

Eplerenone

The first selective aldosterone receptor antagonist for the treatment of hypertension

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Approximately 50 million people in the United States have hypertension, but fewer than one-third maintain adequate blood pressure (BP) control.¹ The high prevalence of hypertension and its link to cardiovascular and renal disease imposes a large economic burden in the United States. It is estimated that hypertension-related morbidity and mortality will cost the United States over \$34.4 billion in healthcare expenditures and an additional \$12.8 billion in lost productivity in 2002.²

The renin-angiotensin-aldosterone system (RAAS) maintains BP and volume homeostasis in the body.³ Aldosterone is the key mineralocorticoid of the RAAS and acts at the epithelial cells in the distal tubule and collecting ducts of the nephron to promote sodium and water reabsorption, consequently increasing BP.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are widely used to manage hypertension as well as myocardial infarction, diabetic nephropathy, and congestive heart failure.^{1,4,5} ACE inhibitors decrease serum aldosterone levels by inhibiting the formation of angiotensin II and ARBs work by blocking angiotensin II's activity, leading to decreased stimulation of aldosterone release.

Recent studies have shown that, although the level of aldosterone is suppressed in patients treated with an ACE inhibitor or an ARB, suppression does

Abstract

Eplerenone is a selective aldosterone receptor antagonist under FDA review for the treatment of hypertension. Eplerenone is a 9 α , 11 α -epoxy-substituted derivative of spironolactone—the only aldosterone antagonist currently approved in the United States. Eplerenone has a trough-to-peak ratio greater than 90%, making it suitable for once-daily dosing. Placebo-controlled trials have shown that eplerenone 25 to 200 mg/d, alone or in combination with other antihypertensives, significantly reduces blood pressure (BP) in patients with mild to severe hypertension. In addition, comparative trials have shown eplerenone to have a potent antihypertensive effect similar to that of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine calcium channel blockers, and spironolactone. Because eplerenone has a lower binding affinity for androgenic and progestogenic receptors than spironolactone does, investigators hope eplerenone will have a lower incidence of endocrine-related adverse effects (gynecomastia, breast tenderness, and menstrual irregularities). Preliminary data seem to support this, but further study is needed. Hyperkalemia ($K^+ > 6$ mEq/l) has been reported in clinical trials, most commonly when eplerenone was given concurrently with an ACE inhibitor. Eplerenone neither induces nor inhibits the CYP P450 isoenzyme system; however, it is extensively metabolized by the 3A4 isoenzyme. Eplerenone's potential for drug interactions has not been extensively investigated, and further studies need to be conducted. The effects of eplerenone on mortality, hospitalization, quality of life, and cost of care in patients with congestive heart failure are currently under investigation in phase III trials. An additional new drug application (NDA) for this potential indication is expected to be filed in early 2003. (*Formulary* 2002;37:514-24.)

not continue with chronic use of these medications.⁶ The RESOLVD trial demonstrated that, with chronic use of either type of medication, levels of aldosterone returned to pretreatment values or higher. This phenomenon has been termed *aldosterone synthesis escape*.

In addition, angiotensin II is not the sole stimulator of aldosterone secretion.

Other factors, such as potassium, endothelin, and various neurotransmitters are also known to do so.⁶ Patients treated with ACE inhibitors and ARBs may remain susceptible to the effects of circulating aldosterone because aldosterone synthesis is not completely inhibited. This may help explain why ACE inhibitors and ARBs often do not adequately control BP in salt-sensitive hypertensive patients, who account for an estimated 60% of non-Black patients with hypertension and 73% of Black hypertensives.^{7,8} Through receptor blockade, spironolactone (Aldactone), a non-selective aldosterone receptor antagonist,

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■ Table 1

Pharmacokinetics of eplerenone and spironolactone in humans

Drug	Tmax (h)	Cmax ng/ml	Food-drug interactions	t½ (h)	Protein binding (%)	Elimination
Eplerenone	1-2	1,721	No†	4-5	49	Hepatic (66% urine, 32% feces)
Spironolactone*	2.6-5.1	80-391	Yes‡	1.4-16.5	90	Hepatic (53% urine, 20% feces)

Tmax = time to maximum plasma concentration; t½ = elimination half-life; AUC = area under the plasma concentration-time curve

* Range of values are for spironolactone and its multiple active metabolites

† Documented in a dog model only.

