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Clinical pearl

Hyperkalemia: newer considerations

by Amar D. Bansal and David S. Goldfarb, MD

Maintenance of potassium balance is a key aspect of electrolyte homeostasis. Potassium is the major intracellular cation, and its transport in the kidneys is tightly regulated. Disruptions in potassium balance, such as severe hyperkalemia ([K+] > 8 mEq/L), can lead to cardiac abnormalities that may progress to ventricular fibrillation if untreated. A diagnosis of hyperkalemia needs to be further contextualized in order to have clinical significance.

Factors to be considered when treating a patient with hyperkalemia are:

- the severity of hyperkalemia
- rate of onset
- existence of other medical conditions
    - renal insufficiency
    - diabetes
    - hypoaldosteronism
    - acidemia
- use of medications that affect the renin-angiotensin-aldosterone system
- dietary intake

Despite our empirical understanding of the physiologic mechanisms of renal function and potassium handling, there is still no clinical consensus on how and when treatment should be administered in the setting of hyperkalemia. The absence of established medical criteria allows some room for clinical subjectivity regarding when to correct hyperkalemia.

Renal physiology of potassium balance

Potassium processing by the kidneys must respond to fluctuations in dietary K+ intake so that intake matches excretion. If there is a mismatch between K+ intake and excretion, then alterations in [K+] are inevitable. After glomerular filtration, the proximal convoluted tubule and thick ascending limbs reabsorb K+. The main adjustments in K+ handling occur in the distal tubule and collecting ducts. In states of high dietary K+ intake, these portions of the nephron are involved in K+ secretion (through the principal cells), whereas in states of low dietary intake they are mainly involved in K+ reabsorption (through alpha-intercalated cells). Despite this efficient system of K+ handling, the exact physiology of how the kidneys act as a sensor for

dietary K+ intake remains unknown. It is even likely that the burden of K+ "sensing" occurs via an extrarenal mechanism that has a downstream effect on the nephron.

Factors other than dietary intake influence K+ homeostasis in the kidneys. Aldosterone causes increased K+ secretion by: (1) increasing the activity of Na+/K+ ATPase and (2) increasing epithelial sodium channels (ENaC) in principal cells [1]. The latter effect enhances the electrochemical gradient for K+ secretion into the lumen. Therefore, attenuated downstream effects of aldosterone due to spironolactone, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or the presence of hypoaldosteronism all lead to elevated K+ levels.

Treatment of hyperkalemia

Treatment consists of three components, summarized here. First, administration of intravenous calcium is appropriate for severe hyperkalemia and significant EKG changes. Next, insulin (and 50 percent dextrose to avoid hypoglycemia), sodium bicarbonate and inhaled beta-agonists like albuterol drive K+ into cells. Finally, treatment requires an increase in renal or intestinal excretion. The latter is achieved by administration of a sodium polystyrene sulfonate suspension (Kayexelate). Some say that the osmotic diarrhea caused by the sorbitol the Kayexelate is mixed in is the effective agent and that the effect of the resin is minimal. In patients who are not yet on dialysis, furosemide may also be useful, particularly in those with hypertension or edema.

When to intervene with chronic hyperkalemia remains uncertain, and as ACE inhibitors and ARBs are used more frequently in patients with chronic kidney disease, hyperkalemia is becoming more common. Is a [K+] of 5.5 mEq/L too high or dangerous? Does it require that an EKG be done? Absolute values that indicate a need for treatment or, alternatively, a benign outcome, remain uncertain. Patients with lower glomerular filtration rates (GFRs), acute reductions in GFR, or rising [K+] and those with unexplained increases in [K+] are all at greater risk than the opposite conditions.

Inpatient versus outpatient management

A recent study investigated clinical trends in management of patients with hyperkalemia [2]. The goal of the study was to see if any significant differences existed between patients who were treated as outpatients and those that were admitted and treated as inpatients. It is important to note that the study did not evaluate differences in outcome, i.e., the success or failure of clinical treatment as measured by adverse events or death; rather, it compared the two patient groups to see if indications for admission clearly distinguished the admitted group from the outpatient group.

The study concluded that the clinical profiles of the patients who underwent outpatient and inpatient treatment for hyperkalemia were not significantly different. The factors examined included age, mean [K+], or other values such as serum urea

nitrogen or creatinine. The indications for admission in the admitted group were not evident: they were not significantly more ill, did not have worse kidney function and did not have higher serum potassium concentrations. This result points to a lack of medical consensus on how to handle hyperkalemia.

The authors suggested that inpatient treatment of hyperkalemia is clearly necessary when there is severe hyperkalemia ([K+] > 8 mM) accompanied by EKG changes, as defined by the Levinsky criteria (table 1) [3]. In this case, the inpatient setting allows for continuous cardiac monitoring. The study also indicated that hyperkalemia associated with serious conditions such as tissue catabolism, an acute decrease in renal function or drug overdose might be an indication for inpatient management.

