Approach to Hyperkalemia

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ABSTRACT

Hyperkalemia is commonly found in hospitalized patients. Given the fact that untreated hyperkalemia is associated with high morbidity and mortality, it is critical to recognize and treat this disorder promptly. Patients at greatest risk for hyperkalemia include those with diabetes or impaired renal function, those with advanced age and those receiving drugs which interfere with renal potassium excretion. Hyperkalemia is likely to become an even more common clinical event, since ACE inhibitors, angiotensin-receptor blockers and aldosterone antagonists are increasingly being used in higher doses and in combination, in the belief that these measures provide additional cardiovascular and renal protection. The urgency of hyperkalemia treatment is dictated by the change in electrocardiogram. Treatment of hyperkalemia includes calcium gluconate, insulin, beta agonists, sodium bicarbonate, cation exchange resin, diuretics and/or dialysis.

Key words: *hyperkalemia, potassium shift, metabolic acidosis, sodium bicarbonate.*

INTRODUCTION

Potassium is the most abundant cations in cells. Approximately 98% of the total potassium is located intracellular, primarily in skeletal muscle and to a lesser extent in liver. The remaining 1 to 2% is located extracellular. Although only 2% of total body potassium is located extracellular, a small change in extracellular K^+ has a major effect on the resting membrane potential. As a result, serum K^+ concentration is normally regulated around the narrow range of 3.5-5.0 mmol/l. Given the fact that untreated hyperkalemia is associated with high morbidity and mortality, it is critical to recognize and treat this disorder promptly.

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REGULATION OF POTASSIUM HOMEOSTASIS

The usual Western diet contains approximately 100 mmol of K^+ per day. The daily dietary K^+ intake in Asian population is lower.[1] After ingestion; K^+ is rapidly absorbed by the gut. Approximately, 90% of K^+ intake is excreted in the urine and the remaining in the stool and (a negligible amount) in sweat. The kidney is, therefore, responsible for long term K^+ homeostasis. However, K^+ excretion by the kidney is a relatively slow process. It takes 6-12 hr to excrete an acute K^+ load. To minimize transient and potentially marked increases in serum K^+ concentration after ingestion, several physiological mechanisms quickly shift potassium intracellularly, pending excretion by the kidney. The major regulators of K^+ shifts into cells are insulin and stimulation of β2-adrenergic receptors. (Table 1) Unlike renal K^+ excretion, potassium shift between the extracellular and intracellular fluid compartment is extremely rapid, occurring within minutes. This will prevent life-threatening hyperkalemia following a potassium-rich meal or potassium administration.

Both insulin and β2-adrenergic catecholamine increase cellular K^+ uptake by stimulating cell-membrane Na^+/K^+-ATPase. The Na^+/K^+-ATPase pumps positive voltage out of cells; it extrudes three Na^+ ions for every two K^+ ions that enter cells.[2] The main hormones that increase the activity of Na^+/K^+-ATPase are β2-adrenergic agonists and thyroid hormone. For insulin, there is a feedback system in which hyperkalemia stimulates insulin secretion and hypokalemia inhibits it.[3] No feedback system has been identified for β2-adrenergic stimulation. Beta2-adrenergic stimulation results in a shift of K^+ into the cell, while a stimulation has the opposite effect.[4] In addition to these physiological regulators, internal K^+ homeostasis is also affected by changes in acid-base and osmolality. Changes in extracellular osmolality can create a solvent drag phenomenon, and shifts K^+ out of the cell, resulting in hyperkalemia. The effect of acid-base status is much more complicated and depends on the nature of the disorder. As a general rule, metabolic alkalosis shifts K^+ into the cells, whereas metabolic acidosis shifts K^+ out of the cells.

