Pharmacology

The current treatment of hyperkalemia in the emergency department (ED) varies considerably because of limited data on the efficacy of available agents [1]. A recent Cochrane review highlighted the limitations of the available studies [2], however, the United Kingdom Renal Association has developed clinical practice guidelines for the treatment of acute hyperkalemia [3]. Following are the commonly used agents for the treatment of hyperkalemia in the emergent setting. A threefold approach is currently adopted by clinicians:

1. Stabilization of the cardiac membranes
2. Redistribution of potassium
3. Elimination of potassium

Stabilization of the Cardiac membranes

Calcium
The effect of potassium on myocytes is counter-balanced by the concurrent calcium concentration such that intravenous calcium antagonizes hyperkalemia induced cardiac membrane excitability and protects the heart against arrhythmias [4]. It is usually effective within minutes, as noted by an improvement in the ECG appearance or reversal of ECG abnormality. It is generally accepted that intravenous (IV) calcium is indicated for potentially life-threatening ECG changes (absent P waves, wide QRS, sine-wave pattern) [2] [5] [6], arrhythmias, or cardiac arrest [7]. The recommended dose of calcium salts ranges from 1000 – 3000 mg of calcium gluconate (10 - 30 mL of a 10% solution) or 500 -1000 mg of calcium chloride (5- 10 mL of a 10% solution) [5] [8]. The dose can be repeated if there is no effect within 5-10 minutes.

Some adverse effects of intravenous calcium are peripheral vasodilation, hypotension, bradycardia, and arrhythmias [9]. A more serious adverse effect of IV calcium is tissue necrosis if extravasation occurs. This can be avoided if calcium gluconate is used, which is considered less toxic on peripheral veins. Historically, caution has been advised with administration of IV calcium in patients with known or suspected digoxin toxicity however, there are reports showing no adverse effects of IV calcium administration in the presence of unrecognized digoxin toxicity [10]. Furthermore, a retrospective study of 23 patients receiving IV calcium in the setting of digoxin toxicity has shown no increased risk of arrhythmia or mortality [11].

Redistribution of potassium

Beta 2 agonists
Beta-2 adrenergic receptor agonists promote the translocation of potassium into the cell by activation of the Na-K ATPase pump. Salbutamol (known as albuterol in the U.S.) and other beta-agonists are equally effective given intravenously or via a nebulizer [2] [20]. Beta-2 adrenergic receptor agonists are not recommended as monotherapy for acute hyperkalemia, but rather in conjunction with insulin and glucose.
The effect of intravenous or nebulized salbutamol is dose-dependent [21], with an onset of action within 30 minutes, and a peak effect within 60 minutes. Nebulized salbutamol is given in doses of 10 or 20 mg. It decreases serum potassium by approximately 1 mEq/L [13] [21] and lasts for at least 2 hours [21] [20].

Non-selective beta-blockers may prevent the hypokalemic response to salbutamol, although, one study shows that even in the absence of beta-blocker use, up to 40% of patients may not respond to salbutamol [17]. Common side effects are tremor, palpitations, anxiety, and headache. Mild hyperglycemia has also been reported [13] [22] and thus there may be a protective role against insulin-induced hypoglycemia when used simultaneously [23].

**Insulin/Dextrose**
A combination of insulin and glucose is the mainstay of hyperkalemia treatment in the acute setting. Administration of 10 units of regular insulin along with 25 g of glucose IV over 15-30 minutes is a suggested regimen [5]. Insulin lowers serum potassium by activating sodium-potassium ATPase (Na-K ATPase) and by moving sodium out of the cell in exchange for the movement of potassium into the cell [12]. Serum potassium concentration starts to decrease within 15 minutes of administration and peaks at 30 to 60 minutes [13] [14]. Multiple small studies have shown the efficacy of insulin in treating hyperkalemia and that its effect may last several hours [2] [14] [15] [16]. Repeat dosing may be necessary in situations where elimination of potassium is not feasible.

A common adverse effect of insulin-glucose therapy is hypoglycemia. This risk is dependent on the doses of insulin and glucose administered, with the incidence of hypoglycemia ranging from 11-75% [14] [17]. A recent ED study found the rate of symptomatic hypoglycemia to be 17% [18], and the effect of insulin may last up to 6 hours in patients with kidney failure [19]. Therefore, glucose monitoring is recommended for several hours after insulin administration in patients with renal failure [19]. Infusion of 10% dextrose at 50 – 75 mL per hour with regular monitoring of glucose may be warranted to minimize the risk of subsequent hypokalemia.

