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;

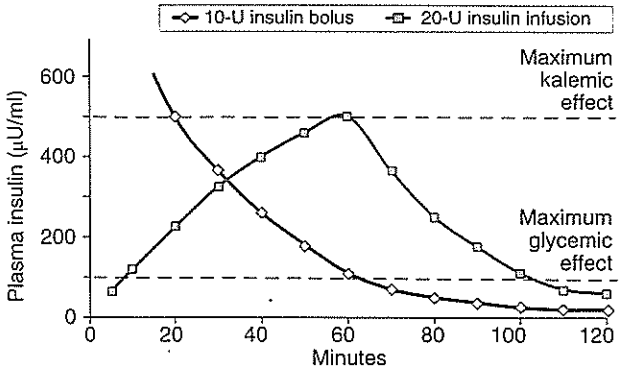

Figure 1 | Idealized plasma insulin levels after commonly used regimens in a patient with ESRD. After a 10-U bolus, insulin levels are transiently very high but quickly become suboptimal. After a 1-hour infusion of 20 U without a loading dose, insulin levels are initially suboptimal. After both regimens, insulin levels persist at levels high enough to cause hypoglycemia unless glucose administration is continued for more than an hour. ESRD, end-stage renal disease.

(ii) insulin's prolonged half-life in end-stage renal disease leads to insulin levels high enough to promote glucose utilization for more than an hour.[40,61–63] Retrospective studies confirm that hypoglycemia commonly occurs within 1 to 3 hours when hyperkalemia is treated with insulin and indicate that its incidence depends more on the dose of glucose than on the dose of insulin; for example, in one study, 2 of 5 patients given only 5 units of insulin with 25 g of glucose developed a blood glucose <2.2 mmol/l.[64]

Short-acting insulins (lispro and aspart) have shorter half-lives than regular insulin and, in contrast to regular insulin, their half-lives are not prolonged by kidney failure.[58,61,65] A randomized, prospective study of infusion therapy to maintain normoglycemia in critical care patients showed the postinfusional drop in blood glucose to be less profound and of briefer duration after lispro than after regular insulin.[62] A retrospective study of outcomes after a 10-U insulin aspart bolus for hyperkalemia found rates of hypoglycemia comparable to previously reported rates after regular insulin; however, only 25 g of glucose were given, an insufficient dose to prevent hypoglycemia.[66]

Based on what is known of physiology and drug kinetics,[40,58,61,67] 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. Particularly if insulin is continued for more than an hour, administration of an adequate amount of glucose intravenously is difficult. Infusion of 10% glucose would require 600 ml/h, causing hyponatremia. High concentrations of glucose to reduce the volume infused would require use of a central vein. It should be possible to give glucose orally to avoid the need for central venous access. Because short-acting insulin is more rapidly absorbed than regular insulin, subcutaneous administration would be expected to be effective, but the dose needed to achieve maximally kalemic insulin levels is not known. Clinical trials to assess these theoretical regimens are needed.

Beta-2 agonists. The beta-2 agonist albuterol (also called salbutamol) administered by inhalation, nebulization, or intravenously has been studied in stable hyperkalemic patients with end-stage renal disease.[47,68] The serum potassium falls by 0.3 to 0.6 mmol/l within 30 minutes, regardless of mode of administration, but some patients fail to respond. The doses used when albuterol is given by inhalation (the only formulation available in the United States) are 4 to 8 times those prescribed for the treatment of acute asthma, and although no severe adverse events have been reported in studies of stable patients, some studies excluded patients with heart disease. At high doses, albuterol may stimulate both beta-1 receptors, which can precipitate arrhythmias, and alpha-receptors, which cause potassium release from the liver and can transiently increase serum potassium by >0.4 mmol/l.[69] Subcutaneous terbutaline, known to cause hypokalemia when used to treat premature labor, also lowers the serum potassium in mildly hyperkalemic patients with end-stage renal disease.

