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EPLERENONE (INSPRA®)

THE FIRST SELECTIVE ALDOSTERONE RECEPTOR ANTAGONIST FOR THE TREATMENT OF HYPERTENSION

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Introduction

Approximately 50 million adult Americans have high blood pressure. Of those, 73 percent are not adequately controlled, and are at increased risk of heart attack, stroke, kidney failure, ocular damage, heart failure, and atherosclerosis.[1] Control of hypertension remains inadequate in many patients despite the availability of several classes of antihypertensives, such as, angiotensin converting enzyme (ACE) inhibitors, β-blockers, calcium channel blockers (CCB), angiotensin receptor blockers (ARBs), and diuretics. The high prevalence of hypertension and its link to cardiovascular and renal disease imposes a large economic burden. It is estimated that hypertension-related morbidity and mortality cost the United States over $34.3 billion in healthcare expenditures and an additional $12.8 billion in loss of productivity in 2002.[2]

Aldosterone, an effector hormone of the renin-angiotensin-aldosterone system (RAAS), plays a critical role in the development and progression of cardiovascular disease.[3] Aldosterone has been linked to hypertension, cardiac hypertrophy, cardiac and vascular fibrosis, and ventricular arrhythmias.[4-7] Recent studies demonstrate that, although the level of aldosterone is suppressed in patients treated with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), suppression does not continue with chronic use of these medications.[8-9] Spironolactone, an aldosterone receptor antagonist, has traditionally been used as a potassium- and magnesium-sparing diuretic in the treatment of hypertension and congestive heart failure or in the management of primary aldosteronism. Although the clinical importance of aldosterone receptor antagonists in the treatment of congestive heart failure and hypertension has been demonstrated with spironolactone, its use has been limited by progestational and antiandrogenic side effects including gynecomastia.[10]

Eplerenone (Inspra®) is a new selective aldosterone blocker approved by the FDA in October 2002. It is marketed by Pharmacia and is expected to be released during the first quarter of 2003. In contrast to spironolactone, eplerenone demonstrates a high degree of selectivity for the aldosterone receptor with a low-binding affinity for progesterone (<1%) and androgen receptors (0.1%).[29] This article will examine the safety, efficacy, and tolerability of eplerenone.

Pharmacology and Pharmacokinetics

Aldosterone synthesis, which occurs primarily in the adrenal gland, is modulated by multiple factors, including angiotensin II and non-RAAS mediators such as adrenocorticotropic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial and non-epithelial tissues and increases blood pressure through induction of sodium reabsorption and possibly other mechanisms. Eplerenone binds to mineralocorticoid receptors and blocks the binding of aldosterone, a component of the RAAS. Eplerenone produces a sustained increase in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on

Table 1. Dose Ranging Studies of Eplerenone [13-14]

Study group	Demographics	Design	Dose	N	Mean Δ BP (mmHg) SBP/DBP	
Burgess et al.[13]	Mild to moderate hypertension	OL, 6 to 16 months Titration to effect Second medication-could be added	50 mg/d	68	-15.9/-10.6	
			100 mg/d	98	-18.1/-12.2	
			200 mg/d	104	-19.1/-12.5	
			200 mg/d	172	-24.9/-14.6	
					Δ Clinic BP (mmHg)	**Δ Ambulatory BP (mmHg)**
White et al.[14]	Mild to severe hypertension	12 weeks DB, PC, FD Clinic and ambulatory BP monitoring	Placebo	90	-0.0/-1.7	-1.3/0.8
			25 mg/d	45	-5.7*/-3.7	-6.4*/-4.4*
			50 mg/d	87	-6.7*/-4.6*	-6.8*/-4.1*
			100 mg/d	90	-10.4*/-6.3*	-9.1*/-5.5*
			200 mg/d	88	-8.8*/-5.4*	-10.3*/-5.7*

DBP = diastolic blood pressure, SBP = systolic blood pressure, OL = open label, DB = double-blinded, PC = placebo=controlled, FD = fixed-dose
* $p < 0.01$ for eplerenone vs. placebo

renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels do not negate the effect of eplerenone on blood pressure.[11]