**Loop Diuretics**
Loop diuretics (furosemide, bumetanide and torsemide) inhibit the luminal Na-K-2Cl cotransporter by binding to the chloride-binding site of the thick ascending limb of the loop of Henle and macula densa. These agents are highly protein bound to albumin and gain access to the site of action via active secretion from blood into urine at the proximal tubule, which then allows for activity downstream in the thick ascending limb to cause the natriuretic effect. They work to lower serum potassium by increasing distal sodium delivery and flow rate to promote potassium secretion into the lumen and subsequent removal. This effect is enhanced with administration of saline solutions to increase distal sodium delivery and flow rate. While loop diuretics are effective at promoting potassium excretion, particularly for individuals with normal kidney function, evidence for use of loop diuretics in the acute management of hyperkalemia is lacking. These agents may be used as adjuncts in a hyperkalemic emergency. Loop diuretics are more advantageous in treatment of chronic hyperkalemia that often occurs in individuals with advanced kidney disease as they promote diuresis to maintain volume status and promote potassium loss. Adverse effects include ototoxicity (associated with higher doses), hypotension,
electrolyte imbalances (hypokalemia, hyponatremia), hypovolemia, hyperuricemia, and hypersensitivity reactions (furosemide, bumetanide and torsemide are sulfonamide-containing agents).

**Sodium bicarbonate**

Sodium bicarbonate infusion promotes uptake of potassium into skeletal muscle by favoring sodium-bicarbonate cotransport and sodium-hydrogen exchange which, by increasing intracellular sodium, increases Na-K ATPase activity [24].

In 1959, Schwarz showed that an infusion of sodium bicarbonate lowered serum potassium in 4 patients with severe acidosis [25]. More recent studies have demonstrated little effect on potassium in stable hemodialysis patients and thus it has fallen out of favor [26]. However, bicarbonate therapy may be beneficial for patients with metabolic acidosis [27]. Overall, there is insufficient evidence to support the use of intravenous sodium bicarbonate for the acute treatment of hyperkalemia and should be used with caution since it can cause sodium and fluid overload [2]. If used in conjunction with other agents for acute hyperkalemia, an isotonic solution is recommended (e.g. 150 mEq in 1 liter of 5% dextrose in water over 2-4 hours).

**Elimination of potassium**

**Dialysis**

Hemodialysis is a modality where blood and a balanced salt solution (dialysate) are perfused to opposite sides of the semi-permeable membrane. This process is highly effective at lowering serum as well as total body potassium. A concentration gradient is established between the blood and the dialysate such that the dialysate concentration is less than plasma. Regular hemodialysis (usually three times per week) is necessary in individuals with end-stage renal disease to maintain potassium concentrations with approximately 80-100 mEq of potassium removed during a standard hemodialysis treatment [28]. As potassium drops with dialysis there is movement of potassium from the intracellular to the extracellular space with the most efficient removal occurring during the first couple of hours of the procedure. Hemodialysis is an option for acute management of hyperkalemia, but usually reserved for individuals with end-stage renal disease who already have vascular access for dialysis making initiation of the procedure more convenient and likely to be initiated more rapidly in the acute care setting. Acute complications of hemodialysis include hypotension, cramping, chest pain, back pain, arrhythmias, headache, and nausea and vomiting, many of which are associated with fluctuations in volume and electrolyte concentrations [29].

**Patiromer**

Patiromer is a cation exchange resin that exchanges calcium for potassium with robust data to show efficacy and safety. It has been studied in 3 trials in approximately 700 patients in short-term (12 week) and long-term (up to 52 weeks) studies. The general objective for these studies was to evaluate use of patiromer to lower potassium and allow for continued use of agents known to contribute to hyperkalemia (e.g., renin-angiotensin-aldosterone system inhibitors, mineralocorticoid receptor antagonists). The onset of action is approximately 2-7 hours and is approved for the management of hyperkalemia [36] [37].
PEARL-HF was a double-blinded, placebo-controlled study, whose focus was on heart failure patients with an indication to start spironolactone [38]. Patiromer lowered potassium levels and enabled more patients to be on spironolactone compared to the placebo group. OPAL-HK was a 12-week evaluation of the efficacy and safety of patiromer in patients with CKD on Renin-Angiotensin-Aldosterone-System inhibitor (RAASI) therapy and with hyperkalemia [39]. At the end of the study, more patients on patiromer (94% vs. 44%) were able to be continued on RAASI therapy compared to placebo. AMETHYST-DN was a 52-week safety and efficacy evaluation of patiromer in patients with hyperkalemia and diabetic nephropathy [40]. This multi-center, dose-titration study evaluated the optimal starting and maintenance doses of patiromer and reported a potassium reduction from baseline to week 4 in all groups.

Patiromer is generally well tolerated both acutely and on a long-term basis [41]. The initial recommended dose is 8.4 g with titrations made in increments of 8.4 grams at one-week intervals (maximum dose 25.2 g/day) based on potassium levels. Adverse effects are related to the gastrointestinal system, with constipation occurring in 7.2% and hypomagnesemia occurring in 5.3%. Lastly, patiromer may interact with certain positively charged drugs and reduce their bioavailability, and therefore recommended administration is at least 3 hours apart from other oral medications [42].