Table 1. Regulators of Potassium Homeostasis

Regulators	Mechanism of action	Effect
Insulin	Activation of Na^+/K^+-ATPase	Hypokalemia
Catecholamines	Activation of β2-receptors Activation of α-receptors	Hypokalemia Hyperkalemia
Thyroid Hormone	Activation of Na^+/K^+-ATPase	Hypokalemia
Mineralocorticoid	Activation of Na^+/K^+-ATPase	Hypokalemia
Metabolic Alkalosis	Exchange H^+ for K^+	Hypokalemia
Mineral (Normal Anion Gap) Acidosis		Hyperkalemia
Organic (High Anion Gap) Acidosis		Normokalemia

RENAL POTASSIUM HANDLING

The primary site that regulates K^+ excretion is the collecting duct (CD). Along the CD, K^+ is both secreted and absorbed. Secretion of K^+ occurs primarily in the initial collecting tubule and the cortical collecting duct. Potassium secretion in the CD is variable and depends on dietary K^+ intake. At least three cell types are present in the CD. (Figure1) The cell that is mainly responsible for K^+ secretion in the CD is the principal cell. This cell possesses a basolateral membrane Na^+/K^+-ATPase, which is responsible for the active transport of Na^+ out of and K^+ into the cell. The resultant low cell Na^+ concentration and high cell K^+ concentration provide favorable diffusion gradients for the movement of Na^+ from lumen to cell and K^+ from cell to lumen across the apical membrane. In contrast to the principal cell, the á-intercalated cell is responsible for reabsorption of K^+ and secretion of H^+. The main pump for luminal H^+ secretion is an apical H^+-ATPase. A second ATPase, the H^+/K^+-ATPase, is also involved in H^+ secretion, but its physiologic role is more related to K^+ than to acid-base homeostasis. Intracellularly formed HCO_3^- leaves the cell by an electroneutral mechanism involving a basolateral band 3-like Cl^-/HCO_3^- exchanger.[5] Thus these pumps contribute to both acidification and K^+ reabsorption.[6] The b-intercalated cell is believed to mediate HCO_3^- secretion and recovery from metabolic alkalosis through an apical membrane Cl^-/HCO_3^- exchanger, that is distinct from the basolateral band-3 like Cl^-/HCO_3^- exchanger in the a-intercalated cells.[7]

Five major physiologic factors stimulate K^+ secretion in the CD: aldosterone, high Na^+ delivery to the CD, high urine flow rate, high serum K^+ level and delivery of negatively charged ions to the CD (e.g., bicarbonate). Aldosterone directly increases the activity of the basolateral membrane Na^+/K^+-ATPase, thereby stimulating secretion of K^+ into the tubular lumen. In addition, aldosterone also increases the permeability of the apical membrane to K^+ and directly stimulates Na^+ reabsorption across the apical membrane, which depolarizes the cell relative to the lumen, thereby increasing the electrical gradient favoring K^+ secretion. Medical conditions that impair aldosterone production (e.g., type IV renal tubular acidosis) or drugs that inhibit aldosterone production (e.g., ACE inhibitors, heparin, spironolactone, eplerenone) decrease K^+ secretion by the kidney and thereby can cause hyperkalemia. Another important factor that effects K^+ secretion is the distal delivery of Na^+ and water. Increased distal delivery of Na^+ stimulates distal Na^+ reabsorption. This creates an electronegative charge within the tubular lumen, which in turn promotes the secretion of cations (K^+ and H^+) into the lumen. Many diuretics increase renal K^+ excretion by a number of mechanisms, including high distal Na^+ delivery, high urine flow rate, metabolic alkalosis and secondary hyperaldosteronism due to volume depletion. Poorly controlled diabetes commonly increases urinary K^+ excretion due to osmotic diuresis with high urinary flow rate and high distal delivery of Na^+. Reabsorption of Na^+ across the apical membrane in the CD occurs through an epithelial sodium channel (ENaC). Therefore, drugs that block the sodium channel in the CD (e.g., amiloride, triamterene, trimethoprim, pentamidine) decreases K^+ secretion. (Figure 1)

CLINICAL MANIFESTATION OF HYPERKALEMIA

Hyperkalemia is often asymptomatic and is discovered on routine laboratory tests. Patients with severe hyperkalemia (serum K^+ >6.5 mmol/l) may, however, present with generalized weakness, ileus, paralysis, respiratory failure and cardiac arrhythmia, including cardiac stand still and sudden death. In addition, hyperkalemia will decrease ammonia production. In general, the severity of clinical presentation does correlate with the severity of hyperkalemia. Changes in the electrocardiogram (ECG)

