Mineralocorticoid Receptor Blockade in Chronic Kidney Disease

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Key Words

Aldosterone • Aldosterone breakthrough • Mineralocorticoid blockade • Chronic kidney disease • Extracellular volume • Bioimpedance • Proteinuria • Tissue inflammation • Hyperkalemia

Abstract

Mineralocorticoid receptor blockers (MRBs) have proven highly successful in the treatment of congestive heart failure and resistant hypertension. In contrast, their use in chronic kidney disease (CKD) has lagged due to the concern of hyperkalemia and, possibly, because of the incorrect assumption that traditional therapy with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers consistently reduce aldosterone activity in all patients. Low-dose MRB therapy may offer additional antihypertensive and unique anti-inflammatory benefits in select CKD populations.

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Background

Therapeutic targeting of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme inhibitors (ACE-Is) and/or angiotensin receptor

blockers (ARBs) has proven only partially successful in controlling hypertension and attenuating the rate of renal functional decline in patients suffering from chronic kidney disease (CKD). Innovative therapies have been sought to keep patients dialysis-free and to lower morbidity and mortality in those already on dialysis. Recently, increased interest has focused on the mineralocorticoid receptor (MR) as a pharmacologic target to achieve better control of hypertension, reduction of proteinuria, and attenuation of the rate of renal functional decline in patients already receiving traditional ACE-I and/or ARB therapy.

This renewed interest is supported by the observation that aldosterone breakthrough occurs in a significant proportion (up to 50%) of CKD patients receiving traditional therapy [1]. Additional interest in mineralocorticoid receptor blocker (MRB) therapy reflects the need to improve cardiovascular disease outcomes in CKD patients: almost half of the annual mortality in dialysis patients is attributable to cardiovascular disease, which cannot fully be explained by traditional Framingham risk factors. It is unknown whether use of MRBs in CKD patients will offer similar cardiovascular benefits as were demonstrated in two landmark clinical trials in patients with congestive heart failure and preserved renal function [2, 3].

While an emerging body of evidence suggests favorable effects of MRB therapy on surrogate renal outcomes,

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to date no large studies have been published examining the effect of MRB therapy on clinically relevant cardiovascular disease or renal outcomes in CKD. Understandably, the pace of inquiry into these unanswered questions has been slow due to concerns about life-threatening hyperkalemia. Careful patient selection and biochemical monitoring (serum potassium and creatinine) are required when prescribing low-dose MRB therapy in CKD.

This review examines the potential risks and benefits of low-dose MRB therapy in CKD as well as the experimental evidence supporting unique anti-inflammatory effects of MR blockade. In addition, because even small degrees of extracellular volume (ECV) expansion greatly magnifies the pathophysiological effects of inappropriate MR activation, this review examines the use of quantitative measurement of ECV to better understand the prohypertensive and proinflammatory effects of MR activation in nonepithelial tissues.

ECV-Aldosterone Physiology

Normal

Our Paleolithic ancestors lived on a very-low-salt (<5 mEq/day sodium intake) diet that utilized an activated RAAS to conserve sodium and maintain ECV, and thus organ perfusion [4]. A reciprocal relationship is noted between serum aldosterone concentration and daily urinary sodium excretion (a surrogate measure of ECV) in healthy humans consuming variable quantities of dietary sodium [5]. The elevations in renin, angiotensin II, and aldosterone in response to low dietary sodium are physiological responses which do not result in hypertension or vascular inflammation. Because of this reciprocal interaction, interpretation of serum aldosterone concentration requires simultaneous assessment of ECV by direct (bioimpedance) or indirect (24-hour urine sodium excretion) methodology.

CKD: A State of Relative Hyperaldosteronism

An abnormal ECV-aldosterone relationship underlies several disease states including primary aldosteronism, the metabolic syndrome [6], and CKD [6]. In spite of ECV expansion, aldosterone secretion in these disease states is inappropriately elevated, thus defining a state of relative hyperaldosteronism. Even small (and perhaps immeasurable by current methods) degrees of ECV expansion greatly magnify the prohypertensive and proinflammatory effects of MR activation. This synergistic effect may account for salt sensitivity (with respect to blood pres-

sure) and hypertension-independent vascular inflammation that characterizes these conditions [7].