Eplerenone's mean peak plasma concentration (C_{max}) is reached approximately 1.5 hours following oral administration. Absorption is not affected by food. The absolute bioavailability of eplerenone is unknown. It is approximately 50% bound to plasma proteins, primarily α-1-acid glycoprotein. Eplerenone's metabolism is primarily mediated via CYP 3A4 and no active metabolites have been identified in human plasma to date. Less than 5% of an eplerenone dose is recovered as unchanged drug in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 32% of the dose was excreted in the feces and approximately 67% was excreted in the urine. The elimination half life of eplerenone is approximately 4 to 6 hours. The apparent plasma clearance is approximately 10 L/hr. Inhibitors of CYP 3A4 (e.g. ketoconazole, saquinavir) increase blood levels of eplerenone. Area under the curve (AUC) and C_{max} were increased by 38% and 24%, respectively, in patients with severe renal impairment and were decreased by 26% and 3% respectively, in patients undergoing hemodialysis when compared with control subjects. The pharmacokinetics of eplerenone did not differ significantly between males and females. However, steady state concentrations of eplerenone appeared to be higher in the elderly and lower in African American subjects. [11]

Clinical Trials

Hypertension

Numerous studies have investigated eplerenone's efficacy in different stages of hypertension. These include: dosing-ranging studies,[13-14] comparison with other antihypertensive monotherapies,[15, 24, 27] and comparisons with other antihypertensive drugs alone or in combination.[25-26]

Dosing-ranging studies

Two double-blinded, placebo-controlled trials evaluated eplerenone's effect on blood pressure in patients with mild to moderate[13] and mild to severe hypertension.[14] Rurgress et al.[13] evaluated eplerenone's ability to achieve a diastolic blood pressure (DBP) <90 mmHg or a systolic blood pressure (SBP) <140 mmHg when titrated from 50 mg/day up to 200 mg/day and found that the dose response relationship began to plateau at 100 mg. If blood pressure remained uncontrolled at anytime from week 6 to the end of month 3, a second medication was added. The mean changes in SBP/DBP from baseline for the different eplerenone doses are summarized in Table 1. A total of 433 patients (74.3%) were classified as responders, that is, patients with a DBP <90 mmHg or a >10 mmHg change from baseline. In addition, 261 of the responders (44.8%) had responded to eplerenone monotherapy. White et al.[14] found eplerenone 100 mg once daily to be the maximum effective dose in patients with mild to severe hypertension. The results of this study are also summarized in Table 1.

Table 2. Mean Blood Pressure Change from Baseline to 16 weeks [15]

	EPL	LOS	PBO	*p*-value	
				EPL vs. PBO	EPL vs. LOS
All patients					
▲ SBP/DBP (mm Hg)	-12.8/-10.3	-6.3/-6.9	-3.4/-5.3	<0.001/<0.001	<0.001/<0.001
African American patients					
▲ SBP/DBP (mm Hg)	-13.5/-10.2	-5.3/-6.0	-3.7/-4.8	<0.001/<0.001	<0.001/<0.001
White patients					
▲ SBP/DBP (mm Hg)	-12.3/-11.1	-8.5/-8.4	-3.2/-6.4	<0.001/0.001	<0.126/<0.068

EPL = eplerenone, LOS = losartan, PBO = placebo

Eplerenone vs. Spironolactone

Eplerenone's effect on blood pressure was evaluated in a double-blinded, placebo controlled trial.[24] Various doses of eplerenone were compared to a fixed dose of spironolactone. The study was an 8-week, multi-center, double-blinded, placebo-controlled trial designed to assess the efficacy, safety, and tolerability of eplerenone. Eligible patients were randomized to eplerenone 50, 100, 200, or 400 mg once daily; eplerenone 25, 50, or 200 mg twice daily; spironolactone 50 mg twice daily; or placebo. Four hundred and nine out of 417 randomized patients were evaluated for efficacy. The adjusted mean change from baseline to final visit in sitting and standing SBP and DBP was significantly greater ($p < 0.05$) in all eplerenone groups compared to the placebo group. The adjusted mean change in 24-h ambulatory blood pressure monitoring (ABPM) measurements of SBP and DBP were significantly greater ($p < 0.05$) in eplerenone-treated patients than placebo. Significant reductions ($p < 0.01$) in SBP and DPB compared to placebo were also observed in the spironolactone group. Adjusted mean changes from baseline to final visit in SBP and DBP for eplerenone 100 mg daily and 50 mg twice daily were approximately 50% to 75% of those observed in the twice daily 50 mg spironolactone group. The incidence of adverse events was similar to placebo with the exception of increased levels of serum potassium observed in both eplerenone-treated and spironolactone-treated patients. No antiandrogenic or progestational effects or clinically relevant safety issues were observed in eplerenone-treated patients. However, one spironolactone-treated patient reported menstrual irregularities.