‡ Spironolactone bioavailability increases by 100% when taken with food.

Formulary/Source: References 9,14-18

offered an alternative and effective approach to controlling the effects of aldosterone. But because spironolactone also has an affinity for progesterone and androgen receptors, its use is associated with endocrine-related adverse effects, such as gynecomastia in men, which may occur in as many as 52% of male patients.^{9,10} The clinical use of spironolactone in hypertension has, therefore, been limited.

The first selective aldosterone receptor antagonist (SARA), eplerenone—a derivative of spironolactone—is nearing approval. SARAs have been shown to have a far lower binding affinity than spironolactone for glucocorticoid receptors,¹¹ so it is hoped that this will translate into a decreased incidence of androgenic and progestogenic adverse events without decreasing efficacy. In February 2002, FDA accepted Pharmacia's NDA for eplerenone to treat hypertension. The estimated user fee goal date for FDA review of this drug and indication is the fourth quarter of this year. Phase III clinical trials of eplerenone for treatment of congestive heart failure are ongoing, and Pharmacia is expected to file an NDA for this application in early 2003.

This article will review the available clinical information, published primarily in abstract form, on eplerenone for its hypertension indication.

PHARMACOLOGY

Eplerenone, also known as epoxymexrenone, CGP-30083 and SC-66110, is

a 9 α , 11 α -epoxy-derivative of spironolactone. It has a molecular weight of 414.50 and an empirical formula of C₂₄H₃₀O₆. Its chemical name is 9 α , 11 α -epoxy-17 α -hydroxy-3-oxo-17 α -pregn-4-ene-7 α , 21-dicarboxylic acid, γ -lactone, 7-methyl ester.¹²

Eplerenone's chemical structure differs from spironolactone only by the introduction of a 9 α , 11 α -epoxy group and the replacement of spironolactone's 7 α -thiomethyl group with a 7 α -methyl ester.¹³ In vitro, structure-activity studies have shown that the 9 α , 11 α -epoxy group gives eplerenone a 15- to 20-fold lower affinity for the mineralocorticoid receptor (IC₅₀ = 220 nM) than spironolactone.^{11,13,14} Eplerenone's affinity for the androgen, progesterone, and glucocorticoid receptors (IC₅₀ > 10,000 nM), however, is up to 500-fold lower than that of spironolactone.^{11,13,14} The change in receptor affinities is attributed to sterical interference of the receptor fit by the 7 α -ester and 9 α , 11 α -substituent.

In vivo, eplerenone has proved to be as potent an aldosterone antagonist as spironolactone, showing 1- to 2-fold the potency of spironolactone in rats, with a 3- to 10-fold reduction in antiandrogenic and progestogenic side effects. Eplerenone's decreased affinity for the aldosterone receptor in vitro but potency in vivo is because of its minimal 49% protein binding.¹³ In contrast, spironolactone is > 90% bound, allowing only a small percentage of drug to diffuse to mineralocorticoid receptors.^{9,11,13}

