Aldosterone Blockers (Mineralocorticoid Receptor Antagonism) and Potassium-Sparing Diuretics

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Key Points and Practical Recommendations

- Mineralocorticoid receptor (MR) antagonists (aldosterone blockers) provide effective antihypertensive treatment, especially in low-renin and salt-sensitive forms of hypertension, including resistant hypertension.
- Newer, more selective MR antagonists (eg, eplerenone) have fewer of the progestational and antiandrogenic effects than spironolactone, enhancing tolerability and potentially improving adherence to therapy.
- MR antagonists provide an additional benefit in the treatment of heart failure when combined with angiotensin-converting enzyme inhibitors, digoxin, and loop diuretics.
- Other potassium-sparing diuretics (amiloride or triamterene) are generally prescribed for essential hypertension as a fixed-dose combination with hydrochlorothiazide.
- The dose range for spironolactone with resistant hypertension is between 25 mg/d and 50 mg/d, and eplerenone is an appropriate alternative if spironolactone is not tolerated because of sexual side effects.
- In general, the combined use of spironolactone and adequate doses of a thiazide diuretic or a thiazide-like agent such as chlorthalidone for the treatment of resistant hypertension maximizes efficacy and reduces the risk of spironolactone-induced hyperkalemia. *J Clin Hypertens (Greenwich).* 2011;13:644–648. ©2011 Wiley Periodicals, Inc.

Spironolactone, a nonselective mineralocorticoid receptor (MR) antagonist, has been in clinical use for several decades. A selective MR antagonist (eplerenone) has also been developed and is now in clinical use.

Before proceeding to review the use of these drugs in clinical practice, we will briefly review how the aldosterone paradigm and current concepts of the mineralocorticoid receptor have changed.

HOW THE ALDOSTERONE PARADIGM HAS CHANGED MARKEDLY: A PLATFORM FOR FORMULATING RATIONAL THERAPEUTICS

A reasonable summary of the prevailing view of aldosterone and the mineralcorticoid receptor (MR) in 1990 (the Traditional or Classical concept) posited that: (1) angiotensin was the major determinant of aldosterone secretion, (2) aldosterone is the physiologic ligand for MR, (3) that aldosterone elevates blood pressure primarily by its sodium-retaining effects with consequent volume expansion, (4) MR antagonists act by blocking the binding of aldosterone to MR, and (5) aldosterone acts genomically and nongenomically.

Twenty years later, we realize that the majority of these concepts are wrong.[1,2] In accordance with the New Paradigm, it is now accepted that: (1) angiotensin does not constitute the major driver of aldosterone secretion; (2) aldosterone is merely one of the physiological ligands for MR. In diverse disorders including congestive heart failure and essential hypertension, cortisol activates the MR; (3) although aldosterone's sodium retaining effects are relevant in defending volume homeostasis in the setting of hypovolemia, recent studies have demonstrated that aldosterone and MR activation raises blood pressure primarily by actions on the vasculature and central nervous system; (4) aldosterone is not the sole physiological ligand for MR. Rather in diverse disorders including congestive heart failure and essential hypertension, cortisol activates the MR.[2,3]

An understanding of this new paradigm for aldosterone constitutes a rational framework for examining the therapeutic potential of MR antagonism in hypertension, cardiovascular disease, and chronic kidney disease (CKD).[4–13]

It is important to understand that the interaction between aldosterone and the MR is necessary to fully comprehend the new paradigm. The mineralocorticoid receptor is an order of magnitude more sensitive to cortisol than to aldosterone. In addition, it is difficult as yet to fully interpret the physiologic relevance of the differing concentration of cortisol and aldosterone at the epithelial MRs,[2,3] and to explain why these receptors, despite being occupied by cortisol, appear not to be activated.

Consideration of these interactions suggests that an alternative and more appropriate term for aldosterone blockade is mineralocorticoid receptor antagonism (MRA). The available experimental evidence provides

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good reason to believe that the culprit in terms of MR activation in the RALES study, and in diverse clinical disorders, is cortisol. Consequently, drugs including spironolactone and eplerenone confer their benefits by antagonizing MR activation, and not merely by blocking aldosterone.

