once daily. The maximum effective dose should be limited to 100 mg daily to avoid the increased risk of hyperkalemia with higher doses.

PREGNANCY CATEGORY

There are no adequate studies in pregnant women; therefore, a pregnancy B category has been assigned.

DRUG INTERACTIONS

Eplerenone does not inhibit any cytochrome isoenzymes. Inhibitors of CYP3A4 such as ketoconazole caused a fivefold increase in exposure, while less potent inhibitors of CYP3A4 (erythromycin, saquinavir, verapamil, and fluconazole) yielded a twofold increase in exposure. St. John's wort caused a small (30%) decrease in the area under the curve. Grapefruit juice caused a small (25%) increase in exposure.

DOSAGE FORMS

Eplerenone is available as 25- and 50-mg tablets. The 100-mg tablet will not be marketed and is no longer included in the labeling.

ECONOMIC ISSUES

The cost of eplerenone is compared with the cost of spironolactone in *Table 2*. All costs are based on BUMC pharmacy acquisition costs.

A 1-month supply of eplerenone is estimated to cost $87.90 for treatment of congestive heart failure and $175.80 for treatment of hypertension based on current maximum dosage recommendations. For the same period, spironolactone is estimated to cost $14.40 for treatment of congestive heart failure and $24.00 for treatment of hypertension based on current maximum dosage recommendations. Therefore, eplerenone is approximately 6 to 7 times more expensive than spironolactone for the treatment of either hypertension or congestive heart failure.

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