PHARMACOKINETICS

The pharmacokinetic properties of eplerenone have been studied in dogs and healthy human volunteers (table 1).^{9,14-18} After a single dose of 100 mg, eplerenone appears to be well absorbed. No interaction was observed following oral administration with food.¹⁸ The area under the plasma concentration-time curve (AUC_{0-∞}) was 9,537 ± 3,201 ng/ml/h.¹⁵ No accumulation of eplerenone was noted following multiple oral doses of 100, 300, and 1,000 mg, and the AUC values were not dose proportional.¹⁴ Peak plasma concentration (C_{max}) obtained was 1,721 ± 290 ng/ml.¹⁵ The time to achieve maximum plasma concentrations (T_{max}) of eplerenone was 1 to 2 hours with an elimination half-life (T_{1/2}) of 4 to 5 hours.¹⁴ Eplerenone was not appreciably bound to plasma proteins.¹⁴ In vitro, eplerenone's primary route of elimination was through hepatic metabolism via the CYP P450 3A4 isoenzyme.¹⁵⁻¹⁷ No active metabolites of eplerenone have been detected.¹⁵ Of the administered dose, 66% was recovered in urine and 32% in feces. Eplerenone was extensively metabolized, with < 1.7% of the dose being excreted unchanged in the urine and 0.8% in the feces.¹⁵

CLINICAL TRIALS IN HYPERTENSION

Numerous studies investigating eplerenone's efficacy in all stages of hypertension have been conducted and were recently presented at major hypertension and cardiology meetings.¹⁹⁻²⁸

■ Table 2

Dose ranging studies of eplerenone

Study/Patient demographics	Study design	Regimen	Mean Δ BP (mm Hg)	
Burgess et al ¹⁹ Mild to moderate hypertension N = 586	6 to 16 mo	50 mg/d	-15.9/-10.6	
	Open label	100 mg/d	-18.1/-12.2	
	Titration to effect	200 mg/d	-19.1/-12.5	
	Second medication could be added	200 mg/d plus other	-24.9/-14.6	
White et al ²⁰ Stage 1 to 3 (mild to severe) hypertension N = 400	12 wk		Clinic	Ambulatory
	Double blind, placebo controlled	25 mg/d (n = 45)	-5.7*/-3.7	-6.4*/-4.4*
	Fixed dose	50 mg/d (n = 87)	-6.7*/-4.6*	-6.8*/-4.1*
	Ambulatory and clinic monitoring	100 mg/d (n = 90)	-10.4*/-6.3*	-9.1*/-5.5*
		200 mg/d (n = 88)	-8.8*/-5.4*	-10.3*/-5.7*
	Placebo (n = 90)	-0.0/-1.7	-1.3/-0.8	

* $p < 0.01$ for eplerenone vs placebo

Formulary/Source: References 19,20

These include dose-ranging studies (table 2), comparisons with other anti-hypertension monotherapies (table 3), and comparisons with other antihypertensive drugs alone or in combination (table 4).

Dose-ranging studies. Two dose-ranging studies were reported at the 2002 American Society of Hypertension meeting, one in patients with mild to moderate hypertension by Burgess and colleagues¹⁹ and the other in patients with mild to severe hypertension by White and colleagues²⁰ (table 2). In the first study, eplerenone was titrated from 50 mg/d up to 200 mg/d to achieve a diastolic BP \leq 90 mm Hg or systolic BP \leq 140 mm Hg, and a second antihypertensive medication of the investigators' choice was added if needed. In this study, the dose-response relationship began to plateau at 100 mg. In the study by White and colleagues, hypertension was assessed by both by 24-hour ambulatory BP monitoring and at clinic visits at fixed doses ranging from 25 to 200 mg/d. In ambulatory monitoring, even the 25 mg/d dose decreased BP significantly compared with placebo. Eplerenone 100 mg once daily was found to be the maximum effective dose according to both clinic and ambulatory BP readings.

Comparative trials. Five clinical trials have compared eplerenone with other antihypertensive agents, including

spironolactone, the ARB losartan, and the ACE inhibitor enalapril, and the calcium channel blocker amlodipine (table 3).²¹⁻²⁵

Eplerenone vs spironolactone. In patients with mild to moderate hypertension, Epstein and colleagues²¹ found that both drugs reduced BP significantly more than placebo, but there was no significant difference in mean change from baseline between any dose of eplerenone and spironolactone ($p > 0.05$). Trough-to-peak ratios were similar for all doses of eplerenone (90% to 96%), indicating sustained 24-hour antihypertensive effects and supporting once-daily dosing.