Expansion and evolution of the classical concept to the new paradigm is characterized by several additional features that subtend aldosterone's role in promoting target organ damage. First, in the presence of high-salt intake, aldosterone produces persistent hypertension with consequent blood-pressure dependent target organ damage. Second, in a permissive milieu with attendant high sodium intake, even "normal" concentrations of aldosterone produce blood-pressure independent target organ damage acting through inflammatory and pro-fibrotic pathways.[1,5]

HIGH SALT ("INAPPROPRIATE SALT") STATE ENHANCES CARDIOVASCULAR AND RENAL INJURY AND THE VASCULAR INFLAMMATORY EFFECTS OF MR ACTIVATION

A "high salt" state facilitates the deleterious effects of MR activation.[2,14] The implications of these observations are relevant for both an understanding of the pathogenesis of MR-induced cardiovascular and renal injury, and a platform for formulating a rational treatment regimen for conferring beneficial cardiovascular and renal effects in the setting of hypertension, cardiovascular disease, and the CKD patient. Simply stated, sodium restriction enhances the beneficial actions of MRA.

BLOOD PRESSURE-INDEPENDENT EFFECTS OF ALDOSTERONE AND MR ACTIVATION TO PRODUCE TARGET ORGAN DAMAGE

Several lines of evidence indicate that aldosterone promotes its deleterious effects on target organs independently of blood pressure. As an example, Mahmud and Feely[15] demonstrated in hypertensive patients that when blood pressure was lowered equally by either spironolactone or a thiazide, only spironolactone but not the thiazide reduced pulse wave velocity. Because this effect was independent of blood pressure lowering, it suggests that aldosterone acts directly on the endothelial cell and the vasculature. Similar blood pressure independent effects have been demonstrated in other target organs including the heart, the vasculature, and the kidney.[6,9–15]

Rationale for Aldosterone Blockade

Hypertension. Aldosterone exerts multiple physiologic actions that raise blood pressure (BP), including mediation of increased extracellular fluid volume and promotion of vasoconstriction (Table I). Aldosterone acts on MRs in epithelial cells in the distal tubule and collecting duct to promote sodium reabsorption and potassium excretion.

TABLE I. Pathophysiologic Actions of Aldosterone That Promote Hypertension and Increase Cardiovascular Risk

Sodium retention/volume expansion
Reduction in vascular compliance
Promotion of endothelial dysfunction
Upregulation of angiotensin II receptors
Potentiation of the pressor responses of angiotensin II
Increases in sodium influx in vascular smooth muscle cells
Fibrosis in the heart, kidneys, and vasculature
Activation of plasminogen activator inhibitor 1
Stimulation of transforming-growth factor β_1
Stimulation of reactive oxygen species
Hypertrophy of vascular smooth muscle cells and myocardial cells
Increase in blood lipid levels
Hypokalemia resulting in increased potential for cardiac arrhythmias, glucose intolerance, insulin resistance
Hypomagnesemia resulting in increased potential for cardiac arrhythmias

Aldosterone appears to constitute an important risk factor for cardiovascular disease and, therefore, the use of MR antagonists, in addition to thiazides, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) could provide additional benefit in the prevention of hypertensive end-organ damage. Thiazides increase aldosterone levels by reducing extracellular fluid volume; thus, the combination of thiazides and aldosterone antagonists has a rational basis. With drugs that block the formation or actions of angiotensin II (ACE inhibitors and ARBs), there is evidence that some patients may experience "aldosterone escape" during long-term treatment, in which aldosterone levels are initially suppressed but gradually return to baseline levels by mechanisms that remain to be fully elucidated. The renal effects of spironolactone include decreased urinary excretion of potassium, magnesium, and calcium.

Hypertensive End-Organ Damage. Pathophysiologic and outcome studies also suggest a rationale for aldosterone blockade as prevention or reversal of cardiac target organ damage, especially fibrosis. In general, the endocrine/paracrine effects of aldosterone transduced via MR ("genomic effects") also affect function of the colon and exocrine (salivary and sweat) glands. In addition to the genomic effects of aldosterone, there is significant more rapid "nongenomic" effects in the heart, kidneys, and vasculature.

