Current and future treatment options for managing hyperkalemia

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Hyperkalemia is associated with life-threatening cardiac arrhythmias and increased mortality. Hyperkalemia is most often observed in patients with chronic kidney disease and/or in those with congestive heart failure being treated with drugs that limit renal potassium excretion, especially drugs that inhibit the renin-angiotensin-aldosterone system. Treatment of hyperkalemia may be either acute, as needed during rapid changes in serum potassium, which are associated with cardiac arrhythmia, or chronic, which stabilizes serum potassium levels and limits the development of life-threatening arrhythmias. There are a number of both acute and chronic treatments available for the treatment of hyperkalemia, but some are limited by complex administration requirements and/or serious side effects. Hyperkalemia remains a vexing problem for clinicians, particularly in the care of patients with chronic kidney disease and cardiovascular disease.

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Hyperkalemia is a common electrolyte disorder with numerous etiologies. Potassium is primarily an intracellular ion whose absorption and secretion occurs in distinct areas of the nephron and gastrointestinal tract.[1,2] The kidneys are the most important site of excretion.[2,3] However, with progressive impairment of kidney function, colonic excretion assumes increasing importance.[1–3] Consequently, patients with chronic kidney disease (CKD) or cardiovascular disease who often are receiving drugs that block the renin-angiotensin-aldosterone system (RAAS) are at greatest risk for hyperkalemia.[4–7] The reader is referred to the in-depth review by Epstein in the fourth article of this supplement.[8] A 5-year database of the prevalence of hyperkalemia illustrated that as CKD progresses from stage 3A to 3B to 4, the frequency of hyperkalemia defined as ≥5.1 mEq/l increased from 23.5% to 33% to 47.7%, respectively.[9] Moreover, clinical and epidemiological data link higher levels of serum potassium (above 5.1 mEq/l) with increased risk of death. Given the frequency and significance of hyperkalemia in patients with CKD and cardiovascular disease,[10–14] it is common for health care providers to underdose or to not use these drugs at all, if there is even a threat of hyperkalemia.

Increases in serum potassium of 0.4 to 0.5 mEq/l are common when a RAAS blocker is used. However, increases can be much more substantial with the concomitant use of nonsteroidal anti-inflammatory drugs, salt substitutes, or nutritional supplements, or if large amounts of fruits containing potassium—such as cantaloupe or watermelon—are consumed.[1,2] Thus, there is an important need for a well-tolerated and simple means of controlling serum potassium in a safe range, even in patients with CKD or cardiovascular disease who require the therapeutic advantage of drugs that block the RAAS.

Acute hyperkalemia

There are 3 different strategies to treat acute elevations in serum potassium leading to cardiac cell membrane instability and potentially lethal arrhythmias.[1,5,9,12,15–17]

The first of these strategies is stabilization of membrane potentials by raising the threshold of the cardiac action potential or altering (flattening) the slope of membrane depolarization as the main physiological considerations.[18–23] Calcium gluconate salts, when acutely administered, can raise serum calcium levels, which elevate the threshold for the cardiac action potential for a brief period and allow time for other measures to be implemented. This is critical because higher extracellular potassium levels facilitate more rapid membrane depolarization.[24,25]

Next, the physician can facilitate potassium redistribution into cells by administering either glucose and insulin or beta-agonists. However, the latter approach can be problematic, especially in people with cardiovascular disease.

Finally, potassium elimination can be facilitated through the use of loop diuretics to enhance kaliuresis. The physician can also administer sodium bicarbonate with loop diuretics to alkalinize the urine and facilitate kaliuresis through the provision of more sodium to exchange distally with potassium. Potassium elimination via the gastrointestinal tract can also be facilitated with the use of potassium-binding resins, such as sodium polystyrene sulfate (SPS) (Kayexalate; Covis Pharmaceuticals, Cary, NC). In patients with advanced kidney disease, acute hemodialysis may be required to acutely reduce serum potassium.[26,27]

Chronic treatment strategies

Reduction of dietary potassium is an important strategy for the chronic management of hyperkalemia. However, there is incomplete knowledge of how best to avoid dietary potassium. For example, a cup of low-fat milk has nearly 11 mEq of potassium, and 1 cup of plain yogurt has almost 14 mEq of potassium. Likewise, vegetables or fruit such as raisins, watermelon, avocado, grapefruit, or cantaloupe are rich in potassium, but other fruits such as blueberries, grapes, or pineapple are quite low. Many vegetables, including squash, spinach, and brussels sprouts, are very rich in potassium, whereas lettuce and beans are much lower. Dietary education is a necessary and critical feature of the chronic management of hyperkalemia.[1,28]