Eplerenone vs losartan. Weinberger and colleagues²² studied the effects of eplerenone and the ARB losartan in patients with low plasma renin levels (morning plasma renin activity \leq 1.0 ng/ml/h or an active renin value \leq 25 pg/ml) because these patients BP may be salt and volume sensitive and should respond better to aldosterone blockade than angiotensin II receptor blockade. If the maximum dose of either drug did not completely control BP, hydrochlorothiazide was added. As expected in these patients, the change in BP was significantly greater in the eplerenone group than in the losartan group. In addition, fewer patients in the eplerenone group than in the losartan group needed add-on therapy (32.5%

vs 55.6%, no p value given).

Because a large proportion of black patients have this type of hypertension,⁷⁻⁸ Pratt and colleagues²³ compared the effects of eplerenone and losartan in black and white patients in the United States and South Africa who had mild to moderate hypertension. Mean plasma renin levels in the black groups ranged from 10.9 to 9.6 mU/l and from 12.0 to 15.4 mU/l in the white groups. As expected, eplerenone was superior to losartan and placebo in lowering BP in black patients but was superior only to placebo and not to losartan in white patients.

Eplerenone vs enalapril. In comparing eplerenone with the ACE inhibitor enalapril in patients with mild to moderate hypertension over a year, Burgess and colleagues²⁴ found that the drugs reduced BP similarly at both 24 and 52 weeks. Patients receiving enalapril, however, had a significantly higher incidence of adverse effects, including cough (6.5% vs 2.4%, $p = 0.029$), hyperglycemia (2.8% vs 0%, $p = 0.007$), and urinary tract infections (2.8% vs 0.4%, $p = 0.035$). No data on the incidence of hyperkalemia were reported.

Eplerenone vs amlodipine. Because systolic hypertension and wide pulse pressures predict cardiovascular risk better than diastolic pressure in older patients, White and colleagues²⁵

Table 3

Eplerenone vs other antihypertensives: Effects on BP

Study/Patient demographics	Eplerenone compared with/Study design	Regimen	Mean Δ BP (mm Hg)
Epstein et al ²¹ Mild to moderate hypertension N = 417	Compared with spironolactone 8 wk, double blind, placebo controlled Fixed dose Ambulatory monitoring	EPL 50, 100, 400 mg/d SPL 100 mg/d Placebo	-6.2 to -16.1/-4 to -9* -15.8/-8.7* Not significant
Weinberger et al ²² Low-renin hypertension N = 168	Compared with losartan 16 wk, randomized, double blind Titration to effect Hydrochlorothiazide 12.5 to 25 mg added if needed after wk 8	EPL 100-200 mg/d (n = 86) LOS 50-100 mg/d (n = 82) EPL + optional HCTZ LOS + optional HCTZ	At wk 8 -15.8 [†] /-9.3 [†] -10.1/-6.7 At wk 16 -18.3/-10.8 -15.0/-9.8
Pratt et al ²³ Black and white patients in United States and South Africa Mild to moderate hypertension N = 551	Compared with losartan 16 wk, randomized, double blind Titration to effect	All patients EPL 50-200 mg/d LOS 50-100 mg/d Placebo Black patients (n = 348) EPL 50-200 mg/d LOS 50-100 mg/d Placebo White patients (n = 203) EPL 50-200 mg/d LOS 50-100 mg/d Placebo	-12.8/-10.3 ^{‡§} -6.3/-6.9 -3.4/-5.3 -13.5/-10.2 ^{‡§} -5.3/-6.0 -3.7/-4.8 -12.3/-11.1 [†] -8.5/-8.4 -3.2/-6.4
Burgess et al ²⁴ Mild to moderate hypertension N = 481	Compared with enalapril 12 mo, double-blind Titration to effect	EPL 50-200 mg/d (n = 235) ENAL 10-40 mg/d (n = 246)	-16.5/-13.3 -14.8/-14.1
White et al ²⁵ Older (mean age 67.7 y) Systolic hypertension and/or widened pulse pressure	Compared with amlodipine 24 wk, double blind Titration to effect	EPL 50-200 mg/d (n = 134) AML 2.5-10 mg/d (n = 135)	Systolic Pulse pressure -20.5 -15.9 -20.1 -13.4

