

REVIEW ARTICLE

CURRENT CONCEPTS

Managing Hyperkalemia Caused by Inhibitors of the Renin–Angiotensin–Aldosterone System

Biff F. Palmer, M.D.

ANGIOTENSIN-CONVERTING-ENZYME (ACE) INHIBITORS AND ANGIOTENSIN-receptor blockers are used commonly in clinical practice to treat hypertension and decrease cardiovascular events in high-risk patients. A side effect of such therapy is the development of hyperkalemia. Hyperkalemia has been attributed to the use of ACE inhibitors in 10 to 38 percent of hospitalized patients with this complication.¹⁻⁴ Hyperkalemia develops in approximately 10 percent of outpatients within a year after these drugs are prescribed.⁵ Patients at greatest risk for hyperkalemia include those with diabetes and those with impaired renal function in whom a defect in the excretion of renal potassium may already exist.

Hyperkalemia is an uncommon complication of therapy with ACE inhibitors or angiotensin-receptor blockers in patients without risk factors. The low incidence of hyperkalemia in controlled trials involving these drugs can be attributed to the enrollment of patients at low risk, frequent follow-up, and intensive monitoring. As an example, the mean serum creatinine concentration in major trials involving patients with congestive heart failure ranged from 1.2 to 1.4 mg per deciliter (106 to 124 μ mol per liter).⁶ Since one third to one half of patients with congestive heart failure have renal insufficiency, in actual practice a large proportion of patients being treated with these drugs are at increased risk for hyperkalemia.⁶ Physicians are willing to prescribe these drugs for such high-risk patients because chronic kidney disease is among the strongest predictors of death in patients with congestive heart failure. The development of hyperkalemia poses a therapeutic dilemma, since the patients at highest risk for this complication are the same patients who derive the greatest cardiovascular benefit from these drugs.

Hyperkalemia is likely to become an even more common clinical event, since ACE inhibitors and angiotensin-receptor blockers are increasingly being used in higher doses and in combination, in the belief that these measures provide additional cardiovascular protection.⁷⁻¹⁰ Further increasing the risk is the practice of adding an aldosterone-receptor blocker to one of these drugs to improve outcomes in patients with congestive heart failure.^{11,12} There is preliminary evidence that this combination of drugs may also be of benefit in slowing the progression of chronic kidney disease.¹³ To the extent that such treatment strategies improve cardiovascular outcomes, it will be of considerable importance for physicians to identify patients at risk (Table 1) and to implement measures designed to lessen the likelihood that hyperkalemia will develop. Although close monitoring is required, such measures will allow the majority of patients to enjoy the cardiovascular benefits of these drugs instead of being considered to have an intolerance to them as a result of hyperkalemia.

From the Department of Medicine, Division of Nephrology, University of Texas Southwestern Medical School, Dallas. Address reprint requests to Dr. Palmer at the Department of Medicine, University of Texas Southwestern Medical School, 5323 Harry Hines Blvd., Dallas, TX 75390-8856, or at biff.palmer@utsouthwestern.edu.

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NORMAL HANDLING OF POTASSIUM IN THE KIDNEY

Potassium is freely filtered by the glomerulus. Most filtered potassium is reabsorbed in the proximal tubule and the loop of Henle, with only 10 percent of the filtered load reaching the distal nephron. Potassium is then secreted in the collecting duct. Potassium secretion in this segment is regulated and varies according to physiological needs. The two most important physiological determinants of potassium excretion are the serum aldosterone concentration and the delivery of sodium to the distal nephron.

