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Management of Hyperkalemia in the ED

A 34 year-old male with a PMH of uncontrolled hypertension presents to the ED with complaints of feeling fatigued, nauseated, diffuse itching and myalgias, and slightly short of breath for 3 days. Physical exam reveals only some bibasilar crackles and 1+ pitting LE edema. Work-up reveals an EKG with a long PR interval, a widened QRS complex, a prolonged QT interval, and peaked T waves. CXR reveals mild bilateral pleural effusions and pulmonary vascular congestion. Labs return with a critical potassium level of 8.3mEq/L. It is assumed that the patient is in renal failure as a result of his uncontrolled hypertension and as a result, is now experiencing symptomatic hyperkalemia.

The most serious manifestations of hyperkalemia are **muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias**. These manifestations usually occur when the serum potassium concentration is **≥ 7.0 mEq/L with chronic hyperkalemia or possibly at lower levels with an acute rise in serum potassium**.[1] While the probability of EKG abnormalities increases with increasing serum potassium concentrations, the **EKG overall is an insensitive tool for the diagnosis of hyperkalemia**.[2]

Hyperkalemia should be aggressively managed to prevent the potentially lethal effects on the cardiac myocyte membrane potential, even in the asymptomatic patient. It has been proposed that hyperkalemia be treated at serum levels **≥ 6.5mEq/L with symptoms, or ≥ 7.0mEq/L without symptoms, or in lesser degrees of hyperkalemia with a serum potassium that is rapidly rising or expected to rise, such as in crush injuries, rhabdomyolysis, or in tumor lysis syndome**. Given the unreliable sensitivity of EKG in detecting hyperkalemia, serial measurements of potassium concentration should guide therapy. It is recommended that serum potassium be **measured at 1-2 hours after the initiation of therapy**, followed by repeat measurements as indicated by the serum potassium levels and patient response to therapy.[1]

The management of hyperkalemia is aimed at three approaches: **1) antagonizing the membrane effect of potassium with calcium, 2) driving extracellular potassium into the cells, and 3) removing excess potassium from the body**.[1] In general, the rapidly-acting interventions are aimed at driving extracellular potassium into the cells and providing time for initiating interventions with a much slower time of onset which remove excess potassium. The following interventions are generally listed in order of their time of onset.[3]

Calcium

Hyperkalemia leads to depolarization of cardiac resting membrane potential, which leads to inactivation of sodium channels and thus decreased membrane excitability. Additionally, hypocalcemia increases the cardiotoxicity of hyperkalemia. Therefore, calcium is given intravenously to **stabilize cardiac membrane potential** and prevent

potentially lethal arrhythmias from occurring. It may be given as either calcium chloride 500mg-1,000mg or calcium gluconate 1,000mg, **both infused over 2-3 minutes, and can both be repeated after 5 minutes if the EKG changes persist or recur**. The only differences are that calcium chloride contains three times the concentration of elemental calcium compared to calcium gluconate and can thus be irritating to peripheral veins and, if extravasation occurs, can cause tissue necrosis. As a result, calcium chloride should only be given via central venous access. The **time of onset is ~5 minutes, and the duration of action is 30-60 minutes**.

Insulin and glucose

Administration of insulin drives potassium into the cells through enhanced Na-K-ATPase pump activity in skeletal muscle. A typical regimen involves administering a bolus dose of 10 units of regular insulin followed by a 50mL dose of 50% dextrose (25g of glucose) to prevent the effects of hypoglycemia that typically occur about 1 hour after the administration of insulin. If the serum glucose is $\geq$ 250mg/dL, insulin should be given alone. The serum glucose should be measured one hour after the administration of insulin and additional glucose can be infused as 10% dextrose at 50-75mL/hr if the patient is hypoglycemic. It is expected that most patients would have their serum potassium **drop by 0.5-1.2mEq/L**. The **time of onset is ~10-20 minutes, with a peak onset of 30-60 minutes, and duration of action of 4-5 hours**.

Beta-2-adrenergic agonists

Beta-2-adrenergic agonists, such as albuterol, work similarly to insulin by driving potassium into the cell through increased Na-K-ATPase pump activity in skeletal muscle. They also, however, increase the activity of the Na-K-2Cl cotransporter which may account for up to one-third of the uptake response to catecholamines.[4] Albuterol may be given as **10-20mg in 4mL of saline by nebulization** over 10 minutes, lowering the serum potassium **by 0.5-1.5mEq/L, with a peak effect seen within 90 minutes with nebulization**. Alternatively, albuterol 0.5mg may be given IV, with similar effects on serum potassium concentrations, but a peak onset seen within 30 minutes. **Albuterol and insulin together have an additive effect**, reducing serum potassium concentration by 1.2-1.5mEq/L.[5]