EPL = eplerenone, SPL = spironolactone, LOS = losartan, HCTZ = hydrochlorothiazide, ENAL = enalapril, AML = amlodipine

* $p \leq 0.01$ EPL and SPL for both systolic and diastolic BP compared with placebo

† $p = 0.017/0.05$ EPL vs LOS for both SBP/DBP changes vs baseline

‡ $p < 0.001$ EPL vs placebo for both SBP/DBP

§ $p < 0.001$ EPL vs LOS for both SBP/DBP

|| Systolic BP ≥ 150 and < 165 mm Hg and pulse pressure ≥ 70 mm Hg or systolic BP ≥ 165 and < 200 mm Hg and diastolic BP < 95 mm Hg

Formulary/Source: References 21-25

compared eplerenone's effects with those of the dihydropyridine calcium channel blocker amlodipine in older patients with systolic hypertension and/or wide pulse pressures. Reductions in BP at 24 weeks were similar with the two drugs, as were changes in arterial compliance.

Combination therapy trials. Eplerenone's efficacy as an adjunct agent in patients already receiving an antihypertensive agent has also been studied in three clinical trials.²⁶⁻²⁸

Krum and colleagues²⁶ studied the

effects of adding eplerenone, which could be titrated to 100 mg/d, to the regimen of patients whose fixed dose of an ACE inhibitor or ARB did not control their hypertension. In both combination groups, the BP reduction was significant compared with monotherapy. The reduction in BP was greater for the ARB combination than the ACE combination, but no p value was given.

Pitt and colleagues²⁷ investigated eplerenone's efficacy in patients with mild to moderate hypertension and left

ventricular hypertrophy. Patients reached target doses after 4 weeks of forced titration to eplerenone 200 mg/d, enalapril 40 mg/d, or eplerenone 200 mg/enalapril 10 mg/d. If hypertension remained uncontrolled at week 8, hydrochlorothiazide 12.5 or 25 mg/d or amlodipine 10 mg/d was added. BP was decreased to a similar extent in all three groups. Eplerenone monotherapy was as effective as enalapril monotherapy in regressing left ventricular hypertrophy (-14.5 g vs -19.7 g; $p = 0.258$), but the combination of eplerenone and

Table 4

Eplerenone in combination therapy: Effects on BP

Study/Patient demographics	Study design	Regimen	Mean ΔBP (mm Hg)
Krum et al ²⁶ Hypertension not controlled by fixed-dose ACE inhibitor or ARB N = 388	8 wk, double blind, placebo controlled Titration (of EPL 50–100 mg/d) to effect	ACE + EPL	–13.7 [†] /–10.7*
		ACE + placebo	–7.2/–8.0
		ARB + EPL	–16.2 [§] /–13.2 [‡]
		ARB + placebo	–9.6/–10.0
Pitt et al ²⁷ Mild to moderate hypertension Left ventricular hypertrophy N = 153	9 mo, double blind, randomized Forced titration Hydrochlorothiazide or amlodipine added at 8 wk if target not achieved	EPL 200 mg	–23.8/–11.9
		ENAL 40 mg/d	–24.7/–13.4
		EPL + ENAL 10 mg	–28.7 [¶] /–14.4
Epstein et al ²⁸ Type 2 diabetes mellitus N = 257	Compared with enalapril and combination 24 wk, randomized Forced titration Hydrochlorothiazide or amlodipine added at 8 wk if target not achieved Forced titration	EPL 50–200 mg (n = 89)	–19.5/–13.2
		ENAL 10–40 mg (n = 83)	–20.5/–15.0
		EPL+ ENAL 10 mg (n = 85)	–21.8 [¶] /–16.2

