Aldosterone Blockade in CKD: Emphasis on Pharmacology

Michael H. Schwenk, Jamie S. Hirsch, and Andrew S. Bomback

Besides its epithelial effect on sodium retention and potassium excretion in the distal tubule, aldosterone promotes inflammation and fibrosis in the heart, kidneys, and blood vessels. As glomerular filtration rate falls, aldosterone is inappropriately elevated relative to extracellular fluid expansion. In addition, studies in CKD patients on angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and/or direct renin inhibitors have shown that aldosterone levels paradoxically rise in approximately 30% to 40% of patients on these renin-angiotensin system-blocking drugs. Hence, there is interest in using mineralocorticoid receptor blockers that directly target the inflammatory and fibrotic effects of aldosterone in CKD patients. This interest, however, is tempered by a number of unresolved issues, including the safety of using such drugs in advanced CKD and ESRD populations, and the potential for differences in drug efficacy according to race and ethnicity of patient populations. A better understanding of mineralocorticoid receptor blocker pharmacology should help inform future research directions and clinical practice decisions as to how best to use these agents in CKD.

Key Words: Mineralocorticoid receptor antagonists, Chronic kidney failure, Pharmacokinetics, Hyperkalemia, Proteinuria

Introduction

Blockade of the renin-angiotensin-aldosterone system (RAAS) is a mainstay of therapy for CKD, recommended by virtually every international guideline as standard of care in this condition. This RAAS blockade is almost always accomplished through use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). The past decade has seen renewed interest in using agents that block aldosterone in the treatment paradigm of CKD. Mineralocorticoid receptor blockers (MRBs), such as spironolactone and eplerenone, have become a standard treatment add-on (ie, on top of ACEIs and ARBs) in patients with chronic heart disease. As the use of dual RAAS blockade with ACEIs and ARBs by nephrologists has fallen into decline and, likely, ultimate extinction, it is conceivable that the combination of MRB plus ACEI or MRB plus ARB will become a new standard treatment strategy in CKD. In this review, we survey the existing data on the rationale, efficacy, and safety of MRB therapy in CKD, with a specific focus on the pharmacology of these agents.

Rationale for Aldosterone Blockade

In addition to its effect on distal tubular salt and potassium handling, numerous animal studies have shown that aldosterone is intimately involved in vascular, myocardial, and kidney fibrosis. Independent of changes in blood pressure and volume homeostasis, aldosterone-mediated activation of mineralocorticoid receptors in nonepithelial tissues of the cardiovascular and kidney system promotes tissue inflammation and injury,[1-8] manifest as myocardial fibrosis, left ventricular hypertrophy (LVH),[9,10] glomerulosclerosis, and severe proteinuria.[3,11,12] Thus, aldosterone's nonepithelial effects may play a more important role in the pathogenesis of chronic heart disease and CKD than its classical epithelial effects.[13] Importantly, blockade of the RAAS at the level of angiotensin I or angiotensin II are, in the least, inefficient and, potentially, completely ineffective against these nonclassical profibrotic actions of aldosterone.

In CKD, this need to directly address aldosterone blockade with MRBs may be critically important for 2 reasons. First, CKD can be considered a state of relative hyperaldosteronism. Aldosterone levels, in relation to a cofactor of plasma renin activity, rise as glomerular filtration rate (GFR) falls.[14-16] In healthy humans, there is an inverse relationship between extracellular volume (ECV) and serum aldosterone concentration. In the setting of low dietary sodium intake, levels of renin, angiotensin II, and aldosterone predictably rise but do not cause vascular inflammation and end-organ damage.[17] Certain diseases, including obesity,[18-20] CKD,[21,22] and ESRD,[23] are notable states of relative hyperaldosteronism despite ECV expansion, leading to proinflammatory mineralocorticoid receptor (MR) activation.[19,21,22,24] ECV expansion, in turn, is invariably caused by excess sodium intake and an inherent defect in excreting salt that becomes more and more profound as GFR declines,[25] with the combination of salt and aldosterone proving toxic.[26-32] This may explain the frequent observation that sodium restriction augments the proteinuria and blood pressure-lowering effects of RAAS blockade.[33,34]

Second, blockade of the distal components of the RAAS by ACEIs and ARBs may often be incomplete. In clinical trials of ACEIs and ARBs, plasma aldosterone levels, after an initial decline, have been shown to increase in some patients over the long term.[35-40] This phenomenon, termed both "aldosterone escape" and "aldosterone breakthrough" in the literature (we prefer and will use the term "aldosterone breakthrough" to avoid confusion

From Clinical Trials Office, Research Pharmacy, Columbia University Medical Center, New York, NY; and Division of Nephrology, Department of Medicine, Columbia University Medical Center, New York, NY.

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Address correspondence to Andrew S. Bomback, MD, MPH, 622 West 168th Street, PH 4-124, New York, NY 10032. E-mail: asb68@columbia.edu

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with "aldosterone escape" from the sodium-retaining action of mineralocorticoids, an unrelated clinical entity), has been associated with important kidney outcomes including refractory proteinuria and steeper declines in GFR. Aldosterone breakthrough occurs in 30% to 50% of patients on long-term ACEI or ARB therapy, and a similar prevalence rate of 30% to 40% has recently been shown in 2 studies examining the phenomenon with direct renin inhibition (Fig 1).[41,42] In the largest study to date of aldosterone breakthrough, a post hoc analysis of the efficacy of telmisartan compared with losartan in reducing proteinuria in hypertensive type 2 diabetic patients with overt nephropathy study found that approximately 30% of 567 patients with diabetic nephropathy demonstrated a rise of 10% or more in aldosterone levels above pretreatment baselines while on ARB therapy.