Eplerenone vs. Losartan

Pratt[15] evaluated eplerenone's ability to lower blood pressure compared to the ARB losartan and placebo. The primary outcome of the study was change from baseline in trough DBP after 16 weeks of therapy. Following a 4-week period, 551 untreated hypertensive patients were randomized to receive either eplerenone 50 mg/d, losartan 50 mg/d, or placebo. After 16 weeks of treatment, the mean change in DBP was 10.3 mmHg for eplerenone, 6.9 mmHg for losartan, and 5.3 mmHg for placebo (Table 2). The study also evaluated the treatment effects according to race. African American patients demonstrated a greater mean change in DBP compared to losartan ($p<0.001$) or placebo ($p<0.001$). However, eplerenone's effect on blood pressure in white patients was similar to that of losartan but significantly better than placebo. Based on this study, eplerenone appears to be more effective than losartan for the treatment of hypertension in African American patients.

Eplerenone vs. Enalapril

Burgess and colleagues[27] compared eplerenone to the ACE inhibitor enalapril in patients with mild to moderate hypertension (95 mmHg < DBP <110 mmHg). Patients were randomized to receive eplerenone 50 mg daily (N=253) or enalapril 10 mg daily (N=246) initially. If DBP was >90 mmHg at week 4, 8, 12, 16, or 20, the doses were increased to 100 mg and 200 mg daily for eplerenone or 20 mg and 40 mg daily for enalapril. Blood Pressure (SBP/DBP) was comparably reduced by both drugs at week 24 (eplerenone –14.5/-11.2 mmHg, enalapril –12.7/-11.3 mmHg) and 12 months (eplerenone –16.5/-13.3 mmHg, enalapril –14.8/-14.1 mmHg). However, patients

Table 3. Rate (%) of adverse events occurring in > 1% of patients treated with eplerenone (25 mg to 400 mg) [11,31]

	Eplerenone (N=945)	Placebo (N=372)
Metabolic		
Hypercholesterolemia	1%	0%
Hyperglycemia	1%	0%
Hyperkalemia	2.7%	1.3%
Digestive		
Diarrhea	2%	1%
Abdominal pain	1%	0%
Urinary		
Albuminuria	1%	0%
Respiratory		
Cough	2%	1%
Central Nervous System		
Dizziness	3%	2%
Miscellaneous		
Fatigue	2%	1%
Influenza like symptoms	2%	1%

receiving enalapril had a significantly higher incidence of adverse effects, including cough (6.5% vs. 2.4 %, P= 0.029) and hyperglycemia (2.8% vs. 0.4%, P = 0.035). No data on the incidence of hyperkalemia was reported.

Combination therapy trials

Eplerenone's efficacy was evaluated as an adjunctive agent with other antihypertensive agents in several clinical trials. Krum et al examined eplerenone's effect on blood pressure when added to a treatment regimen containing either an ACE inhibitor or ARB. Patients were randomized to receive eplerenone 50 mg/d or placebo in addition to the fixed-dose ACE inhibitor or ARB. After 2, 4, or 6 weeks of treatment, the dose of eplerenone or matching placebo was doubled if DBP was >90 mmHg (maximum dose 100 mg/d). Following 8 weeks of treatment, patients taking an ACE inhibitor who received eplerenone had a significantly greater decrease from baseline in mean SBP than patients who received placebo (13.4 vs. 7.5 mmHg; p=0.002). After adding eplerenone, patients taking an ARB also showed significant decreases from baseline in both SBP and DBP compared to placebo (SBP 16.0 vs. 9.2 mmHg, p=0.001; DBP 12.7 vs. 9.3 mmHg; p=0.004). These comparison studies demonstrated that blood pressure can be further decreased when eplerenone is added to either an ACE inhibitor or ARB.