ARB = angiotensin II receptor blocker, EPL = eplerenone, ENAL = enalapril
 * p = 0.016 ACE + EPL, mean DBP decrease from baseline vs ACE monotherapy
 † p = 0.001 for ACE + EPL, mean SBP decrease from baseline vs ACE monotherapy
 ‡ p = 0.003 ARB + EPL, mean DBP decrease from baseline vs ARB monotherapy
 § p = 0.001 ARB + EPL, mean SBP decrease from baseline vs ARB monotherapy
 ¶ p < 0.05 for EPL + ENAL combination vs EPL alone
 ¶ p = 0.015 for combination vs EPL

Formulary/Source: References 26–28

Table 5

Eplerenone's effects on proteinuria

Study	Regimen	Mean ΔUACR (%)
Burgess et al ²⁴ (see table 3 for study details)	EPL 50–200 mg/d	–61.5*
	ENAL 10–40 mg/d	–25.7
White et al ²⁵ (see table 3 for study details)	EPL 50–200 mg/d	–52.3 [†]
	AML 2.5–10 mg/d	–10.4
Epstein et al ²⁸ (see table 4 for study details)	EPL 50–200 mg	–62 [‡]
	ENAL 10–40 mg	–45
	EPL+ ENAL (10 mg)	–74 [§]

UACR = urinary albumin to creatinine ratio
 * p = 0.01 EPL vs ENAL
 † p = 0.002 EPL vs AML
 ‡ p = 0.015 EPL vs ENAL
 § p = 0.018 combination vs EPL, p < 0.001 combination vs ENAL

Formulary/Source: References 24,25,28

effective than monotherapy in reducing BP in patients with type 2 diabetes.

Effects on proteinuria. Eplerenone's ability to reduce proteinuria in hypertensive patients compared with ACE inhibitors and calcium channel blockers has been investigated as part of three clinical trials.^{24,25,28} (table 5) In patients with elevated baseline microalbuminuria (urinary albumin to creatinine ratio [UACR] > 30 mg/g), eplerenone reduced UACR to a greater extent than both enalapril²⁴ (p = 0.01) and amlodipine²⁵ (p = 0.002). In type 2 diabetics, the effects of eplerenone and enalapril when administered together were found to be additive, reducing microalbuminuria to a greater extent than then eplerenone alone (p = 0.015).²⁸ The clinical endpoint of end stage renal disease (ESRD), doubling of serum creatinine, and mortality has not been evaluated in type 2 diabetes patients taking eplerenone.

enalapril regressed left ventricular hypertrophy to a greater extent than eplerenone alone (–27.2 g vs –14.5 g; p = 0.007) and enalapril alone

(–27.2 g vs –19.7g; p = 0.107.) Epstein and colleagues²⁸ also found combination therapy with eplerenone and enalapril to be significantly more

■ Formulary considerations

Eplerenone is the first selective aldosterone-receptor antagonist (SARA) to be reviewed by the FDA for the indication of hypertension. Clinical trials have established eplerenone's efficacy at doses of 25 to 200 mg, with the effects plateauing around 100 mg once daily in patients with mild to severe hypertension.¹⁹⁻²⁸ Eplerenone has been found to lower BP particularly well in patients with low-renin, salt-sensitive hypertension (eg, African-Americans).^{22,23} Comparative studies show that eplerenone's BP lowering effects are no less than those of ACE inhibitors, ARBs, and dihydropyridine calcium channel blockers.²¹⁻²⁵