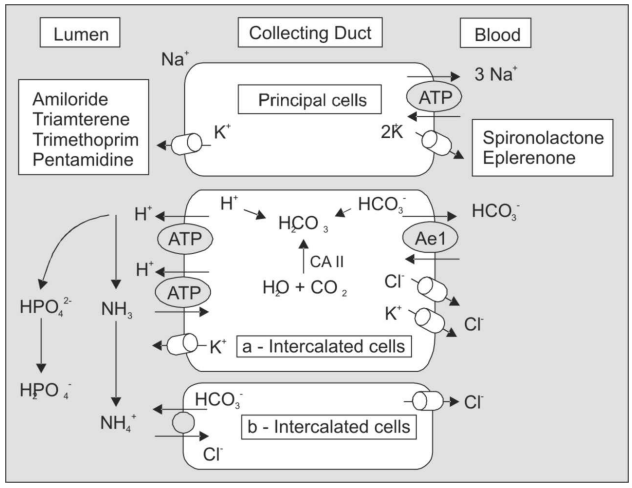

Figure 1. Regulation of renal potassium excretion and absorption in the collecting duct

Table 2. Causes of Hyperkalemia

Pseudohyperkalemia
Hemolysis, improper blood drawing (fist clenching)
Severe leukocytosis or thrombocytosis
Familial pseudohyperkalemia
Abnormal potassium redistribution
Familial hyperkalemic periodic paralysis
Metabolic or respiratory acidosis
Insulin deficiency, hyperosmolality (e.g., hyperglycemia)
Rhabdomyolysis, tumor lysis syndrome
Increased potassium intake
Impaired renal potassium excretion
Acute or chronic renal failure
Mineralocorticoid deficiency
Low renin (diabetic nephropathy, interstitial nephritis)
Normal or high renin (Addison's disease, congenital adrenal hyperplasia, isolated hypoaldosteronism)
Mineralocorticoid resistance (interstitial nephritis, obstructive uropathy, pseudohypoaldosteronism)
Drugs-induced hyperkalemia
ACE inhibitors, ARB, aldosterone antagonist (spironolactone, eplerenone)
NSAIDs
Calcineurin inhibitors (cyclosporine, tacrolimus)
Beta blockers
Inhibitors of aldosterone biosynthesis (heparin, ketoconazole)
Sodium channel blockers (amiloride, triamterene, trimethoprim, pentamidine)
Succinylcholine
Digitalis toxicity

also reflect the severity of hyperkalemia. Peaked, narrow-based T waves are the earliest sign of hyperkalemia. If hyperkalemia is more severe (serum K^+ level above 7 mmol/l), the P wave broadens and the QRS interval widens, followed by loss of P wave. In extreme hyperkalemia, the ECG shows sine wave, often followed by ventricular fibrillation.

APPROACH TO HYPERKALEMIA

Before evaluating the etiology of hyperkalemia, it is important first to address the potential emergency of severe hyperkalemia to determine whether an urgent therapy is needed. Patients with severe hyperkalemia are at increased risk of life-threatening cardiac arrhythmias and respiratory muscles paralysis. This possible threat is best evaluated by examining the ECG. It is important to distinguish between true hyperkalemia and pseudohyperkalemia. Pseudohyperkalemia is suggested by the absence of ECG findings in patients with elevated serum potassium. The most common cause of pseudohyperkalemia is hemolysis and improper blood drawing (fist clenching). Ischemia due to tight or prolonged tourniquet application or fist clenching increases serum potassium concentrations by as much as 1.0 to 1.6 mmol/l. Extreme leukocytosis or thrombocytosis can result in leakage of potassium from these cells. This can be confirmed by remeasuring serum K^+ in a blood sample collected in a heparinized sample tube.[8] Familial pseudohyperkalemia is a rare autosomal disorder of temperature-dependent leakage of K^+ out of the cell.[9]

