Treatment of hyperkalemia: something old, something new

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Treatment options for hyperkalemia have not changed much since the introduction of the cation exchange resin, sodium polystyrene sulfonate (Kayexalate, Covis Pharmaceuticals, Cary, NC), over 50 years ago. Although clinicians of that era did not have ready access to hemodialysis or loop diuretics, the other tools that we use today—calcium, insulin, and bicarbonate—were well known to them. Currently recommended insulin regimens provide too little insulin to achieve blood levels with a maximal kalemic effect and too little glucose to avoid hypoglycemia. Short-acting insulins have theoretical advantages over regular insulin in patients with severe kidney disease. Although bicarbonate is no longer recommended for acute management, it may be useful in patients with metabolic acidosis or intact kidney function. Kayexalate is not effective as acute therapy, but a new randomized controlled trial suggests that it is effective when given more chronically. Gastrointestinal side effects and safety concerns about Kayexalate remain. New investigational potassium binders are likely to be approved in the coming year. Although there are some concerns about hypomagnesemia and positive calcium balance from patiromer, and sodium overload from ZS-9 (ZS Pharma, Coppell, TX), both agents have been shown to be effective and well tolerated when taken chronically. ZS-9 shows promise in the acute treatment of hyperkalemia and may make it possible to avoid or postpone the most effective therapy, emergency hemodialysis.

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Treatment options for hyperkalemia have not changed much since the introduction of the cation exchange resin, sodium polystyrene sulfonate ([SPS]; Kayexalate, Covis Pharmaceuticals, Cary, NC), over 50 years ago.[1–4] Although clinicians of that era did not have ready access to hemodialysis or loop diuretics, the other tools that we use today—calcium, insulin, and bicarbonate—were well known to them.[5,6] In recent years, our comfort with traditional therapies has been shaken by warnings that Kayexalate mixed with sorbitol may be harmful, and by a growing realization that many of our standard treatments for hyperkalemia have little evidence to support them.[4,7–9] The coming year is likely to see the release of 2 new pharmaceutical products, providing clinicians with new therapeutic weapons for their arsenal.[10] This review is intended to weigh the available evidence on both new and old treatments for hyperkalemia.

Confirming the diagnosis

When any degree of hyperkalemia is discovered, the accuracy of the measurement must be verified. A repeat serum potassium concentration is often normal, without therapy, because of distribution or excretion of recently ingested potassium, diurnal variation, or laboratory error.[11–14] Pseudohyperkalemia (a falsely high potassium), caused by poor phlebotomy technique, hemolysis, laboratory processing, thrombocytosis, and leukocytosis, can lead to inappropriate intervention.[15] The serum potassium rises with exercise and falls after.[16] Because contractions of forearm muscles release intracellular potassium, fist clenching during phlebotomy raises both serum and plasma potassium by as much as 1 mmol/l.[17–20] Potassium is released from platelets during clotting, raising the serum but not plasma potassium in patients with thrombocytosis. To exclude pseudohyperkalemia, plasma potassium (obtained from a heparinized sample) or whole blood potassium should be measured, if platelet counts exceed 500,000.[15,21] Leukemic lymphocytes are fragile and release potassium during centrifugation, when exposed to high concentrations of heparin in the test tube, or when shaken by pneumatic tube transport. In patients with lymphocytic leukemia, the potassium concentration can be higher in plasma than in serum; this observation led to the term "reverse pseudohyperkalemia" to contrast it with the previously reported pseudohyperkalemia caused by thrombocytosis (in which the potassium concentration in serum is higher than in plasma).[15] When the potassium concentration is falsely elevated because of mechanical fragmentation of

lymphocytes, both serum and plasma potassium are affected.[22–24] To avoid confusion, we suggest the terms "platelet-induced serum pseudohyperkalemia," "lymphocyte-induced plasma pseudohyperkalemia," and "shaken-lymphocyte pseudohyperkalemia." To exclude lymphocyte-induced plasma pseudohyperkalemia, serum potassium or whole blood potassium from a sample drawn in a blood gas syringe (which contains lower concentrations of heparin) should be measured; if shaken-lymphocyte pseudohyperkalemia is suspected, samples should be hand-carried to the laboratory.[22–24]

The electrocardiogram in hyperkalemia

Hyperkalemia decreases the transmembrane potassium gradient leading to increased potassium conductance, and this shortens the duration of the action potential.[25] As potassium rises to 5.5 to 6.5 mmol/l, peaked T-waves and a prolonged PR segment may be seen, advancing with higher levels of potassium to progressive widening of the QRS complex, fascicular and bundle branch blocks, a "sine-wave" appearance, and asystole.[26–29]