Aldosterone secretion is influenced by the renin-angiotensin system and by the plasma potassium concentration. Renin is secreted by the juxtaglomerular cells in the afferent arteriole when renal perfusion pressure is low, as in states of low blood volume or their functional equivalents such as congestive heart failure or cirrhosis. Renin acts on angiotensinogen to form angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme. Angiotensin II stimulates the release of aldosterone from the zona glomerulosa cells in the adrenal gland. Plasma potassium also has a direct stimulatory effect on aldosterone secretion.¹⁴ The stimulatory effects of angiotensin II and potassium on the release of aldosterone appear to be synergistic, since the presence of one factor increases the response to the other.^{14,15} This interaction between angiotensin II and potassium involves the activation of a local intra-adrenal renin-angiotensin system.¹⁶

INDUCTION OF HYPERKALEMIA

ACE inhibitors and angiotensin-receptor blockers impair urinary potassium excretion by interfering with the stimulatory effect of angiotensin II on aldosterone secretion in the adrenal gland. ACE inhibitors block the formation of angiotensin II, whereas angiotensin-receptor blockers prevent angiotensin II from binding to its adrenal receptor. In addition to their effects on circulating angiotensin II, these drugs may interfere with angiotensin II that is generated locally within the adrenal zona glomerulosa.¹⁶

Hyperkalemia may develop as a complication of therapy with ACE inhibitors or angiotensin-receptor blockers in patients with one or more of three disturbances that impair the excretion of potassium: decreased delivery of sodium to the distal nephron,

Table 1. Risk Factors for Hyperkalemia with the Use of Drugs That Interfere with the Renin-Angiotensin-Aldosterone System.

Chronic kidney disease*
Diabetes mellitus
Decompensated congestive heart failure
Volume depletion
Advanced age
Drugs used concomitantly that interfere in renal potassium excretion
Nonsteroidal antiinflammatory drugs
Beta-blockers
Calcineurin inhibitors: cyclosporine, tacrolimus
Heparin
Ketoconazole
Potassium-sparing diuretics: spironolactone, eplerenone, amiloride, triamterene
Trimethoprim
Pentamidine
Potassium supplements, including salt substitutes and certain herbs

* The risk is inversely related to the glomerular filtration rate and increases substantially when the rate is less than 30 ml per minute.

ron, aldosterone deficiency, and abnormal functioning of the cortical collecting tubule. These abnormalities can result from the effects of other drugs, from underlying disease, or commonly from a combination of both.

DECREASED DISTAL DELIVERY OF SODIUM

Under normal circumstances, there is an inverse relationship between the plasma aldosterone concentration and the delivery of sodium to the distal nephron so that potassium excretion remains independent of changes in extracellular fluid volume. Under conditions of decreased renal perfusion, aldosterone concentrations increase. At the same time, the proximal absorption of sodium and water increases, and as a result, their distal delivery decreases. Renal potassium excretion remains fairly constant under these conditions, since the stimulatory effect of increased aldosterone is counterbalanced by the decreased delivery of filtrate to the distal nephron.

Mild-to-moderate reductions in renal perfusion typically do not cause the distal delivery of sodium to fall to a level that impairs potassium secretion sufficiently to result in clinically significant hyperkalemia. In most patients with untreated congestive heart failure, the serum potassium concentra-

tion is normal or at the high end of the normal range as long as the impairment in cardiac function and renal perfusion is not severe. When such patients are treated with ACE inhibitors or angiotensin-receptor blockers, the fall in the circulating aldosterone concentration typically will be counterbalanced by increased distal delivery of sodium so that the serum potassium concentration remains stable. The increase in the distal delivery of sodium is due to the afterload-reducing effects of these drugs, which cause an improvement in cardiac output and renal perfusion. The reduction in angiotensin II concentration plays an important role in decreasing proximal sodium reabsorption. In addition, most patients are treated with loop diuretics, which further enhance the delivery of sodium to the collecting duct.

When renal perfusion becomes more severely reduced, as in intractable congestive heart failure, proximal reabsorption can become so intense that very little sodium escapes into the distal nephron. Despite increased concentrations of aldosterone, the lack of availability of sodium can begin to impair renal potassium secretion. To the extent that cardiac output and renal perfusion become refractory to the afterload-reducing effects of ACE inhibitors or angiotensin-receptor blockers, the risk of hyperkalemia increases. In this setting, these drugs may also cause the serum creatinine concentration to rise owing to reductions in intraglomerular pressure that are no longer offset by increases in glomerular perfusion.¹⁷ Patients in whom this effect occurs generally have a urinary sodium concentration of less than 10 mmol per liter and a relatively high urinary potassium concentration, often exceeding 40 mmol per liter. Despite the high urinary potassium concentration, total urinary potassium excretion is inadequate because of the low urinary volume.