Vascular Effects. In animal models, aldosterone blockade attenuates cardiac fibrosis in the damaged heart, reduces aortic fibrosis, and improves both large artery compliance as well as endothelial function. Clinical trials have shown that spironolactone reduces cardiac and vascular collagen turnover, improves reflex control (heart rate variability), reduces ventricular arrhythmias, improves endothelial function, and dilates blood vessels.[4,5,15] In concert, these hemodynamic and humoral actions of aldosterone may translate into

specific clinical benefits in hypertension and cardiovascular and renal diseases.

Proteinuria. Extensive preclinical and clinical evidence supports the efficacy of MR antagonists, when added to ACE inhibitors or ARBs, in attenuating proteinuria.[10,11] These data suggest that aldosterone per se or MR activation promotes renal injury. Consequently, add-on aldosterone blockade has the potential for attenuating renal injury.[11]

Clinical Use

Essential Hypertension. *Spironolactone.* Spironolactone is indicated for treating hypertension and is particularly effective when given together with a thiazide-type diuretic. Similar to conventional thiazide-type or loop diuretics, MR antagonists provide effective antihypertensive treatment in most patients with low-renin forms of hypertension, particularly in blacks, the elderly, and many diabetics.[9,11,12] MR antagonists are also effective in the large subgroup of individuals with the metabolic syndrome (obesity, hypertension, insulin resistance, dyslipidemia, accelerated atherogenesis).[16] Thus, the majority of hypertensive patients can be expected to have some level of response to MR antagonists.

Eplerenone. In developmental studies, the selective MR antagonist eplerenone safely and effectively lowered BP in patients with mild to moderate hypertension and diverse comorbidities, including left ventricular hypertrophy and diabetes mellitus. Eplerenone is indicated for hypertension and is equally effective in black and white patients and well tolerated when used alone or in combination with a variety of other agents.[9,11,12]

Resistant Hypertension. Aldosterone blockade has assumed an important role in the treatment of resistant hypertension, defined as failure to achieve goal BP despite treatment with $\geq$3 medications, ideally one of which is a diuretic. Several recent clinical studies indicate that aldosterone blockade provides significant incremental BP reduction when added to treatment regimens of patients with resistant hypertension.[17,18] The dose range for spironolactone in these studies has typically been between 25 mg/d and 50 mg/d. Eplerenone has recently been shown to also provide significant add-on benefit when treating resistant hypertension, making it an appropriate alternative if spironolactone is not tolerated.[18] In general, the combined use of spironolactone and adequate doses of a thiazide diuretic or a thiazide-like agent such as chlorthalidone is recommended for the treatment of resistant hypertension in order to maximize efficacy and reduce risk of spironolactone-induced hyperkalemia.

Hyperaldosteronism. MR antagonists are effective in the therapy of various forms of hyperaldosteronism, including adrenal hyperplasia, adrenal adenoma, and glucocorticoid-remediable aldosteronism. Doses required in these conditions are often higher than those used in essential hypertension (Table II).

Heart Failure. The renin-angiotensin-aldosterone system is markedly activated in heart failure and spironolactone and eplerenone have proved to be beneficial in reducing heart failure morbidity and mortality (the Randomized Aldactone Evaluation Study [RALES][8] and Eplerenone Post-AMI Heart Failure Efficacy and Survival (EPHESUS) trial,[19] respectively) when added to standard therapy. When given in addition to conventional therapy with an ACE inhibitor, digoxin, and loop diuretic, spironolactone, 25 mg daily, reduced mortality and heart failure hospitalizations.

Applied Pharmacology

Receptor Pharmacology. Spironolactone is moderately more potent than eplerenone in competing for MRs. Preclinical studies with eplerenone have demonstrated a >100-fold lower affinity for androgen and progesterone receptors than is the case for spironolactone and its active metabolite, canrenone.

Dosing. In mild to moderate hypertension, the recommended dose of spironolactone is 12.5 mg to 100 mg daily and that of eplerenone is 50 mg to 100 mg daily. Pharmacokinetic studies have not found any correlation between alterations in eplerenone disposition kinetics and degree of renal dysfunction. Spironolactone pharmacokinetics have not been examined in the setting of renal dysfunction.

