

Debates in the Management of Hyperkalemia

Session Overview

Hyperkalemia is a common life-threatening electrolyte emergency managed by health-system pharmacists on a daily basis. However, several controversies exist related to the management of hyperkalemia, some of which include administration of calcium in the absence of ECG changes, the administration of sodium bicarbonate and sodium polystyrene sulfonate, co-administration of dextrose and insulin and practical methods for administration, and clinical trials evaluating novel and newly approved agents such as patiomer and sodium zirconium cyclosilicate. The session is aimed to address practical issues associated with hyperkalemia pharmacotherapy and associated patient-oriented outcomes.

Objectives

1. Evaluate recommendations for dosing and administration of parenteral calcium in the treatment of hyperkalemia.
2. Apply practical methods for co-administration of insulin and dextrose in the management of hyperkalemia.

Calcium

1. Why we give it
 - 1.1. An elevated calcium concentration decreases the depolarization effect of an elevated K⁺ concentration. IV calcium antagonizes the cardiac membrane excitability thereby protecting the heart against dysrhythmias. (Hoffman BF, et al. Am J Physiol 1956;186:317-24) (Treatment of Acute Hyperkalemia in Adults - Clinical Practice Guideline. UK Renal Association 2014)
2. When we give it
 - 2.1. Life-threatening ECG changes, dysrhythmias, & cardiac arrest - YES
 - 2.2. Peaked T waves - PROBABLY
 - 2.3. Normal ECG - PROBABLY NOT
 - 2.3.1. ECG can be normal, but in some cases is an insensitive marker for assessing severity in hyperkalemia (Parham WA. Tex Heart Inst J 2006;33:40-7) (Szerlip HM, et al. Am J Kidney Dis 1986;7:461-5) (Bandyopadhyay S, et al. Int J Clin Pract 2001;55:486-7)
3. How to dose it
 - 3.1. Optimal dose unclear. Start with at least 1 gm CaCl₂ or 2 gm calcium gluconate IV
 - 3.2. Starts to work in about 3 minutes
 - 3.3. Redose in 5-10 minutes if no effect seen from first dose
 - 3.4. Effects last 30-60 minutes (may need to redose if further treatment needed while awaiting emergent hemodialysis)
4. Which salt to give
 - 4.1. Does calcium gluconate act slower than calcium chloride because it needs hepatic activation? No!

- 4.1.1. Serum ionized calcium levels were measured in 15 hypocalcemic patients during the anhepatic stage of liver transplantation. Half received CaCl 10 mg/kg, the other half received calcium gluconate 30 mg/kg. Serum concentrations of ionized calcium were determined before and up to 10 min after calcium therapy. Equally rapid increases in calcium concentration after administration of CaCl and gluconate were observed, suggesting that calcium gluconate does not require hepatic metabolism for the release of calcium and is as effective as CaCl in treating ionic hypocalcemia in the absence of hepatic function. (Martin TJ, et al. *Anesthesiology* 1990;73:62-5)
 - 4.1.2. A weird randomized prospective study in both children and dogs compared ionization of CaCl and calcium gluconate. The authors conclude that equal elemental calcium doses of calcium gluconate (10%) and CaCl (10%) (approximately 3:1), injected over the same period of time:
 - 4.1.2.1. Are equivalent in their ability to raise calcium concentration during normocalcemic states in children and dogs
 - 4.1.2.2. The changes in calcium concentration following calcium administration are short-lived (minutes)
 - 4.1.2.3. The rapidity of ionization seems to exclude hepatic metabolism as an important factor in the dissociation of calcium gluconate (Cote CJ, et al. *Anesthesiology* 1987;66:465-70)
 - 4.1.3. In ferrets and in vitro human blood, equimolar quantities of CaCl and calcium gluconate produced similar changes in plasma ionised calcium concentration when injected IV into anaesthetised ferrets or when added to human blood in vitro. In vivo changes were followed with a calcium electrode positioned in the animal's aorta, and this showed that the ionisation of calcium gluconate on its first pass through the circulation is as great as that of CaCl. This does not support the common suggestion that CaCl is preferable to calcium gluconate because of its greater ionisation. (Heining MP, et al. *Anaesthesia* 1984;39:1079-82)
5. Calcium in digoxin overdose
 - 5.1. There are only 5 case reports suggesting a temporal relationship between calcium administration and death in the setting of digoxin toxicity (primarily from the 1930s and 1950s) — symptoms of digoxin toxicity are not described, no digoxin levels were taken and only 2 cases had a strong temporal relationship (which does not imply causation). There are also case reports of calcium use in patients with digoxin toxicity without any ill effects.
 - 5.2. Original animal models flawed — toxic effects only occurred when animals were made severely hypercalcemic prior to digoxin administration. Subsequent animal models mimicking digoxin toxicity failed to demonstrate adverse effects.
 - 5.3. The most recent study retrospectively reviewed 159 dig toxicity cases, 23 of which received calcium (Levine, J Emerg Med 2011). Death rate was same in both groups and no dysrhythmias were noted. The problem is all except 1 were chronic digoxin overdose. Hyperkalemia is more problematic in the acute overdose.

