Management of severe hyperkalemia

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**Background and Objectives:** Hyperkalemia is one of the few potentially lethal electrolyte disturbances. Prompt recognition and expeditious treatment of severe hyperkalemia are expected to save lives. This review is intended to provide intensivists and other interested clinicians with an understanding of the pathophysiology that underlies hyperkalemia, and a rational approach to its management.  

**Methods:** This article reviews and analyzes literature relevant to the pathophysiology and management of severe hyperkalemia. Methods include search of MEDLINE, and bibliographic search of current textbooks and journal articles.

Hyperkalemia is common in hospitalized patients, and may be associated with adverse clinical outcomes (1, 2). Its prevalence and clinical impact in critically ill patients are unknown. There is no doubt, however, that severe hyperkalemia can be fatal. Proper treatment of hyperkalemia depends on an understanding of the underlying physiology.

The ratio of extracellular to intracellular potassium (K) concentration largely determines the cell membrane resting electrical potential that, in turn, regulates the function of excitable tissues (cardiac and skeletal muscle, and nerve) (1). Small absolute changes in the extracellular K concentration will have large effects on that ratio, and consequently on the function of excitable tissues. Thus, it is not surprising that the plasma K concentration \( [K_p] \) normally is maintained within very narrow limits. This tight regulation is accomplished by two cooperative systems. One system defends against short-term changes in \( [K_p] \) by regulating internal balance: the equilibrium of K across the cell membrane. This equilibrium is modulated by insulin (3–5), catecholamines (6, 7) and, to a lesser extent, by acid-base balance (8–10), plasma toxicity, and several other factors (3). The other system governs K homeostasis over the long-term by regulating external balance: the parity between K intake and elimination. In individuals with normal renal function, the kidneys are responsible for elimination of about 95% of the daily K load with the remainder exiting through the gut. External K balance is maintained largely by modulating renal K elimination.

Almost all the K excreted by the kidney comes from K secreted in the distal nephron (connecting tubule and collecting duct) (11). Virtually all regulation of K excretion takes place at this site in the nephron, under the influence of two principle factors: the rate of flow and solute (sodium and chloride) delivery through that part of the nephron; and the effect of aldosterone (11). K secretion is directly proportional to flow rate and sodium delivery through the lumen of the distal nephron, and to circulating aldosterone levels in the setting of an aldosterone-sensitive epithelium. This explains, in part, why the use of diuretic drugs that work proximal to the K secretory site (loop and thiazide diuretics) often is accompanied by hypokalemia. K secretion is inversely proportional to the chloride concentration of the luminal fluid and is stimulated, for example, by luminal delivery of sodium bicarbonate (12). Conversely, hyperkalemia commonly accompanies acute kidney injury, particularly in the setting of mineralocorticoid deficiency (13–15). Such mineralocorticoid deficiency is often induced by drugs that interfere with the renin-angiotensin-aldosterone axis and commonly causes hyperkalemia in patients with chronic kidney disease, as well (16, 17). Sustained hyperkalemia is always attributable to inadequate renal K elimination. A detailed discussion of the causes of hyperkalemia in critically ill patients is beyond the scope of this article, but may be found in a recent review (18).

**Clinical Manifestations of Hyperkalemia**

Alterations in \( [K_p] \) have a variety of adverse clinical consequences, the expression of which may be magnified in the critically ill patient. The most serious of these manifestations are those involving excitable tissues.