Several studies have documented a substantially greater fall in potassium when beta-2 agonists are combined with insulin than when either agent is given alone and hypoglycemia is less likely with combination therapy than with insulin alone.[47,68,69] However, these studies employed submaximal doses of insulin and glucose, and it is unclear whether coadministration would offer any advantage over an adequate dose of insulin given with sufficient glucose.[8]

Sodium bicarbonate. Administration of bicarbonate promotes uptake of potassium by skeletal muscle by favoring sodium-bicarbonate cotransport and sodium-hydrogen exchange, which, by increasing intracellular sodium, increases the activity of sodium-potassium adenosine triphosphatase.[60] In 1959, Schwarz showed that infusion of between 144 and 408 mmol of sodium bicarbonate over 2 to 4 hours lowered the serum potassium by 2 to 3 mmol/l in 4 patients with severe acidosis.[70] For many years, bicarbonate was often chosen as the first-line treatment for acute hyperkalemia.[71] Bicarbonate ceased to be a recommended intervention for acute hyperkalemia after the publication of studies showing that bicarbonate has little effect on the serum potassium concentration in stable hemodialysis patients.[46,56,57,72,73] However, bicarbonate therapy may be beneficial for patients with metabolic acidosis.[74,75] A 4-hour infusion of sodium bicarbonate in 5% dextrose in patients with chronic kidney disease (CKD) resulted in a substantial fall in serum potassium concentration that was proportional to the increase in serum bicarbonate, with a mean decrease of approximately 2 mmol/l after a 10-mmol/l increase in serum bicarbonate concentration.[76] Bicarbonate is also rational therapy to enhance potassium excretion in patients with intact kidney function.

Combination "cocktails." In 1954, Meroney and Herndon[77] reported on a standard battlefield intravenous solution containing 400 ml of 25% dextrose, 50 U of regular insulin, 50 mmol of sodium bicarbonate, which, along with boluses of intravenous calcium as needed, was effective in controlling hyperkalemia for several days in soldiers with traumatic acute

kidney injury. More recently, Janjua *et al.*[78] reported that a similar standard "cocktail" (containing sodium lactate instead of sodium bicarbonate to permit the inclusion of calcium in the solution) controlled hyperkalemia for up to 32 hours in children and adolescents.

Elimination of potassium

Strategies to shift potassium into cells are temporizing maneuvers that should be followed by efforts to eliminate excess potassium. Reducing total body potassium involves decreased potassium intake, enhanced urinary and fecal potassium excretion, and dialysis. It is important for ambulatory patients with hyperkalemia to see a dietician to guide food choices. Patients should be instructed to limit intake of citrus fruit, potatoes, tomato products, and salt substitutes, which are made of potassium salts.[79]

Patients with hyperkalemia are commonly taking potassium supplements or medications that limit potassium excretion; discontinuation or temporary dose reduction may be all that is required to restore normokalemia.[80] Drug-induced hyperkalemia occurs most often in patients with impaired kidney function and associated hyporeninemic hypoaldosteronism, and it is particularly common in the elderly.[81–86] Common medications that cause hyperkalemia include potassium supplements, angiotensin-converting enzyme inhibitors, angiotensin-II blockers, trimethoprim, calcineurin inhibitors, heparin, potassium-sparing diuretics, digoxin, beta-blockers, and nonsteroidal anti-inflammatory agents.[79] Combinations of these agents are most likely to increase the risk of hyperkalemia and sudden death.[82,85,87–89]

Patients with severe hyperkalemia require active measures to remove potassium. Studies of potassium removal by hemodialysis show that for a given negative potassium balance, patients with higher serum potassium concentrations experience a larger fall in serum potassium (Figure 2a and b).[74,75,90] This phenomenon makes it difficult to interpret studies purporting to show a "dose-response" relationship to potassium binders when patients with higher serum potassium concentrations are given higher doses of the agent.[91]

Dialysis. Hemodialysis is the most effective way to eliminate excess potassium. Although potassium is directly removed from plasma, distribution of potassium between the plasma and interstitial fluid is nearly instantaneous, so potassium is effectively removed from extracellular fluid. The effect of dialysis on the plasma potassium concentration depends on the rate of potassium removal from the extracellular fluid and the rate that potassium is replenished from intracellular stores.[90,92–94] In a 70-kg subject, unreplenished removal of only 14 mmol of potassium from the extracellular fluid will decrease plasma potassium by 1 mmol/l. At a blood pump speed of 0.3 l/min and a plasma-to-dialysate concentration gradient >5 mmol/l, such a decrease can be achieved within minutes. This explains why hemodialysis can be successful during cardiopulmonary resuscitation, when

