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Management of Hyperkalemia: An Update for the Internist

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ABSTRACT

Hyperkalemia is a clinically important electrolyte abnormality that occurs most commonly in patients with chronic kidney disease. Due to its propensity to induce electrophysiological disturbances, severe hyperkalemia is considered a medical emergency. The management of acute and chronic hyperkalemia can be achieved through the implementation of various interventions, one of which is the elimination of medications that can raise serum potassium levels. Because many such medications (especially inhibitors of the renin-angiotensin aldosterone system) have shown beneficial effects in patients with cardiovascular and renal disease, their discontinuation for reasons of hyperkalemia represent an undesirable clinical compromise. The emergence of 2 new potassium-binding medications for acute and chronic therapy of hyperkalemia may soon allow the continued use of medications such as renin-angiotensin-aldosterone system inhibitors even in patients who are prone to hyperkalemia. This review article provides an overview of the physiology and the pathophysiology of potassium metabolism and hyperkalemia, the epidemiology of hyperkalemia, and its acute and chronic management. We discuss in detail emerging data about new potassium-lowering therapies, and their potential future role in clinical practice.

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KEYWORDS: Chronic kidney disease; Glomerular filtration rate; Hyperkalemia; Mortality; Renin-angiotensin-aldosterone system; Serum potassium

Hyperkalemia is one of the most clinically important electrolyte abnormalities due to the cardiac arrhythmias it can cause, which can result in increased mortality.[1-4] Usually, hyperkalemia is caused by excess dietary potassium, disordered cellular redistribution, abnormalities in potassium excretion, or a combination of these. The most common risk factor for hyperkalemia is chronic kidney disease, together with one or more ancillary conditions that cluster with it, such as acute kidney injury, cardiovascular disease, or diabetes mellitus, along with the medications used to treat these conditions.[5] Of the medications causing hyperkalemia, inhibitors of the renin-angiotensin-aldosterone system (RAAS) are beneficial in patients with chronic kidney disease, diabetes mellitus, and cardiovascular disease, yet it is often difficult to apply them for chronic management of these conditions because of associated hyperkalemia.

We will review the pathophysiology of hyperkalemia, and discuss the clinical consequences of hyperkalemia and currently available treatment regimens. We will highlight emerging novel therapies that may allow the more liberal use of RAAS inhibitors in various high-risk patient populations.

EPIDEMIOLOGY OF HYPERKALEMIA

Hyperkalemia is relatively infrequent in the general population, occurring in 2.6% of emergency department visits and 3.5% of hospital admissions in Canada.[6] Two US studies found incidences of hyperkalemia of 3.2%[7] and 2.6%.[8] However, the true frequency of hyperkalemia in the general population could be much higher.[6]

Studies in patients with chronic kidney disease have described significantly higher frequencies of hyperkalemia, ranging from 7.7% to 73%, depending on the studied

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population and on the definition of hyperkalemia (typically defined as >5 or >5.5 mEq/L).[3,7,9,10] An important risk factor of hyperkalemia in patients with chronic kidney disease is the presence of RAAS inhibitors,[7] with the risk increasing significantly in patients treated with dual blockade.[11,12] Enthusiasm about the success of RAAS inhibitors in achieving improved clinical outcomes in major clinical trials has resulted in markedly increased prescription of these agents in patients with clinical characteristics different from those of the clinical trial participants (eg, lower kidney function, higher baseline serum potassium), which could have been the reason for the marked increase in hyperkalemia rates described after the publication of some of these trials, and to an increase in hyperkalemia-related morbidity and mortality rates.[13] It is noteworthy that RAAS inhibitor-related hyperkalemia can occur even in anuric dialysis patients,[14] most likely as a result of blocking gastrointestinal potassium secretion.

