Optimizing Cardiovascular Care With Mineralocorticoid Receptor Antagonists

Kelly S. Mendoza, MS, PharmD

ABSTRACT

Mineralocorticoid receptor antagonists (MRAs) block the action of aldosterone at receptors in the kidneys, causing increased sodium and water excretion in exchange for potassium retention. There are 4 treatment groups in the cardiovascular population that have shown benefit with MRA therapy: resistant hypertension, post–acute coronary syndromes, heart failure with reduced ejection fraction, and heart failure with preserved ejection fraction. Serum potassium and kidney function should be monitored closely, especially if a patient is on a concomitant angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocker, or direct renin inhibitor therapy.

Keywords: aldosterone antagonists, heart failure, mineralocorticoid receptor antagonists, myocardial infarction, potassium-sparing diuretics, resistant hypertension

Mineralocorticoid receptor antagonists (MRAs) (also known as aldosterone antagonists) are agents that block the effect of aldosterone at mineralocorticoid receptors in the distal renal tubules of the kidneys, inhibiting sodium resorption and interfering with sodium/potassium exchange.[1] This results in reduced potassium excretion in the urine and promotes weak diuresis because of increased sodium and water excretion. Therefore, these agents are often referred to as "potassium-sparing diuretics." The 2 agents from this class that are prescribed in the United States are spironolactone (a nonselective antagonist) and eplerenone (a selective antagonist). Spironolactone is structurally similar to progesterone and is considered a nonselective MRA because it cross-reacts with sex steroid (progesterone and androgen) receptors, leading to some of the hormonal side effects observed with spironolactone (Table 1).[2] Eplerenone is a selective aldosterone antagonist with limited affinity for the sex steroid receptors and, therefore, lacks the sex-related adverse effects.[3] Because of their physiologic actions, MRAs have been shown to have beneficial effects in a variety of cardiovascular conditions.

ALDOSTERONE ESCAPE

The benefit of MRAs in cardiac conditions, especially heart failure (HF), can in part be attributed to a tempering of the physiologic phenomenon known as "aldosterone escape."[4] In HF, the renin-angiotensin-aldosterone system (RAAS) is activated. Plasma aldosterone levels have been shown to be significantly increased in HF patients when compared with normal controls. This is caused by reduced hepatic clearance of the hormone in addition to enhanced secretion as a result of increased levels of potassium, which is a powerful secretagogue for aldosterone. Mean aldosterone levels have been shown to correlate with mortality in HF. Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy in HF suppresses aldosterone production through RAAS blockade. However, research has shown that although an acute decrease in aldosterone does occur, the level of aldosterone rises again and returns to baseline in some patients. This "escape" of aldosterone is thought to contribute to a blunting of the effects of ACEIs or ARBs, which leads to a decrease over time of the beneficial effects of ACEIs or ARBs on mortality in HF. Adding an MRA to ACEI or ARB therapy provides an

Table 1. Pharmacologic Properties of Select Mineralocorticoid Receptor Antagonists

Characteristics	Spironolactone[1]	Eplerenone[3]
Select Cardiovascular Indication	Severe (NYHA Class III-IV) HF	HF (LVEF $\leq$ 40%) after MI
Sex steroid receptor cross-reactivity	Yes	Minimal
Metabolism	Hepatic	Hepatic (CYP3A4)
Half-life (h)	1.4	4-6
Excretion	Renal and feces	Renal and feces
Administration	With food to increase absorption and decrease GI upset	With or without food
Recommended dose (mg/d)	Resistant hypertension: 25 mg HF: 12.5-25 mg (max 50 mg)	HF/post-ACS: 25 mg (target 50 mg)
Renal dosage adjustments	HF: SCr $\leq$ 2.5 mg/dL: max dose 25 mg once or twice daily (max 50 mg daily) SCr $>$ 4 mg/dL: not recommended	HF/post-ACS: eGFR $\geq$ 50 mL/min/1.73m^2: max dose 50 mg daily SCr $>$ 2.0 mg/dL (males) or SCr $>$1.8 mg/dL (females) or eGFR $<$ 50 mL/min/1.73m^2: use with caution eGFR $<$ 30 mL/min/1.73m^2: not recommended
Drug interactions	Potentiate hyperkalemia ACEI ARBs NSAIDs Potentiate hypotension Increase digoxin levels	Potentiate hyperkalemia ACEI ARBs NSAIDs CYP3A4 inhibitors (increase eplerenone): clarithromycin, itraconazole, ketoconazole, ritonavir CYP3A4 inducers (decrease eplerenone): carbamazepine, rifampin, St. John's wort
Side effects	Endocrine/metabolic: amenorrhea, gynecomastia, hyperkalemia GI: abdominal cramps, diarrhea, nausea, vomiting (rates of adverse reactions were not reported in package insert)	Endocrine/metabolic: hyperkalemia (3.4%), hypertriglyceridemia (1%) GI: abdominal pain (1%), diarrhea (2%)

ACEI = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndromes; ARB = angiotensin II receptor blocker; CYP3A4 = cytochrome P450 3A4; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSAIDs = nonsteroidal anti-inflammatory drugs; NYHA = New York Heart Association; SCr = serum creatinine.

additional level of RAAS blockade and ensures that the pathway is optimally inhibited.

SAFETY CONSIDERATIONS AND MONITORING PARAMETERS

The mechanism of action of MRAs leads to reduced potassium excretion and can result in clinically significant hyperkalemia, especially if the patient is taking concomitant agents that can increase potassium (eg, ACEIs, ARBs, or potassium supplements). Therefore, it is not recommended to start spironolactone or eplerenone if the baseline serum K+ is $>$ 5.0 mEq/L. The risk of hyperkalemia is increased in kidney impairment, and serum creatinine should be $\leq$ 2.5 mg/dL (men) or $\leq$ 2 mg/dL (women) (estimated glomerular filtration rate $>$ 30 mL/min/1.73 m^2) before the initiation of an MRA. Potassium and kidney function parameters (ie, blood