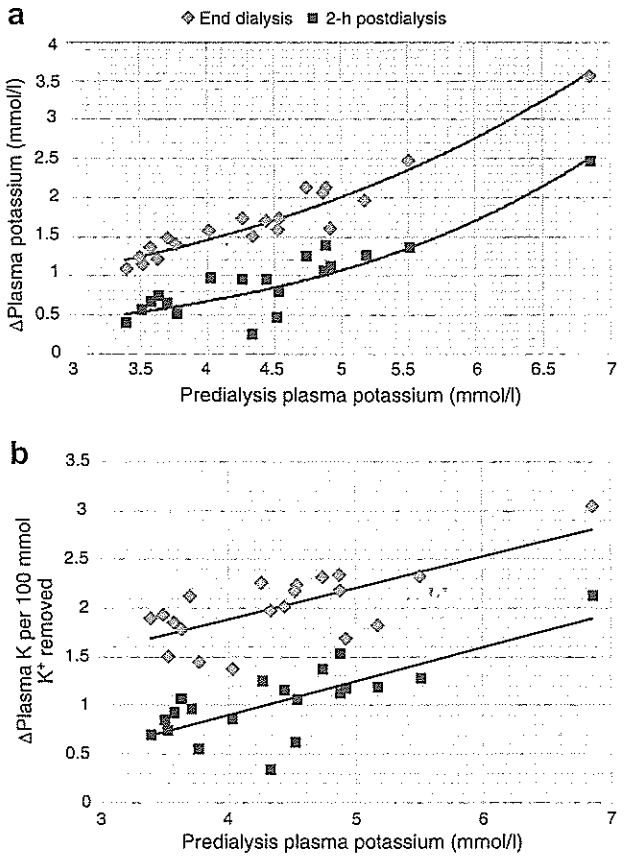

Figure 2 | Response of plasma potassium to potassium removal by dialysis. (**a**) Change in plasma potassium levels at the end of a 3-hour dialysis against a zero potassium dialysate (blue symbols) and 2 hours after dialysis (red symbols). There is a significantly greater fall in plasma potassium when the predialysis potassium concentration is higher. (**b**) The change in plasma potassium per 100 mmol of potassium removed (mmol/kg data normalized to 70-kg subject) at the end of dialysis (blue symbols) and 2 hours after dialysis (red symbols). For a given amount of potassium removal, there is a significantly greater fall in plasma potassium when the predialysis potassium concentration is higher. Based on data in Feig *et al.*,[90] used with permission.

perfusion of peripheral tissues is minimal.[95–97] In more stable patients, over 100 mmol of potassium can be removed during a 4-hour dialysis session; the amount removed depends on the plasma-to-dialysate concentration gradient, blood and dialysate flow rates, and total body potassium stores (a function of muscle mass).[90,92–94] Because replenishment from cellular stores continue when potassium removal stops, there is a substantial postdialysis rebound of plasma potassium (Figure 3).[90,93]

Urinary excretion. In patients with only moderately compromised kidney function, loop diuretics, fludrocortisone, and sodium bicarbonate can substantially increase urinary potassium losses and have been used to manage extremely severe hyperkalemia without dialysis.[60,81,98–100] Although sodium retention and the potential for adverse mineralocorticoid effects on the myocardium make chronic fludrocortisone unattractive for chronic

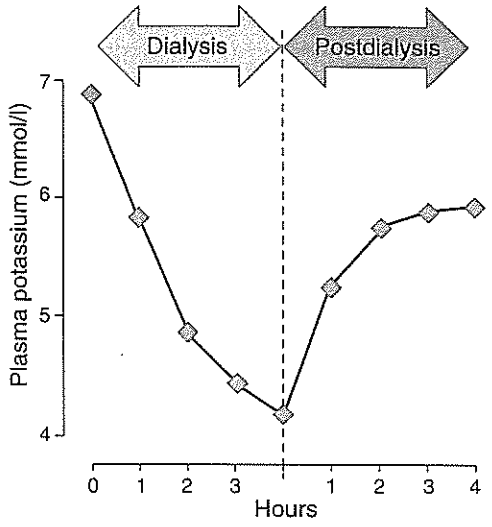

Figure 3 | Plasma potassium concentration during and after dialysis. Modified, with permission, from Figure 3 in Blumberg A, Roser HW, Zehnder C, Muller-Brand J. Plasma potassium in patients with terminal renal failure during and after haemodialysis; relationship with dialytic potassium removal and total body potassium. *Nephrol Dial Transplant*. 1997;12:1629–1634.[93]