**Cardiac Effects.** Hyperkalemia depolarizes the cell membrane, slows ventricular conduction, and decreases the duration of the action potential. These changes produce the classic electrocardiographic (EKG) manifestations of hyperkalemia including (in order of their usual appearance) peaked T waves, widening of the QRS complex, loss of the P wave, “sine wave” configuration, or ventricular fibrillation and asystole (19, 20). These EKG changes may be modified by a multitude of factors such as extracellular fluid pH, calcium concentration, sodium concentration, and the rate of rise of \( [K_p] \).
Table 1. Emergency treatment of hyperkalemia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane stabilization</td>
<td>Calcium gluconate (10%) 10 mL IV over 10 min</td>
<td>Immediate</td>
<td>30–60 min</td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Hypertonic (3%) sodium chloride 50 mL IV push</td>
<td>Immediate</td>
<td>Unknown</td>
<td>Volume overload hypertonicity</td>
</tr>
<tr>
<td>Redistribution</td>
<td>Insulin (short acting) 10 units IV push, with 25–40 g dextrose (50% solution)</td>
<td>20 min</td>
<td>4–6 hrs</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Albuterol 20 mg in 4 mL normal saline solution, nebulized over 10 min</td>
<td>30 min</td>
<td>2 hrs</td>
<td>Tachycardia inconsistent response</td>
</tr>
<tr>
<td>Elimination</td>
<td>Loop diuretics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Piroxic acid 40–80 mg IV</td>
<td>15 min</td>
<td>2–3 hrs</td>
<td>Volume depletion</td>
</tr>
<tr>
<td></td>
<td>bumetanide 2–4 mg IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium bicarbonate 100 mL/L IV at variable rate</td>
<td>Hours</td>
<td>Duration of infusion</td>
<td>Metabolic alkalosis volume overload</td>
</tr>
<tr>
<td></td>
<td>Sodium polystyrene sulfonate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Kayexalate, Kionex)</td>
<td>15–30 g in 15–30 mL (70% sorbitol orally)</td>
<td>&gt;2 hrs</td>
<td>4–6 hrs</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td></td>
<td>Immediate</td>
<td>3 hrs</td>
<td></td>
</tr>
</tbody>
</table>

IV, intravenously.

(19). Hospitalized patients with hyperkalemia are reported to have a higher mortality rate than those without hyperkalemia (21, 22), but the high prevalence of coexistent renal insufficiency in this population is a significant confounding variable that prevents attribution of the increased mortality to the hyperkalemia itself.

EKG changes may not accompany changes in $P_K$. The sensitivity of the electrocardiogram to reveal changes of hyperkalemia is quite low (23). It does increase in proportion to the severity of the hyperkalemia (23), but normal electrocardiograms have been seen even with extreme hyperkalemia (24) and the first cardiac manifestation of hyperkalemia may be ventricular fibrillation (25). (The explanation for a normal electrocardiogram in the setting of extreme hyperkalemia is not entirely clear, but may relate to a slow rate of rise in the $P_K$ (20, 24). Given this insensitivity of the electrocardiogram, EKG changes should not be considered necessary for the emergency treatment of severe hyperkalemia.

**Neuromuscular Effects.** Hyperkalemia may result in paraesthesias and weakness progressing to a flaccid paralysis, which typically spares the diaphragm. Deep tendon reflexes are depressed or absent. Cranial nerves are rarely involved and sensory changes are minimal (26, 27).

**Metabolic Effects.** Hyperkalemia decreases renal ammoniagenesis which by itself may produce a mild hyperchloremic metabolic acidosis (28), and will limit the kidney’s ability to excrete an acid load and, thus, prevent correction of a metabolic acidosis (29).

**Treatment of Severe Hyperkalemia**

In general, the initial treatment of severe hyperkalemia is independent of the cause of the disturbance, whereas the rational therapy of chronic hyperkalemia depends on an understanding of its pathogenesis.

In considering when hyperkalemia constitutes an emergency, several points should be kept in mind. First, the electrophysiologic effects of hyperkalemia are directly proportional to both the absolute $P_K$ and its rate of rise (19). Second, concurrent metabolic disturbances may ameliorate (e.g., hypernatremia, hypercalcemia, alkalosis) or exacerbate (e.g., hyponatremia, hypocalcemia, acidemia) the electrophysiologic consequences of hyperkalemia (20, 24). Third, although the EKG manifestations of hyperkalemia are generally progressive and proportional to the $P_K$, ventricular fibrillation may be the first EKG disturbance of hyperkalemia (25); conversely, a normal EKG may be seen even with extreme hyperkalemia (24).

With this in mind, it is apparent that neither the EKG nor the $P_K$ alone is an adequate index of the urgency of hyperkalemia, and that the clinical context must be considered when assessing a hyperkalemic patient. Thus, any pronouncement on an absolute $P_K$ value constituting an emergency must be seen as arbitrary. Nonetheless, since the treatment for acute hyperkalemia is safe if applied properly and hyperkalemia is potentially and unpredictably lethal, it is prudent to maintain a low threshold for instituting emergency therapy. Because most patients manifest hyperkalemic EKG changes at $P_K$ greater than 6.7 mmol/L (20), hyperkalemia should be treated emergently for 1) $P_K$ >6.5 mmol/L or 2) EKG manifestations of hyperkalemia regardless of the $P_K$ (30).

