A Comparison of the Aldosterone-blocking Agents Eplerenone and Spironolactone

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ABSTRACT

Improved understanding of the adverse pharmacological properties of aldosterone has prompted investigation of the clinical benefits of blocking aldosterone at the receptor level. This article reviews the pharmacology, clinical efficacy, and tolerability of the two available blocking agents, spironolactone and eplerenone. A Medline search identified clinical studies assessing spironolactone and eplerenone. Priority was given to large, well-controlled, clinical trials and comparative studies. Pharmacological differences between spironolactone and eplerenone include lower affinity of eplerenone for progesterone, androgen, and glucocorticoid receptors; more consistently demonstrated nongenomic properties for eplerenone; and the presence of long-acting metabolites for spironolactone. Both agents effectively treat hypertension and heart failure but comparisons are complicated by the deficiency of head-to-head trials and differences between patient populations. There are differences in the tolerability profiles; spironolactone is associated with dose-dependent sexual side effects. Both agents produce dose-dependent increases in potassium concentrations, although the effect with spironolactone appears to be greater when both agents are administered at recommended doses. Choice of a specific agent should be based on individual patient issues, such as the nature of heart failure and patient concerns about adverse events.

Key words: eplerenone, spironolactone, aldosterone blockade, hypertension, heart failure

Introduction

Until recently, our understanding of aldosterone focused on its effects on sodium and water retention and potassium excretion, which are mediated by the binding of aldosterone to the mineralocorticoid receptor (MR) in epithelial tissues, such as the kidney. Recently, the actions of aldosterone in nonepithelial tissues, such as the heart, brain, and vasculature, also have been described. These actions are associated with adverse effects, including impaired synthesis of the vasodilator nitric oxide; promotion of vasoconstriction, endothelial dysfunction, inflammation, and fibrosis in the vasculature; and ventricular hypertrophy, collagen deposition, fibrosis, and remodeling in the heart.[1] The effects of aldosterone are mediated by either genomic (slow) or nongenomic (rapid) mechanisms, and it is yet to be fully elucidated exactly which effects occur by each mechanism. This is discussed in greater detail below. However, regardless of the mechanism, aldosterone is known to produce adverse cardiovascular effects and blockade of aldosterone is proven to mitigate these actions.

Currently, two agents are available that competitively inhibit aldosterone at the MR: spironolactone and eplerenone. The purpose of this study is to review the differences between these agents and to elucidate their roles in clinical treatment.

Pharmacology

Spironolactone, developed in the 1950s, is an antimineralocorticoid with structural elements of the progesterone molecule; thus, it is associated with progestogenic and antiandrogenic adverse effects.[2] Eplerenone is a spironolactone derivative designed to enhance selective binding to the MR while minimizing binding to progesterone and androgen receptors.[2]

There are substantial differences in the pharmacodynamic and pharmacokinetic properties of these agents. For example, eplerenone has a 20-fold lower affinity for the MR in vitro compared with spironolactone, although the in vivo dosage of eplerenone required to inhibit aldosterone binding by 50% was only approximately half that of spironolactone.[2] There is a greater differential effect between eplerenone and spironolactone regarding binding to androgen, glucocorticoid, and progesterone receptors, with binding affinities 100–1000-fold higher for spironolactone.

There are also differences between eplerenone and spironolactone with respect to metabolism and elimination. Spironolactone undergoes rapid extensive metabolism to three active metabolites with prolonged half-lives (13.8–16.5 h).[3] Eplerenone also undergoes extensive metabolism, but its metabolites are inactive and its elimination half-life is short (4–6 h).[4]

The effects of aldosterone are mediated via 1 of 2 mechanisms. Aldosterone's classical effects on fluid and electrolyte homeostasis are well known to be mediated by the MR through a genomic mechanism. This involves binding of aldosterone to the cytosolic intracellular MR and translocation of the steroid–MR complex to the nucleus,

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where it acts as a transcriptional regulator to synthesize proteins. These effects take hours to days to occur. In addition to the well-known MR-mediated genomic effects of aldosterone, nongenomic effects occur at subnanomolar levels of aldosterone. Although it appears that at least some of aldosterone's nongenomic effects occur via the MR, some may occur via MR-independent mechanisms. These nongenomic, or rapid, effects occur within minutes at target tissues and organs, including the kidney, heart, and vasculature.[5] It is not yet fully defined which of the effects of aldosterone occur through genomic versus nongenomic mechanisms. Further, aldosterone may exert both genomic and nongenomic actions within the same tissue, as is seen in the vasculature.[6,7] Effects of aldosterone that have been proven to occur via a nongenomic mechanism include coronary vasoconstriction leading to worsening contractile and metabolic functions in the ischemic heart, increased systemic vascular resistance, negative inotropic response in human trabeculae, and potentiation of the vasoconstrictor effect of angiotensin II in coronary arteries.[5,6,8] That these nongenomic effects of aldosterone are sometimes mediated by MR is supported by the ability of MR blockers to inhibit many of these actions. Overall, eplerenone appears to produce more consistent inhibition of some of the nongenomic effects of aldosterone[7,9] than spironolactone.[10,11] However, until these effects of aldosterone are fully clarified, there is as yet insufficient evidence to draw conclusive distinctions between the two agents based solely on their ability to block aldosterone's nongenomic actions.