therapy, it can be useful acutely as it begins to work within 3 hours.[98,101] Large doses of fludrocortisone (up to 0.4 mg daily) may be required, as patients with kidney disease may have aldosterone resistance as well as aldosterone deficiency.[98] Unfortunately, although many clinicians use such measures routinely, they have not been well studied.

Sodium polystyrene sulfonate (Kayexalate). Kayexalate is a cation exchange resin, first introduced in the 1950s, before the U.S. Food and Drug Administration was required to establish that drugs are safe and effective before approving them.[4] Kayexalate was the name given to the powdered form of SPS, which exchanges sodium for calcium, ammonium, and magnesium in addition to potassium.[102] At an acid pH, its sulfonate groups are occupied by hydrogen ions and are unable to bind potassium. For this reason, and because of higher potassium concentrations in the distal colon, Kayexalate is most effective in binding potassium when it reaches the rectum, either by retention enema or by oral administration with cathartics.[103] Because the resin swells when it contacts water, large doses of Kayexalate can cause bowel obstruction. To avoid this complication and to speed its delivery to the distal colon, Kayexalate has been given together with sorbitol, an osmotic cathartic.[1] A placebo-controlled trial failed to show any difference between the amount of fecal potassium within 12 hours of oral ingestion when sorbitol is given with or without Kayexalate to patients with end-stage renal disease, and there was no effect on the serum potassium concentration.[104] No controlled trials in humans or animals have demonstrated that Kayexalate increases fecal potassium losses.

However, in a double-blind, randomized, placebo-controlled trial, conducted in 33 ambulatory patients with CKD and mild hyperkalemia (5.0–5.9 mmol/l), LePage *et al.*[105] found that 30 g/day of Kayexalate without sorbitol for 7 days was superior to placebo in the reduction of serum potassium (mean difference between groups 1.07 mmol/l; 95% confidence interval: -1.37 to -0.71). There were trends for patients treated with Kayexalate to have more hypomagnesemia ($P = 0.08$), hypocalcemia ($P = 0.10$), nausea, and constipation than those in the control group. Neither urinary nor stool potassium balance was measured.

Chernin *et al.*[106] retrospectively analyzed the course of all patients taking target doses of renin-angiotensin-aldosterone system inhibitors for heart disease who were maintained on long-term therapy with a low dose of sorbitol-free Kayexalate (15 g/day in water) after a serum potassium ≥6.0 mmol/l had been identified. During 289 months of Kayexalate therapy with continued use of renin-angiotensin-aldosterone system inhibitors, the mean serum potassium fell from 6.4 ± 0.3 mmol/l (range 6.0–7.1) to 4.6 ± 0.6 (range 3.0–5.8 mmol/l), $P < 0.01$. The study had no control group, and there was no routine monitoring of serum magnesium. Other than this study, data on long-term use of Kayexalate or SPS in sorbitol are lacking.[107]

Serious gastrointestinal complications from SPS have been reported, given with and without sorbitol, including fatal colonic perforation (reviewed in Harel *et al.*[108]). Because a small study in rats suggested that sorbitol was the cause of colonic perforation,[109] the U.S. Food and Drug Administration issued a warning to avoid administration of Kayexalate with sorbitol.[4] This advice was problematic, because most hospital pharmacies in the United States stock a premixed preparation of SPS suspended in 33% sorbitol rather than powdered Kayexalate. A retrospective cohort study of 123,391 adult inpatients identified 2194 patients who had been treated with SPS in sorbitol, of whom, 0.14% developed colonic necrosis, a rate that did not differ significantly from the rate in patients not receiving the drug (0.07%).[110] Assuming statistical significance, the number needed to harm was estimated at 1395. A much larger population would be required for a rigorous multivariate analysis of the risk of SPS-associated colonic necrosis after acute administration.