Hyperkalemia and pharmacotherapy

Many drugs that interact with the renin-angiotensin-aldosterone system (RAAS) can lead to hyperkalemia [4]. Furthermore, the incidence of drug-related hyperkalemia has increased due to the prevalence of agents that interact with the RAAS. A careful evaluation of a patient's medications is therefore essential in reducing [K+] levels since discontinuation of certain drugs may be required. Drugs that interfere with the release of renin can cause hyperkalemia by inducing hyporeninemic hypoaldosteronism. These drugs include nonsteroidal anti-inflammatories (NSAIDs), beta-blockers and calcineurin inhibitors such as cyclosporin. ACE inhibitors and ARBs can also cause hyperkalemia because they lead to lowered aldosterone levels. Sodium channel blockers such as amiloride and triamterene, or the similarly acting trimethoprim, may also cause hyperkalemia because Na+ reabsorption raises luminal electronegativity, which provides a strong driving force for potassium secretion. Thus, blocking Na+ reabsorption attenuates the luminal electronegativity, reducing the K+ conductance across the apical membrane into the lumen [1].

It is important to weigh the beneficial cardio- and renoprotective effects of some of the drugs mentioned against their deleterious tendency to cause hyperkalemia [4]. Studies have shown that physicians tend to be aware of the association between hyperkalemia and use of ACE inhibitors, but awareness of the potential of NSAIDs to cause hyperkalemia is relatively poor [2]. Thus, NSAIDs should be discontinued in patients with hyperkalemia or at risk for hyperkalemia before other drugs with beneficial cardio- and renoprotective effects are discontinued.

If an NSAID is absent from a patient's medications, and the drug regimen includes an ACE inhibitor, ARB, or aldosterone receptor blocker, or any combination of the three, then reductions in dosage or discontinuation of one of the agents may ameliorate hyperkalemia. ACE inhibitors and ARBs, however, have protective effects to diminish progression of chronic kidney disease, particularly in patients with proteinuria, and should be reinstituted after serum K+ concentration is corrected. Addition of furosemide may reduce blood pressure and edema while helping modulate serum K+ concentration.

Special attention should be given to certain combinations of drugs, such as spironolactone or eplerenone used with an ACE inhibitor [4]. Even when used individually, these agents may cause hyperkalemia, and their concomitant use increases the likelihood of drug-induced hyperkalemia, especially in the setting of chronic kidney disease.

Chronic kidney disease (CKD)

In the context of CKD, non-acute hyperkalemia is not a purely pathological state, rather it can be understood as an adaptive mechanism that helps maintain potassium balance [1]. Studies have shown that correlations of serum aldosterone levels with urinary K+ excretion in patients with CKD are at best uncertain [5]. Studies in rats have also shown that hyperkalemia results in increased K+ secretion that is independent of aldosterone levels [6]. The clinical implication of all these studies is that the management of hyperkalemia in patients with CKD should focus on minimizing disturbances in the newly established K+ balance by realizing that this balance depends on higher [K+] levels [1].

Regardless of the presence of CKD, appropriate action includes dietary counseling (for example, avoidance of dried fruits, popular with the elderly for help with constipation, and salt substitutes that often contain potassium) and a review of medications that might contribute to hyperkalemia.

Conclusion

Hyperkalemia is a common electrolyte abnormality in the current era of ACE inhibitor and ARB use. It is possible that many unnecessary ER visits, EKGs and hospitalizations result from the real anxiety that reasonable physicians experience when varying degrees of hyperkalemia are present. How to define safe, mildly elevated levels to reassure patients and physicians and avoid unneeded treatment is not obvious. While acute treatments like calcium, insulin and Kayexelate are often appropriate, long-term chronic hyperkalemia requires addressing drug choices and diet.

Classification	**[K+] (mmol/L)**	**EKG changes**
Minimal hyperkalemia	5.2 < [K+] < 6.5	Minor
Moderate hyperkalemia	6.5 < [K+] < 8.0	Only peaking of T waves
Severe hyperkalemia	[K+] > 8.0	Presence of widened QRS, AV block or ventricular dysrhythmia

Table 1. Levinsky Criteria

References

1. Gennari JF, Segal AS. Hyperkalemia: An adaptive response in chronic renal insufficiency. *Kidney Int.* 2002;62:1-9.

2. Charytan D, Goldfarb DS. Indications for hospitalization of patients with hyperkalemia. *Arch Intern Med.* 2000;160:1605-1611.
3. Levinsky NG. Management of emergencies, VI. Hyperkalemia. *N Engl J Med.* 1966;274:1076-1077.
4. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med.* 2004;351:585-592.
5. Schambelan M, Sebastian A, Biglieri EG. Prevalence, pathogenesis, and functional significance of aldosterone deficiency in hyperkalemic patients with chronic renal insufficiency. *Kidney Int.* 1980;17:89-101.
6. Field MJ, Stanton BA, Giebisch GH. Differential acute effects of aldosterone, dexamethasone, and hyperkalemia on distal tubular potassium secretion in the rat kidney. *J Clin Invest.* 1984;74:1792-1802.

Amar D. Bansal is a second-year medical student at New York University (NYU) School of Medicine. He graduated with a BSE in bioengineering from the University of Pennsylvania in 2005, where he was involved in tissue engineering research of intervertebral disc cells. He is interested in improving access to health care for those in medically underserved communities and is president of the Patient Advocacy Group at NYU.

David S. Goldfarb, MD, is the clinical chief of nephrology at New York University (NYU) Medical Center, chief of the Nephrology Section at New York Harbor Veterans Affairs Medical Center, and a professor of medicine and physiology at NYU School of Medicine, all in New York City.

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