Both hypertension and the vascular inflammatory effects of MR activation require ECV expansion, frequently called a 'high salt' or 'inappropriate salt' state [8]. The mechanism by which ECV expansion promotes the pathophysiological effects of MR activation is unknown. One possibility is that Rac-1, an intracellular GTP-ase which is released in response to vascular stretch (as would occur in ECV expanded states) and which enhances aldosterone activity at the transcriptional level, may unmask the pathophysiological effects of MR activation [9, 10].

Recent studies suggest that some of these inflammatory effects may be rapid and nongenomic [11]. The renal inflammatory effects of relative hyperaldosteronism are modulated by nonepithelial MR located in podocytes and mesangial cells [12]. Increased expression of MR has been noted in the glomeruli of patients with heavy proteinuria [13]. Furthermore, since renin and angiotensin-II concentrations are suppressed in ECV-expanded animal models, aldosterone appears to be a direct mediator of vascular and renal inflammation [14]. Proteinuria, an inflammatory marker of MR activation in high salt states, is reduced in ACE-I-/ARB-treated CKD patients who then receive add-on low-dose MRB therapy [15]. Even in the absence of MRB therapy, proteinuric patients placed on low-sodium diets show a reduction in urinary albumin excretion which is partly independent of blood pressure [16, 17]. This anti-inflammatory effect may reflect the reduction in ECV associated with low sodium intake.

ECV and Aldosterone in CKD

Understanding quantitative measures of ECV is essential for interpretation of serum aldosterone concentrations and urinary aldosterone excretion. Ultimately, ECV represents the relationship between dietary sodium intake and efficiency of renal sodium excretion. Most CKD patients have ECV expansion even when clinically judged to be euvoletic [18]. Traditionally, 24-hour urine sodium has been utilized as an indirect estimate of ECV and has been used as the referent for interpretation of serum aldosterone concentration. However, in high ECV states caused by impaired urinary sodium excretion (states of natriuretic handicap), including primary aldosteronism, metabolic syndrome, monogenic forms of hypertension [19], and CKD, 24-hour urine sodium may underestimate the true degree of ECV expansion.

While most nonedematous patients are in sodium balance, those with natriuretic handicaps are likely to have

Fig. 1. Relationship between serum aldosterone concentration and ECV measured by bioimpedance spectroscopy in hemodialysis patients ($n = 18$) and normal controls. In order to adjust for different body habitus, ECV is expressed as a percentage of total body water (TBW). Normals were studied on baseline dietary sodium (mean: 162 mM/day) as well as low-sodium (mean: 12 mM/day) and high-sodium (mean: 263 mM/day) diets. Trend lines for both groups were plotted via power regression analysis and extrapolation in Microsoft Excel®. Reprinted with permission from Springer Science+Business Media from Volk et al. [41].

greater degrees of ECV expansion at each level of sodium intake than patients without these salt-excreting impairments [unpubl. data]. In dialysis patients, the urinary sodium cannot be used to assess ECV. Our pilot study utilizing bioimpedance in dialysis patients found ECV expansion and relative hyperaldosteronism in all end-stage renal disease patients (fig. 1). This abnormal ECV-aldosterone relationship represents a pathologic shift of the normal hyperbolic relationship between ECV and serum aldosterone concentration. Figure 2 illustrates the hypothetical effect of the disordered relationship between varying degrees of elevated ECV-aldosterone product and severity of vascular inflammation and hypertension in CKD and several other high ECV disease states.

Surprisingly, in spite of ECV expansion, CKD patients frequently have striking elevations in serum aldosterone concentrations [20, 21]. Possible nonvolume regulators of aldosterone release in CKD include hyperkalemia, hyperreninism (from renal ischemia), adipose-derived aldosterone-releasing factors [22], nitric oxide, and abnormalities of circadian rhythm [23]. One clinical study in CKD patients showed a direct relationship between serum aldosterone concentration and the degree of protein-

Fig. 2. A graphical representation of relative hyperaldosteronism in various disease and experimental states. Selye's rat model was achieved by means of partial renal ablation and high salt intake in the face of MR activation by parenteral administration of DOCA. A more rightward shifted curve should, in theory, coincide with higher blood pressure and increased vascular inflammation. MR activation may be promoted by aldosterone as well as cortisol, redox state, or possibly the intracellular GTP-ase, Rac-1 [9]. Reprinted with permission from Springer Science+Business Media from Volk et al. [41]. HBP = High blood pressure.

uria [24]. Finally, MR activation may occur even in the absence of hyperaldosteronism, possibly from MR activation by cortisol or redox state [25].