Clinical Efficacy

Heart Failure

Both spironolactone and eplerenone have been found to be very effective in distinct populations of heart failure patients, and these drugs are most frequently used in this setting. In the randomized aldactone evaluation study (RALES) and eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS), spironolactone and eplerenone, respectively, significantly reduced mortality and morbidity in patients with heart failure.[12,13] In RALES, a mean dose of 26 mg of spironolactone was associated with a significant 30% decrease in the relative risk of death from all causes compared with placebo after a mean follow-up of 24 months, including reductions in the risk of death from heart failure and sudden cardiac death.[12] In EPHESUS, a mean dose of 43 mg of eplerenone produced a significant 15% reduction in the risk of all-cause mortality compared with placebo, as well as significant reductions in cardiovascular death (17% reduction) and sudden cardiac death (21% reduction).[13] Because there were substantial differences between RALES and EPHESUS in patient populations, baseline heart failure pharmacotherapy, achieved dose, and size of the safety database (Table 1), caution is warranted in directly comparing these trial results or in interchanging these agents within these specific populations. For example, RALES patients had advanced chronic heart failure with a mean ejection fraction of 25.6%, whereas EPHESUS patients were enrolled after acute myocardial infarction (MI) with left ventricular systolic dysfunction (LVSD) and had mild to moderate heart failure and a mean ejection fraction of 33%.[12,13] Baseline heart failure drug therapy was also markedly different between patient populations, with many more EPHESUS patients receiving β-blockers and fewer receiving angiotensin-converting enzyme (ACE) inhibitors and diuretics. The difference in β-blocker use may be particularly important because some of the beneficial effects of β-blockers and spironolactone are produced by similar mechanisms.[14]

Hypertension

Both spironolactone and eplerenone are effective in reducing blood pressure (BP) when used as monotherapy[15,16] and in combination regimens, reducing BP to a similar extent.[15,17] Only one hypertension trial included both spironolactone and eplerenone. This fixed-dose, placebo-controlled trial compared the safety, efficacy, and tolerability of eplerenone (50–400 mg/day) with placebo.[18] A standard dose of spironolactone for the treatment of hypertension, 50 mg twice daily, was included as an MR antagonist positive control. Although statistical analyses between eplerenone and spironolactone were not performed, changes in BP from baseline appeared greater with spironolactone 50 mg twice daily than with eplerenone 50 mg twice daily, suggesting that eplerenone may be only 50%–75% as potent as spironolactone.[18]

Tolerability

Endocrine Effects

Spironolactone is associated with a well-established risk of sexual side effects that are dose and duration dependent.[16] In contrast, eplerenone is associated with no or very low incidence of sexual side effects.[13,18,21] Sexual side effects of drugs are of particular concern because patients are typically unwilling to tolerate these effects, and sexual dysfunction is a major reason for noncompliance among hypertensive patients.[19,20]

Hyperkalemia

Both eplerenone and spironolactone are associated with dose-related increases in serum potassium levels.[16,18] Patients with underlying renal dysfunction or heart failure are at greatest risk of hyperkalemia.[22]

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TABLE 1: Differences between the major clinical trials evaluating eplerenone and spironolactone in heart failure

Parameter	RALES[12]	EPHESUS[13]
Drug	Spironolactone	Eplerenone
Patients enrolled (n)	1663	6632
Population/Inclusion criteria	• NYHA Class III–IV at time of enrollment (Class IV w/in 6 mo prior to enrollment) • LVEF $\leqslant$ 35%	• NYHA Class I–IV • 3–14 d after MI with symptoms of heart failure and/or diabetes • LVEF $\leqslant$ 40%
Target dose	50 mg/d	50 mg/d
Mean dose achieved	26 mg/d	43.5 mg/d
Mean duration of follow-up	24 mo	16 mo
Baseline LVEF	25.6%	33%
Baseline drug therapy		
ACE inhibitor or ARB	95%	86%
β-blocker	11%	75
Diuretic	100%	60%

Abbreviations: ACE = angiotensin-converting enzyme; ARB = aldosterone receptor blocker; EPHESUS = Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; RALES = Randomized Aldactone Evaluation Study.