Drugs prescribed by physicians are the most common causes of hyperkalemia. (Table 2) Thus, the first step in the evaluation of hyperkalemia is to review the patient's drug record. In the absence of an inciting drug, hyperkalemia can result from an acute shift of potassium from the cells to extracellular compartment, from increased intake, or from impaired renal K^+ excretion. Most commonly, the clinical history, review of medications, and physical examination are sufficient in making the diagnosis of hyperkalemia. In some cases however, the etiology of hyperkalemia is not apparent and additional laboratory tests may be needed. To evaluate the adequacy of renal response to hyperkalemia, a calculation called the transtubular potassium gradient (TTKG) has been developed.[10] The TTKG is an index of potassium gradient between the urine and the blood in the CD. To perform this test requires measuring serum and urine K^+ levels and osmolality according to the following equation:

$$TTKG = \frac{(\text{Urine potassium} \times \text{serum osmolality})}{(\text{serum potassium} \times \text{urine osmolality})}$$

In a normal individual and under normal circumstances, the TTKG is about 6 to 8. In patients with hyperkalemia, the TTKG is greater than 8. An inappropriately low TTKG in a hyperkalemic patient suggests hypoaldosteronism or a renal tubule defect.

This test cannot be applied when the urine osmolality is less than the serum osmolality.[11]

If urinary potassium excretion is low, the next step is to measure serum aldosterone level to determine whether it is due to low aldosterone or to resistance to aldosterone effect (Table 2). In patients with underlying renal disease, hypoaldosteronism with or without a low renin level is a very common finding. Diabetic nephropathy and interstitial nephritis account for the majority of cases of hyporeninemic hypoaldosteronism. The causes of hyperkalemia with low aldosterone and normal to increased serum renin level include Addison's disease, congenital adrenal hyperplasia, and isolated hypoaldosteronism. The most important causes of hyperkalemia with mineralocorticoid resistance are interstitial nephritis, obstructive uropathy, and pseudohypoaldosteronism type I and type II. Pseudohypoaldosteronism type I is a rare disorder characterized by mineralocorticoid resistance that typically presents in the newborn. Clinical findings include hyperkalemia, metabolic acidosis, and a tendency toward volume depletion due to renal salt wasting.[12] Pseudohypoaldosteronism type II (Gordon syndrome) is an autosomal dominant disease characterized by severe hypertension, hyperkalemia, metabolic acidosis and sensitivity to thiazide diuretics.[12]

Patients with renal failure can often maintain near normal serum K^+ unless glomerular filtration rate (GFR) decreases below 15 ml/min. Increase in potassium intake could result in hyperkalemia, only if associated with defect in K^+ excretion. Salt substitutes, which may contain as much as 200 mmol of K^+ per table spoon, are major hidden sources of ingested potassium.

Abnormal K^+ redistribution is more important as a cause of hyperkalemia than as a cause of hypokalemia. Sudden increases in serum osmolality will cause K^+ to move out of cells. This occurs most frequently in diabetics when their blood glucose rises. Hyperchloremic metabolic acidosis (in contrast to high anion gap metabolic acidosis) causes K^+ to shift out of cells. Although ketoacidosis and lactic acidosis are associated with K^+ shifts out of cells, this is due to hyperosmolality and insulin deficiency in ketoacidosis and cell ischemia in lactic acidosis. Tissue damage due to rhabdomyolysis or tumor lysis syndrome causes K^+ to move out of cells. Familial hyperkalemic periodic paralysis is a rare disorder due to mutations in the Na^+ channel SCN4A gene.[13] Whereas a high-carbohydrate diet is a risk factor for attacks in the hypokalemic periodic paralysis, fasting increases the risk of attack in the hyperkalemic form. Administration of K^+ can precipitate weakness in the hyperkalemic periodic paralysis.