**Sodium Polystyrene Sulfonate (SPS)**

Sodium polystyrene sulfonate (SPS) exchanges sodium for potassium in the GI tract and may be administered orally or per rectum. Doses of 15 g orally administered up to four times daily or 30 grams rectally (up to 60 g daily) are recommended doses. For acute management of hyperkalemia, SPS may be considered in conjunction with more rapidly acting therapies. However, there is limited prospective data on the efficacy of SPS in the acute management of hyperkalemia. In 1961, Scherr [30] evaluated 32 hyperkalemic patients and reported 23 had mean potassium reduction of 1.0 mEq/L in the first 24hrs of treatment. Nasir [31] randomized 97 CKD patients to SPS or calcium polystyrene sulfonate (CPS) and reported a 1.5 and 1 mEq/L potassium decrease after 3 days of treatment with SPS and CPS, respectively. Lastly, Lepage [32] evaluated 33 mildly hyperkalemia CKD patients in a double-blind randomized trial and found 30 g of SPS administered once daily for 7 days was superior to placebo in reducing serum potassium within 1 week.

Common adverse events of SPS are nausea, vomiting, diarrhea, abdominal bloating and cramps, anorexia, electrolyte imbalance (e.g., hypokalemia) and possibly elevated diastolic blood pressure [33]. Drug-drug interactions are another concern with interactions noted with antacids, laxatives, digoxin, lithium, and thyroxine. A more serious adverse event is bowel necrosis and subsequent death, particularly when SPS is combined with sorbitol. Although this is rare and actual rate of occurrence is unknown, a systematic review documented 58 cases of bowel necrosis, with 33% mortality associated with SPS use [34]. In 2009 the FDA issued a black box warning regarding the risk of colonic necrosis and recommended against concomitant administration of sorbitol. The use of SPS has also been associated with a greater risk of hospitalization for serious adverse GI events (intestinal ischemia/thrombosis, ulceration) when evaluated in individuals over 66 years of age [35]. These findings have led to a more cautious use of SPS and avoidance in patients at risk including those with bowel obstruction or underlying bowel disease.
Sodium Zirconium Cyclosilicate

In 2018, sodium zirconium silicate (SZC formerly known as ZS-9 during development) was approved by the FDA for the treatment of hyperkalemia [43]. SZC is an inorganic zirconium silicate compound that selectively exchanges potassium for sodium and hydrogen in the intestine. It is not systemically absorbed, and the onset of action is approximately 1 hour. Although SZC and Patiromer are not approved for emergency treatment of life-threatening hyperkalemia, they are approved for chronic management of hyperkalemia and as such may have a role after initial stabilization.

The efficacy of SZC in reducing serum potassium has been demonstrated across multiple randomized clinical trials of > 1700 patients. In a phase 2 study in 2015, Ash et al. investigated 90 adult patients with CKD and hyperkalemia. They showed a dose dependent decrease in serum potassium with oral SZC compared to placebo. Interesting, 10 gm three times daily decreased serum potassium by 0.11 mEq/L within just 1 hour (44). Amin et al found in post hoc analysis of 6 patients in a subgroup that started with a potassium level > 6.5 mmol/L experienced a change from a baseline in serum K+ of – 0.83 mmol/L by 2 hours post dose. (45).

Two phase three trials showed similar reductions in serum potassium. The HARMONIZE trial was a phase 3 dose-ranging trial that investigated the efficacy of SZC in ambulatory patients. SZC significantly reduced serum potassium within 1 hour (-0.2 mEq/L compared to placebo), with a difference of -1.1 mEq/L at 48 hours. Median time to normalization of serum potassium was 2.2 hours. Much like patiromer, reductions in serum potassium were dose dependent, and patients with higher baseline potassium experienced greater reductions in serum potassium [46]. Furthermore, another phase 3 trial by Packham et al demonstrated the efficacy of SZC for the management of chronic hyperkalemia[47]. Adverse events of SZC include edema, gastrointestinal symptoms, and hypokalemia. Overall, it appears to be well tolerated with few serious adverse events reported by the prior studies.

The starting dose of SZC is 10 grams three times daily for up to 48 hours with doses adjusted by 5 grams daily at 1-week intervals based on serum potassium levels (maximum maintenance dose is 15 grams per day). This agent has been shown to interact with dabigatran (causing decreased systemic exposure) and atorvastatin and furosemide (causing increased systemic exposure) and the recommendation is to separate administration from other oral medications by at least two hours.

In a study looking at SZC in the emergency department setting, SZC demonstrated a numerically greater proportion of patients achieving a serum potassium of < 6 mmol/L during the study compared to placebo, however, it was not statistically significant. Although the study demonstrated signals indicative of incremental benefits of SZC when used in addition to insulin and glucose for the emergency treatment of hyperkalemia, many of endpoints did not meet statistical significance. No safety concerns in the patient groups were found and this is consistent with previous studies (48)

References