Efforts to reduce proteinuria and abrogate the progression of CKD by inhibition of the RAAS using ACE-Is and/or ARBs have only been partially successful, possibly due to aldosterone breakthrough and/or the effects of above-mentioned aldosterone secretagogues. Therefore, judicious use of low-dose MRB in early-phase CKD (stage I-II), as well as in patients on dialysis, may offer an opportunity to more completely block both the prohypertensive and tissue inflammatory effects of inappropriate MR activation.

MR Blockade in Diabetic CKD

Proteinuria reduction by means of ACE-I and/or ARB therapy is associated with a decreased risk of renal disease progression in diabetic CKD [26]. A small number of short-term clinical studies have examined the effects of adding MRBs to conventional RAAS blockade in proteinuric diabetics. Two meta-analyses found that the addition of MRB therapy reduced proteinuria by up to 50% from baseline. Since most of these patients were nonnephrotic, the absolute degree of proteinuria reduction was small [15, 27]. A component of this antiproteinuric effect

in these studies was independent of blood pressure. Since the majority of patients were diabetic, these studies support the use of low-dose MRB therapy in the treatment of proteinuric diabetic nephropathy.

Mehdi et al. [28] recently reported the results of a randomized, double-blind, placebo-controlled trial of 81 patients with diabetic nephropathy, all treated with lisinopril 80 mg daily – a relatively high dose of ACE inhibition. 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% ($p = 0.007$) in the spironolactone group and by 17% ($p = 0.2$) in the losartan group. Clinic and ambulatory blood pressure did not differ between treatment groups, suggesting that the renoprotection afforded by MRB therapy was via blockade of the nonepithelial actions of aldosterone.

This study can be considered alongside a larger study of diabetic nephropathy by Epstein et al. [29] in which eplerenone, rather than spironolactone, was the preferred MRB. After open-label run-in with enalapril 20 mg daily, 268 patients 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, $p < 0.001$ vs. placebo). All treatment groups experienced similar decreases in blood pressure (amlodipine 2.5–10 mg daily was allowed as an additional therapy to achieve the target blood pressure of $\leq 130/80$ mm Hg). These results, akin to those reported by Mehdi et al. [28], suggest a blood pressure-independent, non-epithelial effect of aldosterone blockade in reducing proteinuria in diabetic nephropathy. Notably, this beneficial effect was achieved with very low doses of MRB therapy (spironolactone 25 mg daily or eplerenone 50 mg daily), dosages below that considered antihypertensive or diuretic. Furthermore, Epstein et al. [29] showed that higher doses of MRBs (eplerenone 100 mg daily vs. 50 mg daily) do not provide any additional benefit with regard to proteinuria. Taken together, these results suggest that diabetic nephropathy is a disease of inappropriate MR activation.

MR Blockade in Nondiabetic CKD

The data supporting the use of MRBs in nondiabetic kidney diseases are not as robust as those in diabetic nephropathy. Bianchi et al. [30] randomized 128 patients with idiopathic glomerular diseases to intensive therapy

(ACE-I, ARB, high-dose statin, and spironolactone) or conventional therapy (ACE-I and low-dose statin). Significantly greater proteinuria reduction and eGFR stabilization were noted with intensive versus conventional therapy. Furumatsu et al. [31] performed an open-label study in 32 nondiabetic patients with proteinuria exceeding 0.5 g/day. After more than 12 weeks of combined ACE-I and ARB treatment, patients were assigned to either spironolactone 25 mg daily (a triple blockade group of ACE-I + ARB + MRB) or diuretic (trichlormethiazide 1 mg daily or furosemide 20 mg daily, a control group). After 1 year of treatment, the urinary protein level decreased by 58% ($p < 0.05$) and urinary type IV collagen (a measure of renal fibrosis) decreased by 40% ($p < 0.05$) with triple blockade, but remained unchanged in the controls. Mean serum creatinine, potassium, and blood pressure did not change significantly in either treatment arm.