Although eplerenone has shown comparable antihypertensive efficacy to other commonly used agents, the degree of BP lowering is not the only factor that should be considered when choosing an antihypertensive agent.¹ The effect an agent has on cardiovascular morbidity and mortality should also be considered. Antihypertensive agents such as, thiazide diuretics, beta adrenergic blockers calcium channel blockers, ACE inhibitors, and ARBs have been associated with decreases in stroke, coronary events, heart failure, progression of renal disease and all cause-mortality.¹ To date, eplerenone has not shown any evidence of mortality benefit associated with its use in treating hypertension. Based on the lack of morbidity and mortality data as compared to other antihypertensive agents, eplerenone should not be used as a first-line agent for the treatment of hypertension. Current

hypertension guidelines¹ award no role to spironolactone in the treatment of primary hypertension and this will likely hold true for eplerenone as well.

In a small number of trials, eplerenone has demonstrated an ability to decrease levels of microalbuminuria in patients with elevated baseline levels.^{24,25,28} These studies were not long term (≤ 12 mo), however, and patient populations were small. The clinical end points of end-stage renal disease (ESRD), doubling of serum creatinine, and mortality have not been evaluated in type 2 diabetes patients taking eplerenone.

In the short-term trials to date with small patient numbers, eplerenone has demonstrated positive effects on left ventricular hypertrophy, showing as much regression with monotherapy as with enalapril monotherapy and improving regression to a greater extent when combined with enalapril compared with eplerenone or enalapril monotherapy.²⁷ Positive effects on mortality in heart failure patients might be expected based on the 30% mortality benefit realized by severe heart failure patients taking spironolactone in the RALES trial.³² Eplerenone's effects on heart failure are now being investigated in the EPHESUS trial,^{29,30} which will investigate eplerenone added to standard heart failure therapy in recent myocardial infarction patients with associated heart failure. This will be the first trial of eplerenone in which mortality is an end point.

Through in vitro and animal studies,

eplerenone has been shown to have a much lower binding affinity than spironolactone for steroid receptors other than the mineralocorticoid receptor.¹¹ Investigators hope that this will translate into fewer androgenic and progestogenic adverse effects than with spironolactone. Although recently published trials investigating eplerenone in hypertensive and heart failure patients^{19-28,34} have shown eplerenone to have a low level of these endocrine-related adverse effects, these trials have been published only in abstract form and are relatively small and short term. Long-term, head-to-head trials need to be conducted to reflect the true incidence of adverse effects. Hyperkalemia may be eplerenone's major side effect. In short-term hypertension trials, the incidence of hyperkalemia with eplerenone was very low, but higher than that for placebo. The highest incidence of hyperkalemia reported so far (12%) was in a study in patients with heart failure who also received an ACE inhibitor.³⁴

Because eplerenone is metabolized extensively by the CYP P450 3A4 isoenzyme,¹⁵⁻¹⁷ additional studies investigating eplerenone's drug interaction potential need to be conducted. Dosing in hepatic and renal failure also warrants further study.

The expected cost of eplerenone is unknown, but because no generic version will be marketed for some time, eplerenone will likely cost significantly more than other antihypertensive agents with well-established mortality or morbidity benefits.

EVALUATION IN HEART FAILURE

In January 2000, the Eplerenone Neurohormonal Efficacy and Survival Trial (EPHESUS) began investigating eplerenone in the treatment of heart failure.^{29,30} The stimulus for EPHESUS likely stems from the Randomized Aldactone Evaluation Study (RALES), which demonstrated a 30% survival benefit in patients with severe congestive heart failure when spironolactone (versus placebo) was added to standard therapy (an ACE inhibitor, a loop diuretic, and—in most cases—digoxin).^{31,32} EPHESUS will evaluate

the effect of 25 up to 50 mg/d of eplerenone in addition to standard therapy with ACE inhibitors or ARBs, beta blockers, digoxin, and diuretics in 6,200 recent patients with myocardial infarction and associated heart failure. This randomized, double-blind, placebo controlled, two-arm, parallel-group trial will last approximately 2.5 years or until 1,012 deaths occur. Eligible patients will be 3 to 14 days post-acute myocardial infarction and have heart failure and an ejection fraction $< 40\%$. The primary end points are all-cause mortality and the time to first occurrence

of either cardiovascular mortality or morbidity leading to hospitalization. Secondary end points include cardiovascular mortality, cardiovascular hospitalizations, all-cause hospitalizations, and all-cause mortality and all-cause hospitalizations.²⁹ In addition to the end points of survival and hospitalization, health status will be assessed and economic evaluations conducted.³⁰