- 5.4. Stone heart theory is probably false. Calcium appears safe, but we don't even know if it would work the same as in hyperK from other causes. Little evidence in acute OD where hyperK more problematic. If known digoxin-induced hyperkalemia, give antidote. Otherwise give calcium.

Insulin and Dextrose

1. Treating Hyperkalemia with Insulin
 - 1.1. How it works
 - 1.1.1. Insulin remains one of the cornerstones of early severe hyperkalemia management. Insulin works via a complex process to temporarily shift potassium intracellularly.
 - 1.1.2. Insulin lowers serum potassium by activating Na⁺-K⁺ ATPase and by recruitment of intracellular pump components into the plasma membrane. Insulin binding to specific membrane receptors results in extrusion of Na⁺ and cellular uptake of K⁺. (Hundal HS, et al. J Biol Chem 1992;267:5040-3)
 - 1.2. The right insulin dose
 - 1.2.1. Doses of 5 units boluses up to 20 unit/hr infusions have been used. The most common dose studies is 10 units IV regular insulin as a bolus. This lowers the potassium level by about 1 mEq/L. Neither of these regimens provides sustained effect.
 - 1.2.2. Based on what is known of physiology and drug kinetics, one group suggests the most logical regimen for a 70-kg subject (with weight adjustment of dosages for others) would be an infusion of short-acting insulin at 20 U/h after a 6-U loading dose, given with 60 g of glucose per hour (Sterns, Kidney Int 2016). This needs to be studied before it can be recommended.
 - 1.3. Preventing hypoglycemia
 - 1.3.1. Though insulin certainly lowers plasma potassium concentrations, we often underestimate the hypoglycemic potential of a 10 unit IV insulin dose in this setting.
 - 1.3.2. Incidence of hypoglycemia
 - 1.3.2.1. A 10 unit dose of IV regular insulin has an onset of action of about 5-10 minutes, peaks at 25-30 minutes, and lasts 2-3 hours. Herein lies the problem in that IV dextrose only lasts about an hour (at most). Allon et al reported up to 75% of hemodialysis patients with hyperkalemia developed hypoglycemia at 60 minutes after insulin administration (Kidney Int 1990;38:869-72). A retrospective review of 219 hyperkalemic patients reported an 8.7% incidence of hypoglycemia after insulin treatment (Schafers S, et al. J Hosp Med 2012;7:239-42). More than half of the hypoglycemic episodes occurred with the commonly used regimen of 10 units of IV insulin with 25 gm of dextrose. A more recent study of 221 end-stage renal disease patients who received insulin for treatment of hyperkalemia

reported a 13% incidence of hypoglycemia (Apel J, et al. Clin Kidney J 2014;0:1-3)

1.3.2.2. **The overall incidence of hypoglycemia appears to be ~10%, but could be higher.**

1.3.3. Risk factors for developing hypoglycemia

1.3.3.1. The study by Apel et al identified three factors associated with a higher risk of developing hypoglycemia:

1.3.3.1.1. No prior diagnosis of diabetes [odds ratio (OR) 2.3, 95% confidence interval (CI) 1.0–5.1, P = 0.05]

1.3.3.1.2. No use of diabetes medication prior to admission [OR 3.6, 95% CI 1.2–10.7, P = 0.02]

1.3.3.1.3. A lower pretreatment glucose level

1.3.3.1.3.1. In mg/dL: mean 104 ± 12 mg/dL vs 162 ± 11 mg/dL, P = 0.04

1.3.3.1.3.2. In mmol/L: mean 5.8 ± 0.7 mmol/L vs 9.0 ± 0.6 mmol/L, P = 0.04

1.3.3.2. Renal dysfunction in and of itself may also be a risk factor for developing hypoglycemia. Some evidence suggests that insulin is metabolized by the kidneys to some extent. Furthermore, patients with acute kidney injury (AKI) have clinically relevant changes in insulin metabolism, as evidenced by increased hypoglycemic events and lower insulin requirements upon developing AKI (Dickerson RN, et al. Nutrition 2011;27:766-72).

1.3.4. Strategies for avoiding hypoglycemia

1.3.4.1. Preventing hypoglycemia is important. Some clinicians use up to 20 units of IV regular insulin as the hypokalemic effect is dose dependent (Blumberg A, et al. Am J Med 1988;85:507-12). Here is a suggested strategy for administering enough dextrose to counter the initial insulin bolus of 10 or 20 units:
<https://www.aliem.com/2015/hyperkalemia-management-preventing-hypoglycemia-from-insulin/>. It is loosely based on the Rush University protocol (Apel 2014).