The physiology behind aldosterone breakthrough remains unclear, although proposed theories suggest that the phenomenon is more likely to occur when GFR declines. Plasma aldosterone levels are primarily regulated by potassium and angiotensin II, the latter in response to salt balance and plasma volume. Therefore, rising aldosterone levels in CKD patients on ACEIs or ARBs could simply reflect low GFR-associated alterations in plasma potassium concentration, total extracellular sodium, and effective blood volume in the systemic arterial circulation. Indeed, if aldosterone breakthrough is mediated through angiotensin II levels, the greater tendency toward breakthrough in patients with declining kidney function would have to be viewed as a consequence, and not a cause, of target organ injury. An alternative explanation for breakthrough emerged in a comparison study of proteinuric CKD patients receiving an ARB, a direct renin inhibitor, or a combination, in which approximately one-quarter of patients had an average rise in 24-hour urine and serum aldosterone levels of 73% and 60%, respectively. In this study, aldosterone breakthrough was associated with body mass index, and the authors speculated that obesity itself was a non-potassium non-volume stimulus to aldosterone production.[42]

CLINICAL SUMMARY

- Aldosterone has deleterious inflammatory and profibrotic actions that affect the heart, kidneys, and blood vessels.
- Aldosterone is inappropriately elevated with respect to extracellular volume in CKD and oftentimes will rise after an initial decline during renin-angiotensin-aldosterone system-blocking therapy (aldosterone breakthrough).
- In proteinuric CKD, mineralocorticoid-blocking therapy lowers proteinuria and blood pressure, but glomerular filtration rate decline is unchanged, with attendant risks of hyperkalemia and gynecomastia.
- In Stage 5 hemodialysis patients, preliminary studies have not seen significant hyperkalemia with mineralocorticoid receptor blocker use, laying the groundwork for large clinical trials to explore aldosterone blockade's effects on cardiovascular morbidity and mortality in ESRD.

Aldosterone Blockade in CKD

A number of small short-term clinical studies have examined the effects of adding MRBs to ACEIs or ARBs in proteinuric kidney disease. Two groups of authors have performed meta-analyses of these small trials and found that the addition of MRB therapy can reduce proteinuria by up to 50% from baseline.[43,44] Some, but not all, of this effect can be explained by reductions in blood pressure.

Notably, the vast majority of patients in these studies were diabetic; hence, the best evidence for using aldosterone blockade in proteinuric CKD is in the treatment of diabetic nephropathy. Mehdi and colleagues[45] reported the results of a randomized, double-blind, placebo-controlled trial of 81 patients with diabetic nephropathy, all of whom received lisinopril 80 mg daily. The subjects were then randomly assigned to placebo, losartan 100 mg daily, or spironolactone 25 mg daily for 48 weeks. Compared with placebo, albuminuria decreased by 34% ($P = .007$) in the spironolactone group and by 17% ($P = .2$) in the losartan group, with no difference in clinic and ambulatory blood pressures between treatment groups. Epstein and colleagues,[46] in a larger study of diabetic patients using eplerenone rather than spironolactone, reported similarly impressive results independent of blood pressure reductions. Two hundred sixty-eight patients, after open-label run-in with enalapril 20 mg daily, were randomized to placebo, eplerenone 50 mg daily, or eplerenone 100 mg daily. By Week 12, albuminuria was reduced by 7% in the placebo group, by 41% in the eplerenone 50 mg daily group, and by 48% in the eplerenone 100 mg daily group (both eplerenone groups, $P < .001$ vs placebo). More recently, in an open-label randomized trial, Esteghamati and colleagues[47] examined spironolactone as add-on for ARBs in patients with urinary albumin excretion of 30 mg/d or more vs an ARB-ACEI combination. The combination of spironolactone and an ARB significantly decreased blood pressure, albuminuria (by 59%), and estimated glomerular filtration rate (eGFR; by approximately 8 mL/min/m^2) at 18 months, whereas an ARB-ACEI combination had no significant effect on blood pressure or albuminuria but caused a drop in eGFR (by approximately 9 mL/min/m^2).

The data supporting the use of MRBs in nondiabetic kidney diseases are not as robust as those in diabetic nephropathy. Bianchi and colleagues[48] randomized 128 patients with idiopathic glomerular diseases to intensive therapy (ACEI, ARB, high-dose statin, and spironolactone) or conventional therapy (ACEI and low-dose statin). Significantly greater proteinuria reduction and eGFR stabilization was noted with intensive vs conventional therapy, although it is difficult to determine whether this benefit comes solely from the use of spironolactone. Furumatsu and colleagues[49] performed an open-label study in 32 nondiabetic patients with proteinuria exceeding 0.5 g/d. After more than 12 weeks of combined ACEI and ARB treatment, patients were assigned to either spironolactone 25 mg daily (a triple blockade group of ACEI + ARB + MRB) or diuretic (trichlormethiazide 1 mg daily or furosemide