DECREASED ALDOSTERONE ACTIVITY

The decline in serum aldosterone concentrations that occurs with the use of ACE inhibitors and angiotensin-receptor blockers is not sufficient to impair the excretion of potassium in most patients. The development of hyperkalemia as a result of decreased aldosterone concentrations is usually seen when aldosterone concentrations have already decreased before the administration of the drugs. Decreased aldosterone concentrations can result from disturbances that originate at any point in the renin-angiotensin-aldosterone system. Such dis-

turbances can result from a disease state or from the effects of other drugs (Fig. 1).

Several conditions affect this system at its point of origin and lead to the impaired release of renin with subsequent hypoaldosteronism — a syndrome commonly referred to as hyporeninemic hypoaldosteronism. The normal aging process is accompanied by impaired release of renin, placing elderly patients at slightly increased risk for hyperkalemia.¹⁸ Diabetic nephropathy is the most common cause of hyporeninemic hypoaldosteronism, accounting for 43 to 63 percent of cases.^{19,20} The risk of hyperkalemia is further increased in diabetic patients as a result of insulin deficiency, which in turn limits the body's ability to shift potassium into cells.

Several medications are known to interfere with the release of renin. Nonsteroidal antiinflammatory drugs have been reported to cause hyperkalemia in up to 46 percent of hospitalized patients.²¹ These drugs interfere with the stimulatory effect of prostaglandins on the release of renin.²² The subsequent fall in aldosterone concentrations is exacerbated when these drugs are used with inhibitors of the renin-angiotensin system, since prostaglandins serve an intermediary role in the stimulatory effect of angiotensin II on aldosterone secretion.²³ The cyclooxygenase-2-selective inhibitors should be used with the same caution that applies to the use of traditional nonsteroidal antiinflammatory drugs.²⁴

Hyperkalemia has been reported to develop in 44 to 73 percent of transplant recipients who receive immunosuppressive therapy with cyclosporine or tacrolimus.²⁵ These drugs suppress the release of renin and directly interfere with the secretion of potassium in the collecting duct.²⁶ The use of ACE inhibitors and angiotensin-receptor blockers to slow the progression of chronic allograft nephropathy can be expected to increase the risk of hyperkalemia.²⁷

Beta-adrenergic blocking agents can confer a predisposition to the development of hyperkalemia through two potential mechanisms.²⁸ These drugs block the stimulatory effect of the sympathetic nervous system on the release of renin. In addition, they can interfere with the cellular uptake of potassium through decreased activity of sodium-potassium ATPase.²⁹

Heparin can cause hyperkalemia by blocking the biosynthesis of aldosterone in the adrenal gland.³⁰ This complication can develop irrespective of the dose used and may be seen after either intravenous or subcutaneous administration. The azole antifun-