DRUG-INDUCED HYPERKALEMIA

Drugs that alter K^+ redistribution or interfere with renin angiotensin aldosterone system can induce hyperkalemia. ACE inhibitors, angiotensin-receptor blockers (ARB) and aldosterone antagonists are increasingly being used in higher doses and in combination, in the belief that these measures provide additional cardiovascular and renal protection.[14-16] ACE inhibitors and ARB impair urinary potassium excretion by interfering with the stimulatory effect of angiotensin II on aldosterone secretion. Nonsteroidal anti-inflammatory drugs (NSAIDs) interfere with the stimulatory effect of prostaglandins on the release of renin with the subsequent fall in aldosterone concentrations. Cyclosporine or tacrolimus suppresses the release of renin and directly interferes with the secretion of K^+ in the CD. Beta blockers alone are rarely associated with significant hyperkalemia; however, they could play a contributory part. These drugs cause hyperkalemia by inhibiting the release of renin and by interfering with the cellular uptake of K^+ through decreased activity of Na^+/K^+-ATPase. Heparin impairs aldosterone synthesis by inhibiting the enzyme 18-hydroxylase. Despite its frequent use, heparin is rarely associated with overt hyperkalemia. Ketoconazole interferes with the biosynthesis of adrenal steroids and therefore can predispose patients to aldosterone deficiency. Drugs that block ENaC in the CD such as amiloride, triamterene, trimethoprim, and pentamidine decrease K^+ secretion. Depolarizing muscle relaxants such as succinylcholine increase permeability of muscle cells and should be avoided by hyperkalemic patients. Digitalis overdose can cause hyperkalemia because digitalis impairs the function of the Na^+-K^+-ATPase pumps and blocks the entry of K^+ into cells.

TREATMENT OF HYPERKALEMIA

In general, the risk of hyperkalemia increases as renal function declines. However, an estimated GFR of 30 ml per minute should be considered a threshold below which the likelihood that hyperkalemia will develop substantially increases. Drugs that can induce hyperkalemia should be reduced or discontinued. (Table 2) The initial management should be dictated by the changes in ECG. Thus, hyperkalemia with any ECG changes should be treated as an emergency and treatment should begin immediately with infusion of 10 ml of 10% calcium gluconate to stabilize the myocardium. Onset of action is 1-2 minutes. This should be followed by administering 50 ml of 50% dextrose and 10 U of regular insulin IV to help shift K^+ into the cell. The serum K^+ usually starts to decrease within 15 minutes. Another way to shift K^+

intracellularly is to give β2-adrenergic agonist by inhalation over 10 minutes (e.g., 10 ml of salbutamol). The concentrated form (5 mg/ml) of the drug should be used to minimize the volume that need to be inhaled. The onset of action is 30 minutes. Sodium bicarbonate (e.g., 100 ml of 8.4% $NaHCO_3$) can also be given intravenously over 5 minutes to move K^+ into the cells if there is no contraindication (e.g., hypernatremia). The onset of action is 15-30 minutes. Following these emergent therapies, a more definitive treatment with caution exchange resin, diuretics and/or dialysis should be done to remove K^+ from the body. Diuretics can be used if the patient has adequate renal function. Caution exchange resin mixed with sorbitol should be used orally if hyperkalemia is not life threatening. However, resin mixed with water (and not sorbitol) can be repeated hourly for rapid removal of potassium.

After the acute treatment of hyperkalemia, a long term plan should be devised to prevent recurrence of hyperkalemia.[17] Patients should follow a low-potassium diet with specific counseling against the use of salt substitutes that contain potassium. Diuretics are particularly effective in minimizing hyperkalemia. Sodium bicarbonate can be prescribed to correct metabolic acidosis in patients with chronic kidney disease. It is best to begin treatment with an ACE inhibitor or an ARB with low doses. Serum potassium should be checked within one week. If serum potassium is normal, the dose can be titrated upward. If serum potassium increases above 5.5 mmol/l, the dose can be lowered. Whenever possible, drugs that interfere in renal potassium secretion should be discontinued. Patients should be asked specifically about the use of over-the-counter NSAIDs and herbal preparations, since a lot of herbs contain potassium.

CONCLUSION

Hyperkalemia is commonly found in hospitalized patients. Severe hyperkalemia is associated with high morbidity and mortality. Patients at greatest risk for hyperkalemia include those with diabetes or impaired renal function, those with advanced age and those receiving drugs which interfere with renal potassium excretion. The urgency of hyperkalemia treatment is dictated by the change in electrocardiogram. Drugs that impair renal potassium excretion should be reduced or discontinued. Over-the-counter use of NSAIDs, herbal remedies or salt substitutes should be inquired and discontinued whenever possible. Treatment of hyperkalemia includes calcium gluconate, insulin, beta agonists, sodium bicarbonate, cation exchange resin, diuretics and/or dialysis.

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