Sodium bicarbonate tablets may occasionally be used in hyperkalemia patients with severe acidemia. If utilized, it should be administered with loop diuretics on a chronic basis to control serum potassium. However, this may require multiple pills and numerous medication adjustments, as it is often difficult to give salt to patients with CKD or cardiovascular disease without exacerbating their volume status or blood pressure.

SPS was approved by the US Food and Drug Administration (FDA) in 1958.[26,27] This was 4 years before the requirement to prove safety and effectiveness of medications as noted in the 1962 Kefauver-Harris Drug Amendments. There is limited evidence that SPS increases fecal potassium losses in experimental animals or in humans and no evidence that adding sorbitol to the resin increases its effectiveness. SPS can be administered in doses of 50 to 60 g from 1 to 4 times per day. It is an irregular bulk gel material with sharp edges, nonuniform size, and a clay-like consistency. It is not well dissolved in water and is sodium-loaded; there are approximately 100 mg of sodium per gram of SPS.

SPS directly exchanges sodium for potassium and may be associated with increases in volume and pedal edema.[27] In patients with CKD, it may be associated with increases in blood pressure. Because of the danger of acquisition of sodium in patients with severe congestive heart failure, the Heart Failure Society of America has issued a caution for the use of SPS in patients with heart failure. A systematic review of case reports noted that gastrointestinal necrosis has been reported as frequently in patients receiving SPS alone as in patients receiving SPS with sorbitol.[27,29,30] Harel *et al.*[29] recently identified 58 cases in 30 reports. Necrosis was reported in patients receiving SPS with ($n = 41$) and without ($n = 17$) sorbitol. Mortality due to gastrointestinal injury was reported in 33% of these cases. Consequently, SPS must be used very cautiously and sparingly, with close monitoring of volume and blood pressure.

In 2009, the FDA issued a warning noting that there were cases of colonic necrosis and other serious gastrointestinal events associated with the use of SPS.[31,32] The FDA also recommended against the use of sorbitol with SPS. The FDA also warned that only people with normal bowel function should use SPS and recommended strongly against its use in people with problems with constipation, inflammatory bowel disease, ischemic colitis, and intestinal vascular atherosclerosis.

In perspective, the chronic treatment strategies for hyperkalemia, short of discontinuing the RAAS blocker, are limited.[28] The health care provider should advise patients about avoiding nonsteroidal anti-inflammatory drugs and herbal/nutritional supplements and should instruct patients on reduced dietary potassium, which, unfortunately, requires the elimination of many healthy foods. The health care provider can also adjust sodium bicarbonate tablets coupled with loop diuretics to facilitate kaliuresis. Finally, the health care provider can use SPS sparingly, preferably only in those individuals with good bowel function and no concerns about constipation.

Future treatments

Two new therapies will likely alter the landscape for the management of both acute and chronic hyperkalemia: patiromer (Veltassa; Relypsa, Redwood City, CA) and sodium zirconium cyclosilicate (ZS Pharma, San Mateo, CA).

The first agent, patiromer, was recently approved by the FDA in October 2015. The active moiety for oral suspension is a nonabsorbed polymer that binds potassium in exchange for calcium.[30] It binds potassium throughout the gastrointestinal tract, but it is believed to act predominantly in the distal colon, where the concentration of free potassium is highest.[30] The net result is an increase in secretion and reduction of serum potassium levels. Patiromer is stable and nonsystemically absorbed. It has been studied in a variety of populations, but primarily in people with CKD or cardiovascular disease.

The initial phase 3 trial by Weir *et al.*,[33] was designed to examine patients with CKD on RAAS blockers with serum potassium levels between 5.1 and <6.5 mEq/l. A total of 243 patients were randomized to receive patiromer, either 4.2 or 8.4 g, twice daily for a period of 4 weeks. The second part of the study involved 107 patients whose baseline potassium was 5.5 to <6.5 mEq/l and in whom the potassium levels decreased to 3.8 to <5.1 mEq/l with patiromer in the initial part of the study. These patients were then entered into