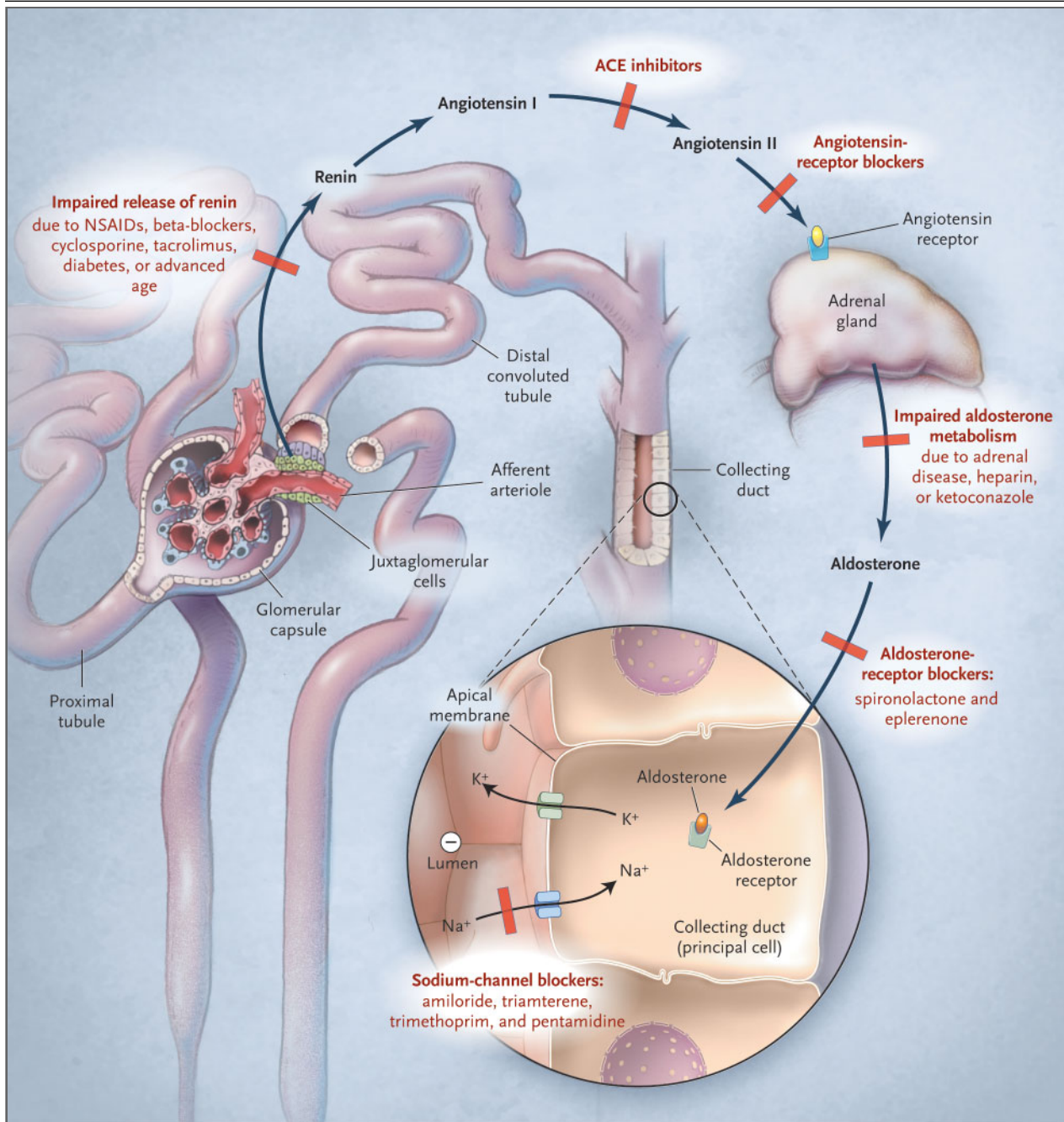


Figure 1. The Renin–Angiotensin–Aldosterone System and Regulation of Potassium Excretion in the Kidney.

Aldosterone binds to a cytosolic receptor in the principal cell and stimulates sodium reabsorption across the luminal membrane through a well-defined sodium channel. As sodium is reabsorbed, the electronegativity of the lumen increases, thereby providing a more favorable driving force for the secretion of potassium through an apically located potassium channel. The permeability of the anion that accompanies sodium also influences the secretion of potassium, with less permeable anions having a greater stimulatory effect on this secretion. Disease states or drugs that interfere at any point along this system can impair the secretion of potassium in the kidney and increase the risk of hyperkalemia when ACE inhibitors or angiotensin-receptor blockers are used. In many patients, this risk is magnified because of disturbances at multiple points in this system. NSAIDs denotes nonsteroidal antiinflammatory drugs.

gals, such as ketoconazole, interfere with the biosynthesis of adrenal steroids and therefore can predispose patients to aldosterone deficiency.