ADVERSE EFFECTS

Complete data on adverse events for eplerenone have not yet been published. The best information from current

placebo-controlled and comparative trials using eplerenone in doses ranging from 25 to 400 mg/d indicates that the incidence of adverse effects with eplerenone is similar to that of placebo.¹⁹⁻²⁵ Although the incidence was very low, the most common adverse effect seen in clinical trials for hypertension was hyperkalemia, with a reported incidence of 2.7% compared with 1.3% for placebo.³³ In Pitt and colleagues³⁴ dose-ranging study of eplerenone in patients with congestive heart failure, hyperkalemia ($K^+ >6$ mEq/l) was seen in 12% of patients receiving eplerenone 100 mg/day compared with 8.7% of patients receiving spironolactone 25 mg/day (*p* value not given). Most patients in the study were receiving concurrent ACE inhibitor therapy. In Epstein and colleagues²⁸ study of eplerenone, the ACE inhibitor enalapril, and combination therapy, more patients in the combination therapy group (21%) were withdrawn for hyperkalemia than in the eplerenone (8%) or enalapril (8%) groups. Therefore, eplerenone should be used cautiously with ACE inhibitors or other drugs that may raise serum potassium levels. In addition, eplerenone should be used cautiously in patients with renal impairment.

Evidence indicates that eplerenone's selectivity does, indeed, result in fewer androgenic and progestogenic side effects than spironolactone, which binds to sex steroid receptors.⁹ The side effect of gynecomastia (reversible in most cases) is dose related, with the incidence ranging from 6.9% in men receiving < 50 mg/d to 52.2% in those receiving ≥ 150 mg/d in a hypertension study.¹⁰ In the RALES trial investigating spironolactone 25 mg/d, 10% of men reported gynecomastia or breast pain compared with only 1% of men receiving placebo (*p* < 0.001).³² In contrast, in the dose-ranging trial of Burgess and colleagues,¹⁹ the incidences of sex steroid-binding side effects were low with eplerenone—impotence 3%, gynecomastia 0.7%, and menstrual abnormalities 2.5%—for all possible doses up to 200 mg/d for 16 months. Most

of these events were considered to be of an uncertain relationship to eplerenone.

DRUG INTERACTIONS

Data on drug interactions with eplerenone are limited. Eplerenone does not appear to inhibit or induce the CYP P450 enzyme system,³⁵ but studies in vitro and in healthy human volunteers indicate eplerenone is metabolized primarily by the CYP P450 3A4 isoenzyme.¹⁵⁻¹⁷ Additional studies investigating the interaction between eplerenone and other drugs that affect the 3A4 isoenzyme need to be conducted.

As with other potassium-sparing diuretics, eplerenone may increase a patient's risk of hyperkalemia when given with potassium supplements or ACE inhibitors.⁹ Caution should be exercised when administering these drugs concomitantly.

DOSING AND ADMINISTRATION

Eplerenone doses ranging from 25 to 400 mg/d (once or divided into two doses) have been evaluated in clinical hypertension trials.¹⁹⁻²⁸ Doses ≥ 25 mg have been shown to reduce both systolic and diastolic BP to a greater extent than placebo.^{20,21,23} The dose-response curve appears to plateau at 100 mg/d.¹⁹ Based on the data from clinical trials, maintenance doses ranging from 25 to 100 mg/d would be reasonable for patients with mild to moderate hypertension.

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