Sodium Bicarbonate

Administration of sodium bicarbonate results in an elevated serum pH, which results in hydrogen ion release from cells as a buffering reaction. The release of hydrogen ions into the serum then stimulates the potassium ion movement into the cell to maintain electroneutrality.[1] It has been recommended that bicarbonate be given for the treatment of hyperkalemia, but this recommendation was based upon small uncontrolled clinical studies.[1,6-8] However, in a study that compared different potassium-lowering modalities in 10 patients undergoing maintenance hemodialysis, a bicarbonate infusion for up to 60 minutes had **no effect on the serum potassium concentration**.[1,9] This lack of benefit was confirmed in several subsequent studies of hemodialysis patients.[1,10-12]

Given the limited efficacy, it is not recommended to administer sodium bicarbonate as monotherapy for the acute management of hyperkalemia, even in patients with mild to

moderate metabolic acidosis.[1,9-12] However, prolonged bicarbonate therapy appears to be beneficial in patients with metabolic acidosis. In one series, for example, the administration of isotonic sodium bicarbonate in a constant infusion to patients with a baseline serum bicarbonate of 18mEq/L had little effect at one and two hours, but significantly lowered the potassium from 6mEq/L at baseline to 5.4 and 5.3 mEq/L at four and six hours; the serum bicarbonate increased to 28mEq/L at one hour and 30mEq/L at six hours.[1,11] However, this may not be a likely treatment intervention in the setting of the emergency department given the time duration required for treatment effect.

Efficacy in End-Stage Renal Disease

In the setting of ESRD, one report found the following mean changes in the serum concentration at one hour after the initiation of the following therapies in hyperkalemic patients requiring maintenance hemodialysis[9]:

- A 0.85 meq/L reduction with **insulin and glucose**
- A 0.3 meq/L reduction with epinephrine; a greater response, similar to that with insulin and glucose, is typically seen with **albuterol** which has no alpha-adrenergic activity
- No change with sodium bicarbonate
- A 1.3 meq/L reduction with **hemodialysis**

Care should be taken in patients on maintenance dialysis for ESRD who present with acute symptomatic hyperkalemia. In attempting to lower their serum potassium with any of the temporizing measures listed above, the provider will drive potassium into the patient's cells which can **diminish subsequent potassium removal during the dialysis session (from 50mEq to 29mEq in one report)**, possibly leading to rebound hyperkalemia after dialysis due to a large intracellular-to-extracellular potassium gradient.[17]

Loop or Thiazide Diuretics

Loop or thiazide diuretics increase potassium loss in the urine in patients with normal or mild to moderately impaired renal function, particularly when combined with saline hydration to maintain distal sodium delivery and flow. However, patients with persistent hyperkalemia typically have impaired renal potassium secretion, and there are **no data demonstrating a clinically important short-term kaliuretic response to diuretic therapy**.[1] In patients with mild to moderate chronic kidney disease, long-term diuretic therapy may be effective by increasing urinary potassium excretion. However, this therapy will not have a role in the acute management of hyperkalemia in the emergency department.

Cation Exchange Resins

Cation exchange resins are effective in lowering the serum potassium after multiple doses, and are usually not effective immediately and do not appear to be more effective in removing potassium from the body than laxative therapy. Although uncommon, cation exchange resins can produce severe side effects, particularly intestinal necrosis, which may be fatal. Thus, it is recommended that cation exchange resins **only be used in**

patients who have potentially life-threatening hyperkalemia where dialysis is not readily available and other therapies to remove potassium, such as diuretics and rapid restoration of kidney function, have failed or are not possible. Additionally, cation exchange resins **should never be used in postoperative patients, in patients with an ileus or who are receiving opiates, or in patients with a large or small bowel obstruction**.[1]

Cation exchange resins work by taking up potassium and releasing sodium. Each gram of resin may bind as much as 1mEq of potassium and release 1-2mEq of sodium, which may possibly lead to a **side effect of edema due to sodium retention**. It may be given as a 15-30g oral dose every 4-6 hours or as a 50g retention enema mixed with 150mL of sterile water remaining in the intestine for 30-60 minutes and repeated every 2-4 hours as necessary.[1]

Weak evidence suggests that cation exchange resins can lower the serum potassium, usually after multiple doses are given over 1-5 days. **Single doses are not every effective**.[1,13-16] However, laxative therapy may produce an equivalent reduction in the serum potassium.[1]

In the largest published series, 30 patients with hyperkalemia due to acute or chronic kidney disease were treated with 10-60g per day of sodium polystyrene sulfonate orally or rectally.[14] During the first 24 hours of therapy, the serum potassium decreased by an average of 1mEq/L with oral administration and 0.8mEq/L with rectal administration. 23 of 30 patients had a decrease in the serum potassium of at least 0.4mEq/L in the first 24 hours. However, all of these patients received a low-potassium diet, and some received other therapies to lower the serum potassium, such as insulin, glucose, and sodium bicarbonate, which calls into question the efficacy of sodium polystyrene sulfonate as monotherapy or even adjuvant therapy, especially when considering the increased side effect profile of cation exchange resins.