ABNORMAL FUNCTIONING OF THE CORTICAL COLLECTING TUBULE

The risk of hyperkalemia increases when ACE inhibitors and angiotensin-receptor blockers are used with drugs or in disease states that interfere with the function of the cortical collecting tubule. Acute or chronic tubulointerstitial renal disease is characterized by the early onset of impaired renal potassium secretion, even though renal function may be only mildly depressed. These disorders cause early damage of the tubules, which results in end-organ resistance to the effects of aldosterone such that even a small decline in the circulating aldosterone concentration can limit renal potassium excretion. Many of the diseases that affect tubular function also impair the release of renin; as a result, hyporeninemic hypoaldosteronism and impaired tubular function may coexist. Patients who may have these coexisting conditions include those with diabetic nephropathy, renal transplants, systemic lupus erythematosus, amyloidosis, sickle cell disease, or obstruction of the urinary tract.

The potassium-sparing diuretics impair the ability of the cortical collecting tubule to secrete potassium. In an analysis of elderly subjects who were treated with ACE inhibitors, those admitted to the hospital because of hyperkalemia were 27 times as likely to have received a prescription for a potassium-sparing diuretic during the previous week as were those taking ACE inhibitors who were not admitted to the hospital.³¹ Amiloride and triamterene block the epithelial sodium channel in the collecting duct. Blockade of sodium reabsorption through this channel abolishes the negative potential of the lumen and therefore removes a major driving force for the secretion of potassium. A similar effect can be seen with trimethoprim and pentamidine.^{32,33} Spironolactone and eplerenone are potassium-sparing diuretics that block the interaction of aldosterone with the aldosterone receptor.

MINIMIZING THE RISK OF HYPERKALEMIA

Consider the hypothetical case of a 58-year-old white woman with type 2 diabetes mellitus, congestive heart failure, and diabetic nephropathy. The serum creatinine concentration is 1.8 mg per

deciliter (159 μmol per liter), and the estimated glomerular filtration rate is 31 ml per minute. Such a patient is likely to have hyporeninemic hypoaldosteronism and abnormal functioning of the collecting duct. Depending on the severity of the heart failure, there may also be decreased distal delivery of sodium. This patient is clearly at increased risk for the development of hyperkalemia. At the same time, drugs that interfere in the renin-angiotensin system can provide this patient with considerable cardiovascular benefit. An ACE inhibitor or an angiotensin-receptor blocker would be useful to slow the progression of renal disease, to treat the underlying heart failure, to reduce the risk of a future cardiovascular event, and to reduce the risk of death.³⁴⁻³⁷ Given the presence of heart failure, an aldosterone-receptor blocker might be added to reduce the chance of death further.¹¹

The initial approach to such a patient is to determine the specific risk of hyperkalemia by accurately assessing the level of renal function (Table 2).³⁸ In general, the risk will increase as renal function declines; however, an estimated glomerular filtration rate of 30 ml per minute should be considered a threshold below which the likelihood that hyperkalemia will develop substantially increases. Patients with diabetic nephropathy who have only mild-to-moderate reductions in the glomerular filtration rate (30 to 90 ml per minute) should be considered at higher risk because of the frequent presence of hyporeninemic hypoaldosteronism. In patients with chronic kidney disease, the level of renal function should not be the sole criterion for deciding whether use of these drugs should be initiated or continued. When they are used in patients with severe reductions in the glomerular filtration rate (i.e., those with rates below 30 ml per minute), close monitoring is required. Withholding these drugs solely on the basis of the level of renal function will unnecessarily deprive many patients of the cardiovascular benefit that they otherwise would have received, particularly since numerous steps can be taken to minimize the risk of hyperkalemia (Table 2).

One should review the patient's medication profile and, whenever possible, discontinue drugs that can impair the excretion of potassium in the kidney. Patients should be asked specifically about the use of over-the-counter nonsteroidal antiinflammatory drugs as well as herbal remedies, since herbs may be a hidden source of dietary potassium. An example of such foods is noni juice, which

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