Heart failure trials: In RALES and EPHESUS, spironolactone and eplerenone were associated with small increases in serum potassium concentrations. In RALES, 1 year of therapy with spironolactone 25 mg/day was associated with a statistically significant increase in median potassium concentration (0.3 mmol/L versus no change in placebo group).[12] However, there was no significant difference between the spironolactone and placebo groups for the occurrence of serious hyperkalemia (potassium $\geqslant$ 6 mEq/L; 2% versus 1%; $p = 0.42$).[12]

Eplerenone was associated with similar changes in serum potassium concentrations in EPHESUS. After 1 year of therapy at mean eplerenone dosage of 43.5 mg/day, potassium levels increased in both the placebo (0.2 mmol/L) and active therapy groups (0.3 mmol/L; $p<0.001$).[13] Serious hyperkalemia was more common with eplerenone than placebo (5.5% versus 3.9%; $p = 0.002$).[13]

Hypertension trials: It is difficult to compare incidence of hyperkalemia between eplerenone and spironolactone in hypertension trials because not all studies provided information on potassium levels and the definition of hyperkalemia differed across studies. In two studies that defined hyperkalemia as serum potassium $\geqslant$5.5 mEq/L, the incidence of hyperkalemia ranged from 3% to 6% at spironolactone doses of 12.5 to 400 mg/day.[23,24] At the $\geqslant$5.5 mEq/L threshold, the incidence of eplerenone-induced hyperkalemia ranged from 1%–3% at doses of 50–200 mg/day.[25–27] For studies that used a serum potassium threshold $\geqslant$6.0 mEq/L, the incidence of hyperkalemia ranged from 0% to 11% at eplerenone doses of 50–200 mg/day.[27,28]

Figure 1 displays the mean change from baseline in serum potassium associated with spironolactone and eplerenone from the previously described trial evaluating spironolactone 100 mg/day and eplerenone 50–400 mg/day. The change in potassium with eplerenone $\leqslant$100 mg/day was significantly less than that of spironolactone 50 mg twice daily, although none of the patients experienced clinical symptoms related to hyperkalemia.[18]

Although caution is warranted when comparing the rates of hyperkalemia between spironolactone and eplerenone, it has been speculated that the extended half-life of the active metabolites of spironolactone could increase the risk of hyperkalemia or its associated complications.[22,29] Conversely, the relatively short half-life of eplerenone and lack of inactive metabolites may lessen the risk of hyperkalemia; (i.e., when serum potassium approaches high

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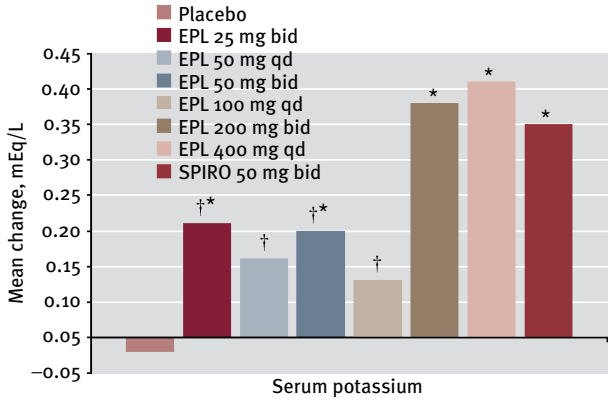

Figure 1: Mean change in serum potassium levels from baseline with eplerenone and spironolactone.[18] *$p<0.05$ versus placebo (Dunnett's test for eplerenone or contrast-based *t* test for spironolactone); †$p<0.05$ versus spironolactone (Dunnett's test). *Abbreviations:* EPL = eplerenone; SPIRO = spironolactone; 1x/d, once daily; 2x/d, twice daily.

levels, the effects of the drug should regress soon after discontinuation). These theories are yet only speculative.

Changing patterns of use of agents that affect potassium homeostasis may also influence rates of hyperkalemia. For example, the use of β-blockers has risen in patients with systolic heart failure, and the use of these medications and other inhibitors of the renin-angiotensin-aldosterone system (RAAS) may increase the risk of hyperkalemia.[30] It has been postulated that the higher rate of hyperkalemia observed with active treatment in EPHESUS versus RALES may be due to greater β-blocker use in EPHESUS.[30,31] To definitively determine whether there are any clinically meaningful differences in the risk of hyperkalemia between these two agents would require direct comparative trials, although available evidence suggests that the risk is lower with eplerenone than spironolactone when the drugs are administered at recommended doses.