Therapy of acute or severe hyperkalemia is directed at preventing or ameliorating its untoward electrophysiologic effects on the myocardium. The goals of therapy, in chronologic order, are as follows (Table 1):

1. Antagonize the effect of K on excitable cell membranes.
2. Redistribute extracellular K into cells.
3. Enhance elimination of K from the body.

**Membrane Antagonism**

**Calcium.** Calcium directly antagonizes the myocardial effects of hyperkalemia without lowering $P_K$ (31, 32). It does so by reducing the threshold potential of cardiac myocytes, thereby restoring the normal gradient with the resting membrane potential, which is distorted by hyperkalemia (19, 20, 33). Calcium is beneficial even in patients who are normocalcemic. Calcium for injection is available as the chloride or gluconate salt, both 10% by weight. The preferred
agent is the gluconate salt, since it is less likely than calcium chloride to cause tissue necrosis if it extravasates (34). The recommended dose is 10 mL intravenous over 10 mins. The onset of action is <3 mins. The EKG should be monitored continuously. The dose may be repeated in 5 mins if there is no improvement in the EKG, or if the EKG deteriorates after an initial improvement. The duration of action is 30–60 mins, during which time further measures may be undertaken to lower $P_K$ (30).

There are several case reports of sudden death in patients given intravenous calcium while also receiving digitalis glycosides (35, 36). Although these anecdotes do not provide clear guidance, it is wise to administer intravenous calcium under very close supervision to patients known or strongly suspected to have toxic levels of digitalis glycosides.

**Hypertonic Saline.** Intravenous hypertonic sodium chloride has been shown to reverse the EKG changes of hyperkalemia in patients with concurrent hypotremia (37). This effect seems to be mediated by a change in the electrical properties of cardiomyocytes rather than by a reduction in $P_K$ (38). Whether hypertonic saline is effective in the treatment of eunatremic patients has not been known or strongly suspected to have toxic levels of digitalis glycosides.

**Intravenous hypertonic sodium chloride** has not been recommended for two reasons: first, endogenous insulin levels are unlikely to rise to the level necessary for a therapeutic effect; and second, there is a risk of exacerbating the hyperkalemia by inducing hypertoncity (46).

**β-adrenoceptor Agonists.** An appreciation for the effect of catecholamines on internal potassium balance recently has been applied to the clinic. Patients with renal failure given the selective β2-adrenoceptor agonist, albuterol, by intravenous infusion (0.5 mg over 15 mins) show a significant decline in $P_K$ (about 1 mmol/L) that is maximal between 30 and 60 mins (47). Because injectable albuterol is unavailable in the United States, it is encouraging to note that nebulized albuterol in a high dose, administered to patients with end-stage renal disease, has a similar effect: $P_K$ declines by 0.6 mmol/L after inhalation of 10 mg of albuterol, and by about 1.0 mmol/L after 20 mg (41, 42, 48, 49). Note that the effective dose is at least four times higher than that typically used for bronchodilation (50), although a smaller decline in $P_K$ (about 0.4 mmol/L after 60 mins) is seen even with a metered-dose inhaler (51). The effect of high-dose therapy is apparent at 30 mins and persists for at least 2 hrs (48). The effect of insulin is additive with that of albuterol, with the combination reported to result in a decline in $P_K$ by about 1.2 mmol/L at 60 mins (42).

**Enhanced Renal Elimination.** Hyperkalemia occurs most often in patients with renal insufficiency. However, renal K excretion may be enhanced even in patients with significant renal impairment by increasing the delivery of solute to the distal nephron, the site of K secretion.