The electrocardiogram is insensitive in assessing the severity of hyperkalemia.[30] Profound hyperkalemia can occur without electrocardiographic manifestations.[31–34] Cardiac conduction defects, most commonly severe bradycardia, can be the presenting manifestation of hyperkalemia and hyperkalemia can cause malfunction of pacemakers and implantable cardioverter-defibrillators.[35,36] Abnormalities include widening of the QRS complex, increased pacing thresholds, which can lead to failure to capture, as well as oversensing of the paced or spontaneous T-wave by the implantable cardioverter-defibrillator and potentially inappropriate shocks.[36]

Intravenous calcium

Calcium antagonizes the effects of hyperkalemia at the cellular level through effects on the threshold potential and the speed of impulse propagation.[25] In 1964, Chamberlain[37] reported 5 patients with serum potassium concentrations ranging from 8.6 to 10 mmol/l, illustrating "immediate" (within 5 minutes) resolution of the most advanced electrocardiographic findings after intravenous calcium. Our knowledge of when to use this intervention, or what dose and formulation (calcium gluconate or calcium chloride) to use has not advanced since these early observations. The most common dose of calcium recommended today is 10 to 20 ml of 10% calcium gluconate given intravenously as a bolus and repeated as needed.

Because digoxin, an inhibitor of sodium-potassium adenosine triphosphatase, increases intracellular calcium, there are theoretical concerns about calcium treatment for hyperkalemia caused by or associated with digitalis toxicity, and there have been case reports of adverse effects.[38] A small case-controlled study found no mortality differences between 23 patients with hyperkalemia and digitalis toxicity who were treated with calcium and 136 patients who were not.[38] Nonetheless, the risk of hyperkalemia on the cardiac rhythm should be balanced against the potential adverse effect of intravenous calcium in the presence of digoxin toxicity.

Promoting uptake of potassium by cells

Skeletal muscle is the reservoir for more than 70% of body potassium. Transport of extracellular potassium into muscle cells in exchange for intracellular sodium, by the membrane-bound sodium pump, sodium-potassium adenosine triphosphatase, serves as the primary extrarenal mechanism for achieving potassium homeostasis, with a calculated maximal transport rate of 134 mmol/min—enough to transfer one-half of the potassium normally residing in the extracellular space (or the potassium absorbed in a large meal) within 15 seconds. Insulin, beta-2 agonists, and bicarbonate accelerate the movement of potassium into muscle cells, and these agents are widely used to treat "severe" hyperkalemia.

Insulin. When insulin binds to its receptor on skeletal muscle, the abundance and activity of sodium-potassium adenosine triphosphatase and the abundance of the glucose transporter, GLUT4, on the cell membrane increase through independent signaling pathways (reviewed in Ho[39]). Thus, while the glycemic response is maximal at insulin levels of approximately 100 μU/ml, the kalemic effect of the hormone continues to increase as insulin levels rise. Studies utilizing the euglycemic insulin clamp technique show that infusion of regular insulin at 20 U/h after a 6.6-U priming dose in a 70-kg healthy subject will rapidly raise insulin levels to approximately 500 μU/ml, with a near maximal kalemic effect; to maintain euglycemia at these insulin levels, infusion of glucose at 40 g/h is required.[40,41] Although uremia and type-2 diabetes cause resistance to the glycemic effect, insulin's ability to enhance potassium uptake by skeletal muscle and liver are unimpaired.[42,43]

The most commonly recommended regimen for emergency treatment of severe hyperkalemia is a bolus intravenous injection of 10 U of regular insulin, which, if blood glucose is <250 mg/dl, is given with a bolus injection of 25 g of glucose (50 ml of a 50% solution).[7,44,45] This regimen and others have been studied under standardized conditions in several small trials of stable, mildly hyperkalemic patients with dialysis-dependent kidney disease.[43,46–57] Although insulin given as a 10-U bolus or as a 1-hour 20-U infusion without a loading dose lowers the serum potassium by about 1 mmol/l within an hour, Figure 1 illustrates why both of these regimens are suboptimal.[58] Neither regimen provides maximal kalemic insulin levels for very long, and both lead to persistently elevated insulin levels that can cause hypoglycemia. If glucose is given as a bolus, hyperglycemia occurs in the first few minutes, which may blunt the kalemic effect of insulin; hyperglycemia leads to water movement from the intracellular to extracellular compartment, favoring potassium efflux from cells through solvent drag.[59,60] Hypoglycemia often develops an hour or more after the start of therapy for 2 reasons: (i) the amount of glucose is insufficient to replace the glucose utilized in response to exogenous insulin;