Finally, with respect to blood pressure, many CKD patients fail to achieve the target blood pressure ($<130/90$) on traditional therapy. Low-dose MRB therapy has been shown to significantly reduce blood pressure in CKD patients with resistant hypertension [32]. Indeed, experimental models suggest that MRB therapy is particularly effective in high salt states, where hypertension is most likely to be resistant. Given the high dietary sodium associated with modern diets, low-dose MRB therapy in carefully selected and closely monitored patients may be more attainable than a strict low-sodium diet.

Safety of MR Blockade in CKD

The issue of safety when using MRB therapy in CKD is critically important. Most patients for whom MRB therapy is considered are already on pre-existent ACE-I and/or ARB; therefore, the risk of hyperkalemia cannot be overlooked [33]. Most patients in the CKD trials mentioned above had estimated GFR levels above 50 ml/min/1.73 m², and all trials of MRB therapy used baseline potassium level as an exclusion criteria (usually restricting the medication to those whose potassium levels are clearly and consistently <5.0 mEq/l).

A recent retrospective study by Khosla et al. [34] adds important safety data on using MRB therapy in CKD. Patients with resistant hypertension and CKD stage 2 or 3 were evaluated after MRB was added to preexisting blood pressure-lowering regimens (including a diuretic and RAAS blocker). Patients with a baseline estimated GFR of ≤ 45 ml/min/1.73 m² and baseline serum potassium >4.5 mEq/l were identified as having the highest

risk for hyperkalemia (serum potassium >5.5 mEq/l), which occurred in 8 of the 46 patients in this cohort. It is important to note that the RALES trial excluded patients with serum creatinine concentrations >2.0 mg/dl [2].

The risk of hyperkalemia in CKD patients treated with low-dose MRB therapy can be lessened by a low-potassium diet, adjunctive loop diuretic therapy, and avoidance of NSAIDs. The effect of a low-sodium diet plus MRB therapy, while synergistic, may increase the risk of hyperkalemia. Studies to date suggest that MRB therapy is safe in dialysis patients [21, 35].

Several studies suggest that low-dose MRB add-on therapy in CKD is associated with early-phase reduction of GFR, which is short-lived and most likely a consequence of hemodynamic changes. Preliminary studies suggest that long-term MRB therapy decreases the rate of GFR decline compared with pretreatment baseline [36, 37]. If confirmed in future clinical studies, this renoprotective effect stands in contrast with neutral or perhaps deleterious effects on GFR seen with dual RAAS blockade with ACE-Is and ARBs [36, 38].

Conclusions

Studies have confirmed the efficacy of MRBs in treating advanced congestive heart failure [2, 3] and resistant hypertension [22]. In CKD, blockade of the RAAS with ACE-Is and/or ARB therapy has only been partially successful in attenuating the rate of renal function decline and achieving target blood pressure. Judicious use of low-

dose MRB therapy in early stages of CKD (I–II) and in dialysis may offer therapeutic benefits not achieved with ACE-I and/or ARB therapy alone. Even in the absence of low-dose MRB therapy, better control of subclinical ECV expansion may attenuate the adverse effects of MR activation.

The major concern using low-dose MRB therapy in CKD is the risk of hyperkalemia. Use of low-dose MRBs appears to be safe in patients with GFR >45 ml/min and baseline potassium <4.5 mmol/l [39]. However, even under these guidelines, low-dose MRB requires careful patient monitoring. It is unclear whether patients demonstrating aldosterone breakthrough should be specifically targeted for low-dose MRD add-on therapy [40]. Large-scale prospective studies are needed to examine the safety as well as renal and cardiovascular outcomes in CKD patients receiving low-dose MRB therapy. While there is good evidence supporting use of low-dose MRB to reduce proteinuria in diabetic CKD patients with preserved renal function, there is little data relating to the effect of MRBs on disease progression. Larger trials will be needed to develop consensus guidelines for the appropriate use of MRB therapy in select CKD populations.

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