Patiromer. Patiromer is an investigational nonabsorbable synthetic polymer consisting of smooth spherical beads approximately 100 μm in diameter; unlike Kayexalate, patiromer does not swell appreciably when exposed to water and it does not require a laxative to reach the distal colon. Patiromer's active groups are comprised of alpha-fluorocarboxylic acids that are paired with calcium ions rather than sodium. As the resin travels through the gastrointestinal tract, some of the calcium is replaced with hydrogen ions. The pKa of Patiromer's cation binding groups is such that at the prevailing pH in the colon, the acid groups are dissociated, allowing them to bind potassium, which is present in high concentrations in this bowel segment, as well as ammonium and magnesium.[86] Controlled experiments in both experimental animals and normal volunteers have demonstrated that when taken orally, the polymer increases fecal potassium in a dose-related fashion; doses of 15 to 30 g/day increased

daily fecal potassium by approximately 15 to 20 mmol.[111] In subjects studied while on a potassium-restricted and sodium-restricted diet, patiromer decreased serum potassium by 0.23 mmol/l within 7 hours.[112] The drug's ability to achieve normokalemia has been proven in randomized multicenter placebo-controlled trials involving a total of 603 hyperkalemic patients on active treatment;[113–115] its safety was demonstrated in an open-label 52-week trial.[115] In addition to minor and infrequent gastrointestinal side effects, the most important recognized adverse drug effect is hypomagnesemia (0.58 mmol/l), which developed in the first month of therapy in 8.6% of patients; hypomagnesemia responded readily to magnesium supplementation and did not progress. Because patiromer exchanges calcium for potassium it has the potential of causing positive calcium balance and ectopic calcifications; this theoretical concern would be difficult to disprove without very long-term studies. Patiromer was approved by the United States Food and Drug Administration in October 2015 and should be available in early 2016. Based on *in vitro* data showing that Patiromer binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness, a black-box warning was issued indicating that the drug should be separated by 6 hours from other orally administered medications.

Sodium zirconium cyclosilicate (ZS-9). Unlike patiromer and SPS, the investigational drug, ZS-9 (ZS Pharma, Coppell, TX) is not a polymer. It is a crystal that is highly selective for potassium and ammonium ions through mechanisms that are very similar to those of naturally occurring ion channels.[116] Potassium and ammonium ions, which are nearly identical in size, must first shed their hydration shells before they enter the crystal structure, a process that requires energy; unhydrated ions are of the right size to form thermodynamically stable and energetically favorable hydrogen bonds to surrounding oxygen atoms in the crystal structure. After shedding their hydration shells, sodium, calcium, and magnesium ions are too small to form such stable bonds, making it thermodynamically unfavorable for them to be bound by the crystal. Controlled trials have proven that ZS-9 increases fecal potassium losses in rats, in a dose-dependent manner.[117] ZS-9 has been shown to be effective in maintaining normokalemia in randomized placebo controlled trials involving 1101 hyperkalemic patients taking the active drug.[117–119] Its safety has been studied in an open-label 28-day trial,[119] and it is currently being studied in a larger 52-week trial. In addition to minor gastrointestinal side effects, edema developed in 6% of patients taking 10 g/day and 14% of patients taking 15 g/day (as compared to 2% of control subjects).[119] ZS-9 exchanges sodium and hydrogen ions for potassium and maintenance doses of the drug (5, 10, or 15 g/day) provide approximately 17, 34, and 50 mmol of sodium per day.