CLINICAL SIGNIFICANCE

- Severe hyperkalemia represents a clinical emergency that is associated with malignant arrhythmias and increased deaths.
- Hyperkalemia often causes the elimination of beneficial medications such as inhibitors of the renin-angiotensin aldosterone system.
- The emergence of new potassium binders may soon allow the continued use of medications such as renin-angiotensin-aldosterone system inhibitors even in patients who are prone to hyperkalemia. This may result in improved outcomes in patients with cardiovascular and renal diseases.

Hyperkalemia has been associated with increased mortality in patients with normal kidney function,[7] and in patients with chronic kidney disease[3,15] and end-stage renal disease.[1,2,4,16]

PATHOPHYSIOLOGY AND RISK FACTORS OF HYPERKALEMIA

Most of the potassium in the human body is intracellular, with a concentration gradient of 30:1 between the intra- and extracellular compartments.[17] This gradient is paramount for the resting cell membrane potential, neuromuscular excitability, and cardiac pacemaker activity,[18] and even relatively small changes in extracellular potassium concentration can result in major electrophysiological disturbances. Extracellular hyperkalemia results in a lesser negative resting potential, with a decreased conduction velocity and an increased repolarization rate,[19] leading to fascicular and atrioventricular nodal blocks.[20] Clinically, these manifest in electrocardiogram changes characterized by peaked T-waves, PR-interval prolongation, and QRS widening, and in more severe cases, bradyarrhythmias, ventricular fibrillation, or asystole.[7] There is no single threshold above which hyperkalemia is considered imminently dangerous. Adverse events have been described with levels >5 mEq/L,[21] but the risk increases substantially with higher concentrations of serum potassium.[7]

The kidneys are the principal organs responsible for maintaining potassium homeostasis, and therefore, patients with chronic kidney disease and end-stage renal disease are at especially increased risk of hyperkalemia.[22] The kidneys regulate potassium balance by adjusting its secretion in the distal convoluted tubule and the proximal collecting duct, a process that is stimulated by aldosterone receptor activation and requires the presence of sufficient tubular flow, functional principal cells, and normal aldosterone secretion. The development of hyperkalemia is most often a result of abnormalities in one or more of these mechanisms, especially under circumstances where rapid adaptation of potassium excretion is needed (eg, after an increased endogenous or exogenous potassium load).[23] The inherent decreased ability of the kidneys to increase potassium excretion is often exacerbated by ancillary conditions that tend to occur in individuals with chronic kidney disease and can lead to hyperkalemia through various mechanisms (**Figure**). These include the typical dietary modifications in patients with chronic kidney disease (eg, sodium restriction resulting in decreased tubular flow, use of salt substitutes containing potassium salts, or potassium-rich heart-healthy diets), metabolic acidosis (potassium shift from the intracellular to the extracellular space), anaemia (blood transfusion with acute potassium load), and kidney transplantation (renal tubular acidosis, or effects of calcineurin inhibitors).[10,24] Patients with chronic kidney disease also suffer from numerous comorbidities, which can conspire with chronic kidney disease and its various complications to cause hyperkalemia. Acute kidney injury is characterized by decreased glomerular filtration rate and tubular flow, and often also by acute internal potassium loads (eg, gastrointestinal bleeding or tissue injury). Diabetes mellitus and cardiovascular disease are 2 of the most common comorbidities of patients with chronic kidney disease, and both can worsen hyperkalemia. Diabetic patients suffering from insulin deficiency and hypertonicity may have difficulty redistributing acute potassium loads into the intracellular space, and also, they can suffer from hyporeninemic hypoaldosteronism and diminished tubular potassium secretion.[25] Patients with cardiovascular disease, acute myocardial ischemia, left ventricular hypertrophy, and congestive heart failure typically are treated with various combinations of medications that have become some of the most important etiologies of hyperkalemia (**Figure**). Beta-2 receptor blockers inhibit renin production and decrease the ability to redistribute potassium to the intracellular space.[26] Heparin decreases production of aldosterone, and digitalis glycosides inhibit Na-K-ATPase;