

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.

Results and Conclusions: A more complete understanding of potassium homeostasis in recent years has led to new approaches to the management of severe hyperkalemia. The physiologically based sequential approach still applies. The efficacy, pitfalls, and risks of the agents available for use at each step in the sequence are critically reviewed. Rational use of the available tools will allow clinicians to successfully treat severe hyperkalemia. (Crit Care Med 2008; 36:000–000)

KEY WORDS: ●●●

Hyperkalemia 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 (P_K) normally is maintained within very narrow limits. This tight regulation is accomplished by two cooperative systems. One system defends against short-term changes in P_K 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 tonicity, 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 defi-

ciency (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 P_K 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 P_K (19). Hospitalized patients with hyperkalemia are reported to have a higher mor-

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DOI: 10.1097/CCM.0b013e31818f222b

Table 1. Emergency treatment of hyperkalemia

Agent	Dose	Onset	Duration	Complications
Membrane stabilization				
Calcium gluconate (10%)	10 mL IV over 10 min	Immediate	30–60 min	Hypercalcemia Volume overload hypertonicity
Hypertonic (3%) sodium chloride	50 mL IV push	Immediate	Unknown	
Redistribution				
Insulin (short acting)	10 units IV push, with 25–40 g dextrose (50% solution)	20 min	4–6 hrs	hypoglycemia
Albuterol	20 mg in 4 mL normal saline solution, nebulized over 10 min	30 min	2 hrs	Tachycardia inconsistent response
Elimination				
Loop diuretics				
Furosemide	40–80 mg IV	15 min	2–3 hrs	Volume depletion
Bumetanide	2–4 mg IV			
Sodium bicarbonate	150 mmol/L IV at variable rate	Hrs	Duration of infusion	Metabolic alkalosis volume overload
Sodium polystyrene sulfonate (SPS, Kayexalate, Kionex)	15–30 g in 15–30 mL (70% sorbitol orally)	>2 hrs	4–6 hrs	Variable efficacy intestinal necrosis
Hemodialysis		Immediate	3 hrs	Arrhythmias (?)

tality 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 ammoniogenesis 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, alkalemia) 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 that 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 hyponatremia (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 established. Until such benefit has been demonstrated, the use of hypertonic (3%) saline should be restricted to hyponatremic patients with hyperkalemia, with an awareness of the volume overload that may ensue.

Redistribution of Potassium into Cells

Insulin. Insulin reliably lowers P_K in patients with end-stage renal disease (39–43), confirming its effect to shift K into cells. The effect of insulin on potassium is dose dependent from the physiologic through the pharmacologic range (5). It is mediated by activation of Na, K-ATPase, apparently by recruitment of intracellular pump components into the plasma membrane (4, 44). An intravenous dose of ten units of regular insulin given as a bolus along with an intravenous bolus of dextrose (25 g as a 50% solution) to anephric adult patients lowers the P_K by about 0.6 mmol/L (42). The onset of action is <15 mins and the effect is maximal between 30 and 60 mins after a single bolus (41, 42). After the initial bolus, a dextrose infusion should be started, since a single bolus of 25 g of dextrose has been shown to be inadequate to prevent hypoglycemia at 60 mins (42). It is interesting to note that when insulin was given by continuous intravenous infusion for 4 hrs to normal volunteers, P_K

fell over the first 90 mins and rose thereafter (45). Based on that observation, there seems to be no advantage of a continuous infusion over a bolus injection.

Insulin should be used without dextrose in hyperglycemic patients; indeed, the cause of the hyperkalemia in those patients may be the hyperglycemia itself (46). The administration of hypertonic dextrose alone for hyperkalemia is not 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 hypertonicity (46).

B-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 β_2 -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 ESRD, 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). More recently, subcutaneous terbutaline (7 $\mu\text{g}/\text{kg}$ body weight) has been shown to reduce P_K in selected dialysis patients by an average of 1.3 mmol/L within 60 mins (52). Mild tachycardia is the most common reported side effect of high-dose nebulized albuterol or terbutaline. Patients taking nonselective β -adrenoceptor blockers will be unlikely to manifest the hypokalemic effect of albuterol. Even among patients not taking β -blockers, as many as 40% seem to be resistant to the hypokalemic effect of albuterol (42, 48). The mechanism for this resistance is unknown, and there is currently no basis for predicting which patients will respond. For that reason, albuterol should never be used as a single

agent for the treatment of urgent hyperkalemia in patients with renal failure.

Bicarbonate. The putative benefits of a bolus injection of sodium bicarbonate in the emergency treatment of hyperkalemia pervaded the literature until the past decade. Ironically, this dogma was based on studies using a prolonged (4–6 hrs) infusion of bicarbonate (53). It has now been clearly demonstrated that short-term bicarbonate infusion does not reduce P_K in patients with dialysis-dependent kidney failure, implying that it does not cause K shift into cells. Infusion of a hypertonic or an isotonic bicarbonate solution for 60 mins has been shown to have no effect on P_K in dialysis patients, despite a substantial increase in serum bicarbonate concentration (40, 54–56). Only after a 4-hr infusion was a small (0.6 mmol/L) but significant decrease in P_K is detectable (57). Whether bicarbonate infusion might enhance insulin-mediated cellular K uptake remains unresolved by two contradictory studies (54, 56). The absence of a demonstrable effect of bicarbonate to shift K into cells over the short term is not to imply that bicarbonate might not be useful in the emergency treatment of hyperkalemia; rather, that its onset and mechanism of action are quite different from conventional wisdom has held (see below). Furthermore, the foregoing is not meant to imply that sodium bicarbonate should be withheld from the hyperkalemic patient with metabolic acidosis; rather, that no short-term effect on the P_K should be anticipated.

Elimination of Potassium from the Body

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 alkalinize 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, Kayexalate, 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 postrebound 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 its 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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