Studies using acetazolamide show that bicarbonate delivery to this site in the nephron has a particular kaliuretic effect (58), even in patients with renal insufficiency (59). It would be unwise to
administer acetazolamide alone to most patients with hyperkalemia, since they tend to present with a concomitant metabolic acidosis that would be exacerbated by the drug. But a sodium bicarbonate infusion administered during 4–6 hrs at a rate designed to alkalize the urine may enhance urinary K excretion (53), and would be desirable especially in patients with metabolic acidosis. The risk of volume expansion with the bicarbonate infusion can be mitigated by the use of loop-acting diuretics, which would be likely to further enhance the kaliuretic effect. Loop-acting diuretics alone or in combination with a thiazide diuretic will induce a kaliuresis and will be beneficial in the volume expanded patient. Diuretic-induced volume contraction must be avoided since this will lead to decreased distal nephron flow and reduced K excretion (30).

Exchange Resin. Sodium polystyrene sulfonate (SPS, Kresylate, Kionex) is a cation-exchange resin that is prepared in the sodium phase but has a higher affinity for potassium than sodium (60). In the lumen of the intestine, it exchanges sodium for secreted potassium. Most of this exchange takes place in the colon, the site of most potassium secretion in the gut (61, 62). Each gram of resin binds approximately 0.65 mmol of potassium in vivo, although the effect is highly variable and unpredictable (63). The resin causes constipation and, hence, almost always is given with a cathartic. It may be given orally or by retention enema, although the oral route is considered to be more effective because of the longer transit time through the gut lumen (3).

There are two concerns with the use of SPS for the treatment of urgent hyperkalemia. The first is its slow effect. When given orally, the onset of action is at least 2 hrs and the maximum effect may not be seen for 6 hrs or more (60). The effect of SPS as a retention enema is more rapid but of lesser magnitude. One recent study in normokalemic hemodialysis patients failed to show any effect on P_k during 12 hrs after an oral dose of 30 g of SPS with cathartic (64). Indeed, early studies with this agent showed very little effect over and above that of sorbitol alone (60). The second concern with SPS is its possible toxicity. There are numerous case reports of patients who have developed intestinal necrosis after exposure to SPS in sorbitol as an enema (63, 65–69), and as an oral agent (66, 70–74). A retrospective study estimated the prevalence of colonic necrosis to be 1.8% among postoperative patients receiving SPS (75). Thus, the slow onset of action and serious, albeit infrequent, toxicity make SPS a poor choice for the treatment of urgent hyperkalemia.

Dialysis. Hemodialysis is the method of choice for removal of potassium from the body. P_k falls by over 1 mmol/L in the first 60 mins of hemodialysis and a total of 2 mmol/L by 180 mins, after which it reaches a plateau (3, 76). Rebound always occurs after dialysis, with 35% of the reduction abolished after an hour and nearly 70% after 6 hr; the magnitude of the postdialysis P_k is proportional to the predialysis P_k (77). There is controversy as to whether dialysis for severe hyperkalemia precipitates serious ventricular arrhythmias (78–84). Because of that possibility, patients dialyzed for severe hyperkalemia should have continuous EKG monitoring (3).

The rate of potassium removal with peritoneal dialysis is much slower than with hemodialysis. Indeed, much of the decrement in P_k with peritoneal dialysis seems to be due to translocation of potassium into cells as a result of the glucose load rather than extracorporeal disposal. This modality may be used for patients on maintenance peritoneal dialysis who have modest hyperkalemia (3).

CONCLUSION

Hyperkalemia is one of the few potentially lethal electrolyte disorders. Its rational treatment has evolved as a result of our more complete understanding of the physiology of potassium homeostasis. The sequential approach to the treatment of urgent hyperkalemia still pertains. Calcium gluconate is the preferred agent to immediately reverse the adverse electrophysiologic effects of hyperkalemia, although hypertonic saline may be used in selected circumstances. Insulin is the most reliable agent for translocating K into cells, but β-adrenoceptor agonists provide some additional benefit in about 60% of patients. Terbutaline may have some utility in this regard, but its use has never been studied in patients with heart disease. β-adrenoceptor agonists should never be used without insulin for this purpose, since about 40% of patients will have no response. Sodium bicarbonate seems to have no effect to shift K into cells, even after several hours. It is likely to be effective, especially in combination with a diuretic drug, in enhancing urinary K elimination in patients with some kidney function, although it use for this purpose has not been systematically evaluated. SPS resin has a slow onset of action and debatable efficacy. Furthermore, it carries the small risk of intestinal necrosis. Hemodialysis remains the most reliable tool for removing K from the body in patients with kidney failure.

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