Because ZS-9 does not contain acid groups that dissociate, it binds potassium throughout the gastrointestinal tract.[116] This suggests that it will be effective in the management of acute hyperkalemia. In a subgroup of 45 patients with serum potassium concentrations of at least 6 mmol/l (6.1 to 7.2 mmol/l), who participated in 2 controlled trials, administration of 10 g of ZS-9 significantly reduced the serum potassium concentration below baseline by 0.4 mmol/l at 1 hour, by 0.6 mmol/l at 2 hours, and by 0.7 mmol/l at 4 hours ($P < 0.001$).[120]

Who to treat

Our knowledge of how to decrease the serum potassium concentration, while imperfect, has improved substantially in the past 2 years. Our understanding of when to treat hyperkalemia has lagged behind. Opinions vary widely as to what level of serum potassium should be defined as "severe" or what level constitutes a hyperkalemic emergency (Table 1).[5,44,45,121] Hospital admission is often recommended for patients with a serum potassium >6 mmol/l and electrocardiographic monitoring and acute interventions for any patient with a serum potassium >6.5 mmol/l.[73] Although that is our practice, we recognize that it has not been established that this is necessary; 1 small study showed favorable outcomes among patients with serum potassium concentrations >6 mmol/l (6.7 ± 0.5 mmol/l) who were managed as outpatients,[122] and no deaths were recorded in another study of 242 consecutively admitted patients with a serum potassium >6 mmol/l despite substantial delays in treatment.[80]

Recent studies have reported increased risk of mortality among patients with hyperkalemia, findings that are likely to be emphasized when the new potassium binders reach the market.[28,123–126] For example, a 1-year retrospective analysis of a national cohort of 245,808 veterans with at least 1 hospital admission and 1 inpatient or outpatient potassium value

Table 1 | Definitions of the severity of hyperkalemia

Author	Year	Minimal or mild hyperkalemia	Moderate hyperkalemia	Severe hyperkalemia
Levinsky[5]	1966	<6.5 mmol/l	6.5–8 mmol/l with ECG limited to peaked T-waves	>8 mmol/l or any level associated with prolongation of the QRS complex, ventricular arrhythmias, or heart block
Vanden Hoek *et al.*, for the American Heart Association[45]	2005	5.1–5.9 mmol/l	6.0–6.9 mmol/l	>7 mmol/l
Soar *et al.*, for the European Resuscitation Council[44]	2010	5.5–5.9 mmol/l	6.0–6.4 mmol/l	≥6.5 mmol/l
El-Sherif and Turitto[121]	2011	5.5–7.5 mmol/l	7.5–10 mmol/l	>10 mmol/l

ECG, electrocardiogram.

found that among patients with CKD the risk of dying within a day of documenting potassium between 5.5 and <6 mmol/l as an outpatient, values usually labeled as "mild or minimal hyperkalemia" (Table 1), was 2.73 times higher than with potassium <5.5 mmol/l; the risk was 13 times higher for potassium >6 mmol/l.[123] These alarming statistics should be placed in perspective. The absolute mortality rates were 0.2% for potassium between 5.5 and <6 mmol/l and 0.9% for potassium >6 mmol/l (although much higher rates were recorded among hospitalized patients). Curiously, both relative risks (6.17 and 27.4) and absolute risks (0.4% and 1.7%) of dying within 24 hours for the same potassium values were much higher among patients *without* CKD. One may speculate with the authors that this finding reflects an adaptation to more chronic hyperkalemia, but the paradoxical finding that CKD (a powerful predictor of mortality) was protective may also mean that deaths in patients without CKD were not caused by hyperkalemia *per se*, but rather from underlying cardiovascular disease.

Retrospectively determined associations between hyperkalemia and mortality or between resolution of hyperkalemia and improved mortality do not prove cause and effect, and they are a poor basis for therapeutic strategies that are likely to be expensive[127] and potentially risky. Currently, because of hyperkalemia, many patients cannot be treated with inhibitors of the renin-angiotensin-aldosterone system that have been shown to prolong life. This population is likely to be the major beneficiary of new agents to treat hyperkalemia. However, as pointed out in a recent editorial,[128] it is quite possible that development of hyperkalemia under renin-angiotensin-aldosterone system blockade is a marker for underlying pathology that may lead to mortality regardless of treatment; control of the plasma potassium concentration is ultimately a surrogate marker for the hard outcomes that should be studied: mortality rates, reduced progression of CKD, deferral of dialysis, improved heart failure outcomes. It is highly unlikely that we will see such outcome trials in the foreseeable future. Without them, the next 50 years may be as frustrating as the last for those who must treat hyperkalemia.

DISCLOSURE

All the authors declared no competing interests.

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