Clinical Considerations

Table 2 summarizes the most important clinical considerations for the use of spironolactone and eplerenone. When selecting patients for treatment, it is important to consider study and regimen differences. For example, spironolactone is usually used in combination with other drugs, but eplerenone may be used alone or in combination regimens. Either drug can be combined with a number of different antihypertensive agents (e.g., ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers, β-blockers, thiazide diuretics). In addition, both agents have been evaluated in heart failure patients, but the populations were very different, thus, the efficacy results are not necessarily interchangeable. The results from EPHESUS support the use of eplerenone for post acute myocardial infarction (AMI) patients with heart failure due to LVSD (left ventricular ejection fraction [LVEF] $\leqslant$ 40%), whereas RALES established the use of spironolactone for patients with more severe and chronic heart failure due to LVSD.

On the basis of their demonstrated ability to reduce overall mortality, MR antagonists have an established role in the treatment of heart failure among patients receiving optimized standard medical treatment. All patients who meet the criteria for which these drugs have demonstrated efficacy (Table 1) should be strongly considered for treatment initiation. Because spironolactone and eplerenone have demonstrated similar efficacy in patients with heart failure, the issue of class effect for aldosterone blockers has been raised.[12,29,33] However, pharmacological differences and lack of a simple surrogate for effect (such as BP) make dose conversions difficult.[33] Furthermore, there are differences in the neurohormonal and inflammatory milieus between post-AMI heart failure (where eplerenone was studied) and severe chronic heart failure (where spironolactone was studied).[34–36] For example, in the acute post-AMI setting, the sympathetic nervous system and the RAAS are acutely activated but rapidly return to normal. In contrast, neuroactivation tends to be more persistent in chronic heart failure.[34] It is also unknown whether the effects of spironolactone at androgen and progesterone receptors could have a beneficial or harmful effect in patients with heart failure in the immediate post-AMI setting. Therefore, the efficacy data of these drugs are not necessarily interchangeable.

Recent studies of other drug classes confirm that class effects are not universal. For example, although statins share a common mechanism of action, clinically they have important differences in efficacy and safety, suggesting that the safety of statins is not a class effect. For example, a higher rate of myotoxicity with cerivastatin compared with other statins led to its withdrawal from the worldwide market.[37] On the basis of current data, we cannot know for certain whether or not there is a class effect with respect to efficacy and safety of aldosterone blockers in heart failure patients. A direct comparative trial between these agents would be necessary to determine whether the clinical benefits produced by these drugs can be considered a class effect. Thus, it seems prudent to assume that, for the outcome and population being studied, the benefits of aldosterone blockers derive from the compound at the per-protocol dose amount and frequency.[33]

Proper patient selection, dosing, and monitoring are the keys to optimizing treatment outcomes and minimizing adverse effects. Because the risk of hyperkalemia is

TABLE 2: Clinical considerations regarding differences between spironolactone and eplerenone

Variable	Spironolactone	Eplerenone
Patient selection		
Hypertension	Usually in combination with other drugs, for patients who cannot be treated adequately with other agents[32]	May be used alone or in combination with other antihypertensive agents[4]
Heart failure	Chronic, severe[12]	Mild to moderate, post-MI[13]
Dosing		
Hypertension	50–100 mg/d, either single or divided[32] Doses of 200–400 mg/d provide little additional BP reduction versus 100 mg/d[24]	50 mg/d increased to 50 mg twice daily if needed[4] • Doses >100 mg/d are not recommended because there is no greater effect on BP lowering[4] • Twice-daily dosing produces a significantly greater reduction in BP than once-daily dosing[18]
Heart failure	25 mg/d[12]	25 mg/d titrated to 50 mg/d as tolerated[13]

Abbreviations:BP = blood pressure; MI = myocardial infarction.

dose dependent, keeping the dose to recommended levels (Table 2) should minimize the incidence of hyperkalemia.

The choice of a specific aldosterone-blocking agent should be based on a variety of factors such as patient preference, adverse event profile, and cost. Eplerenone's selectivity for the MR yields a superior tolerability profile in terms of sexual side effects, an effect that may be very important to some patients. However, since spironolactone is off patent, the cost to the patient is considerably lower than for eplerenone (approximately $24 versus $113 per month).[38] The potential differences in the ability of these agents to counter the rapid nongenomic effects of aldosterone should also be considered.

Conclusions

Both eplerenone and spironolactone are efficacious and safe in the treatment of hypertension and heart failure, although eplerenone's selectivity yields a superior tolerability profile in terms of sexual side effects. There is a general lack of direct comparative data for spironolactone and eplerenone; an evidence-based approach to their use seems reasonable.

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