Dialysis

Dialysis is indicated in the event that the hyperkalemia persists despite the interventions above, or if the hyperkalemia is expected to increase rapidly as could potentially be seen in situations such as crush injuries, rhabdomyolysis, or tumor lysis syndrome. **Hemodialysis** is preferred over peritoneal dialysis since it is more effective in removing serum potassium, potentially **up to 25-50mEq of potassium per hour** depending on many factors and variables.

References / Further Reading:

1. Mount DB, Sterns RH, Forman JP. Treatment and prevention of hyperkalemia in adults. UpToDate. https://www-uptodate-com.foyer.swmed.edu/contents/clinical-manifestations-of-hyperkalemia-in-adults?source=machineLearning&search=ekg+changes+in+hyperkalemia&selectedTitle=1%7E150&sectionRank=1&anchor=H2#H2. Updated December 3, 2014. Referenced January 12, 2104.

2. Mount DB, Sterns RH, Forman JP. Clinical manifestations of hyperkalemia in adults. UpToDate. https://www-uptodate-com.foyer.swmed.edu/contents/clinical-manifestations-of-hyperkalemia-in-adults?source=machineLearning&search=ekg+changes+in+hyperkalemia&selectedTitle=1%7E150&sectionRank=1&anchor=H2#H2. Updated June 6, 2013. Referenced January 12, 2104.
3. Mount DB, Zandi-Nejad K. Disorders of potassium balance. In: Brenner and Rector's The Kidney, 8th ed, Brenner BM (Ed), WB Saunders Co, Philadelphia 2008. p.547. Referenced from https://www-uptodate-com.foyer.swmed.edu/contents/clinical-manifestations-of-hyperkalemia-in-adults?source=machineLearning&search=ekg+changes+in+hyperkalemia&selectedTitle=1%7E150&sectionRank=1&anchor=H2#H2. January 12, 2014.
4. Gosmanov AR, Wong JA, Thomason DB. Duality of G protein-coupled mechanisms for beta-adrenergic activation of NKCC activity in skeletal muscle. Am J Physiol Cell Physiol 2002; 283:C1025.
5. Allon M, Copkney C. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. Kidney Int 1990; 38:869.
6. Burnell JM, Scribner BH, Uyeno BT, Villamil MF. The effect in humans of extracellular pH change on the relationship between serum potassium concentration and intracellular potassium. J Clin Invest 1956; 35:935.
7. Schwarz KC, Cohen BD, Lubash GD, Rubin AL. Severe acidosis and hyperpotassemia treated with sodium bicarbonate infusion. Circulation 1959; 19:215.
8. Fraley DS, Adler S. Correction of hyperkalemia by bicarbonate despite constant blood pH. Kidney Int 1977; 12:354.
9. Blumberg A, Weidmann P, Shaw S, Gnädinger M. Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. Am J Med 1988; 85:507.
10. Gutierrez R, Schlessinger F, Oster JR, et al. Effect of hypertonic versus isotonic sodium bicarbonate on plasma potassium concentration in patients with end-stage renal disease. Miner Electrolyte Metab 1991; 17:297.
11. Blumberg A, Weidmann P, Ferrari P. Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. Kidney Int 1992; 41:369.
12. Allon M, Shanklin N. Effect of bicarbonate administration on plasma potassium in dialysis patients: interactions with insulin and albuterol. Am J Kidney Dis 1996; 28:508.
13. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? J Am Soc Nephrol 2010; 21:733.
14. Scherr L, Ogden DA, Mead AW, et al. Management of hyperkalemia with a cation-exchange resin. N Engl J Med 1961; 264:115.
15. Flinn RB, Merrill JP, Welzant WR. Treatment of the oliguric patient with a new sodium-exchange resin and sorbitol; a preliminary report. N Engl J Med 1961; 264:111.

16. Fleisher DS. Cation exchange resin therapy for hyperkalemia in infants and children. J Pediatr 1961; 58:486.
17. Allon M, Shanklin N. Effect of albuterol treatment on subsequent dialytic potassium removal. Am J Kidney Dis 1995; 26:607.
18. http://www.ncbi.nlm.nih.gov/pubmed/24766936