Pitt et al.[26] investigated eplerenone's efficacy in patients with mild to moderate hypertension and left ventricular hypertrophy. One hundred and fifty three patients were assigned to eplerenone 200 mg/d, enalapril 40 mg/d, or the combination of eplerenone 200 mg and enalapril 10 mg/d. The investigator titrated the doses over 4 weeks. If at week 8 BP remained uncontrolled (DBP >90 mmHg or SBP >180 mmHg) with the full daily dose, hydrochlorothiazide 12.5 mg and 25 mg, or amlodipine 10 mg was added. The primary end point was change from baseline in left-ventricular mass (LVM). Secondary endpoints included blood pressure control, change in microalbuminuria, and treatment safety and tolerability. There was a significant reduction in LVM in the combination and eplerenone groups (p=0.007), but not for the enalapril group (p=0.107). Both SBP and DBP were significantly reduced from baseline in both groups. SBP decreased by 23.8 mmHg in the eplerenone group, 24.7 mmHg in the enalapril group (p=0.718 for the between-group comparison), and 28.7 mmHg in the combination group (p=0.048 for eplerenone vs. combination; p=0.098 for enalapril vs. combination). Finally, the percent change from baseline in microalbuminuria was significantly reduced among the 3 groups. Interestingly, they found that the combination produced significant reductions when compared with either agent alone (p=0.001 vs. eplerenone; p=0.038 vs. enalapril). Based on these data, it appears that eplerenone can lower blood pressure, reduce LVM, and decrease microalbuminuria similar to enalapril.

Heart Failure

The Eplerenone Neurohormonal Efficacy and Survival Trial (EPHESUS)[19, 28] is an ongoing study that will evaluate eplerenone in the treatment of heart failure. Approximately 6200 patients will receive eplerenone 25–50 mg/d or placebo and will be followed for a total of 2.5 years. The rationale for this study was based on the results from the Randomized Aldactone Evaluation Study (RALES) in patients with chronic stable heart failure.[30] The primary endpoints are rate of all-cause mortality and combined rate of cardiovascular mortality or morbidity due to hospitalization. Additional end-

Table 4. Changes in serum potassium with eplerenone[11]

Dose	N	Mean change (mEq/d)	% > 5.5 (mEq/L)
Placebo	194	0	1
25	97	0.08	0
50	245	0.14	0
100	193	0.09	1

points include hospitalizations, functional class, quality of life, new-onset atrial fibrillation/flutter, and economic evaluations. Subgroup analysis will examine eplerenone's effect on cardiac remodeling, collagen metabolism, vascular compliance, heart rate variability, thrombolytic balance, and proteinuria. The results from this trial will provide health care professionals with important data regarding the use of eplerenone as part of the heart failure treatment regimen, as well as, data concerning the effects of aldosterone receptor blockade following acute myocardial infarction.

Dosing and Administration

Eplerenone doses ranging from 25 mg to 400 mg/day in one or two divided doses have been evaluated in clinical hypertension trials. The dose response curve appears to plateau at 100 mg/day. Based on this data, the recommended starting dose of eplerenone is 50 mg administered once daily. The full therapeutic effect of eplerenone is apparent within 4 weeks. For patients with an inadequate blood pressure response at 50 mg once daily, the dosage should be increased to 50 mg twice daily. Eplerenone may be used alone or in combination with other antihypertensive agents. Higher dosages of eplerenone are not recommended because they have no greater effect on blood pressure or because they are associated with an increased risk of hyperkalemia.

Toxicity and Safety

Complete data on adverse events for eplerenone has not been published. Based on the available information from clinical trials, the incidence of adverse events from eplerenone (25 mg to 400 mg) is similar to that of placebo. One of the most common adverse effects seen in clinical trials for hypertension was hyperkalemia, with a reported incidence of 2.7% compared to 1.3% for placebo.[31] In the combined losartan and add-on hypertension trials,[24] of the 269 patients treated with eplerenone, only 1% experienced hyperkalemia or hyperuricemia. There was a clinically significant higher incidence of hyperkalemia (defined as K^+ >6.0 mEq/L) among heart failure patients receiving eplerenone 100 mg/d (12.0%) compared to spironolactone 25 mg/d (8.7%). However, most of the patients in this study also received concurrent ACE inhibitor therapy.[23] The most common reasons for discontinuation were headache, dizziness, and increased serum gamma glutamyl transpeptidase (GGT).[11] Less than 1% of patients reported impotence or menstrual abnormalities. These results are summarized in Table 3 and 4.

Cost

Eplerenone is not marketed yet. Therefore, price information is not available at this time.

Summary

Eplerenone is a novel agent that selectively blocks aldosterone. It is indicated for the treatment of hypertension alone or in combination with other antihypertensive agents. Eplerenone appears be more beneficial than other non-selective aldosterone blockers, such as spironolactone, due to it's limited progestational and antiandrogenic side effects. It is also being investigated for its potential use in heart failure patients. However, much of this data has only appeared in review and abstract form. Until additional research on the clinical use of eplerenone in heart failure patients and results from the ongoing EPHESUS trial are published, eplerenone's role in heart failure patients will remain uncertain.

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