Drug Interactions. Favorable interactions include enhanced natriuresis and a potassium-sparing effect when MR antagonists are combined with loop or thiazide diuretics. Potentially unfavorable interactions include hyperkalemia when aldosterone antagonists

TABLE II. Doses of Aldosterone Antagonists in Various Clinical Conditions

		Total Usual Dose Ranges, mg/d		
Drug	Dosing Frequency	Essential Hypertension	Hyperaldosteronism	Heart Failure
Spironolactone (Aldactone)	qd or bid	25–200	50–200[a]	25–50
Eplerenone (Inspra)	qd or bid	50–100	—	—

Abbreviations: bid, twice a day; qd, once a day. [a]Similar doses may be effective in polycystic ovary syndrome, but the drug has not been approved specifically for that purpose.

are combined with ACE inhibitors or ARBs, particularly in patients who have renal insufficiency, diabetes mellitus, or hyporeninemic hypoaldosteronism (type IV renal tubular acidosis). Eplerenone's metabolism is CYP3A4-dependent and it should be used carefully with inhibitors of CYP3A4 activity (eg, ketoconazole or verapamil).

Major Adverse Effects of MR Blockers

Sexual Function. Although spironolactone is an effective anti-aldosterone agent, its use in patients is limited by its tendency to produce undesirable sexual adverse effects. At standard doses, breast tenderness, gynecomastia, and erectile dysfunction can occur in men, whereas menstrual abnormalities may occur in premenopausal women. These adverse effects are due to the binding of spironolactone to progesterone and androgen receptors and represent a substantial reason for drug discontinuation. RALES reported a 10% incidence of gynecomastia or breast pain in its male patients receiving 25 mg/d to 50 mg/d of spironolactone vs 1% on placebo ($P<.001$).[8] In the treatment of hypertension, when compared with spironolactone, the selective MR antagonist eplerenone provides a reduced incidence of gynecomastia.[19]

Hyperkalemia. Particularly in the setting of reduced renal function (primarily chronic kidney disease and heart failure), potassium excretion is diminished. Another condition that predisposes to hyperkalemia is type IV renal tubular acidosis (hyporeninemic hypoaldosteronism) that is usually seen in long-standing diabetics. The obligatory tendency toward hyperkalemia in these conditions is further exacerbated by attenuation of aldosterone-dependent kaliuresis by MR blockade. In these conditions, careful monitoring of serum potassium, attention to dietary potassium restriction, and consideration for concomitant use of loop diuretics are important.

OTHER POTASSIUM-SPARING DIURETICS

Other weaker diuretic compounds, such as amiloride and triamterene, can increase renal sodium excretion with relative potassium-sparing. These agents tend to be relatively ineffective when used as monotherapy for hypertension but can be useful in combination with hydrochlorothiazide.

Amiloride

Mechanisms of Action. Amiloride blocks epithelial sodium transport channels selectively. In the distal tubule, this action indirectly reduces aldosterone-sensitive sodium-potassium exchange and leads to increased urinary sodium excretion, with relative potassium-sparing. Additional vasodilatory effects have been proposed. Comparing amiloride with MR antagonists, the former works at the basolateral membrane, whereas the latter works at the epithelial membrane and nuclear level.

Clinical Use. In essential hypertension, amiloride is usually given as part of a fixed-dose combination with hydrochlorothiazide. It is also sometimes used alone or in combination to treat glucocorticoid-remediable aldosteronism and other forms of hyperaldosteronism. Amiloride can be substituted for spironolactone when sexual side effects limit the use of the latter. Adverse effects associated with amiloride are usually mild and transient and typically include gastrointestinal discomfort or occasionally muscle cramps. Hyperkalemia can occur with amiloride, particularly in patients with chronic kidney disease or in those receiving other compounds known to limit the renal excretion of potassium, such as ACE inhibitors, ARBs, and nonsteroidal anti-inflammatory drugs.

Triamterene

Triamterene also blocks epithelial sodium transport channels, although less avidly than amiloride. Used alone, triamterene has little effect on BP. Triamterene-thiazide combinations may reduce potassium wasting. Triamterene is a weak folic acid antagonist, but megaloblastic anemia is rare. Triamterene is incompletely absorbed and can crystallize in the urine, potentially contributing to renal stone formation. Its use can be accompanied by an increase in serum concentrations or increased urinary uric acid excretion, requiring that it be used carefully, if at all, in patients with gout.

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