CPQ Medicine (2018) 3:5
Review Article

Novel Hyperkalemia Drugs

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Received: 08 November 2018

Published: 03 December 2018

Keywords: *Hyperkalemia Drugs; Chronic Diseases; Pathophysiology*

Abstract

In this mini-review pathophysiology, diagnosis and management of hyperkalemia are discussed with a special emphasis on the introduction of two novel potassium binders, patiromer and sodium zirconium cyclosilicate. These novel potassium binders enable patients to continue RAASi therapy in CHF, diabetes and CKD. Both have tested well as safe and efficacious and may result in a change in our therapeutic paradigm, by favouring their chronic use over discontinuation of RAASi treatment. Whether the effects of such a novel strategy translates to improved long-term clinical outcomes should be investigated in future trials.

Introduction

Hyperkalemia occurs more frequently in clinical practice due to the increasing incidence and prevalence of common chronic diseases and chronic kidney diseases (CKD)- [1,2]. Along with their treatment hyperkalemia may arise which is defined as a serum potassium concentration greater than 5,0 to 5,5mmol/l, a potential life-threatening complication [3]. Hyperkalemia can induce or worsen cardiac arrythmias, and is associated with significantly increased mortality [2,4].

Besides CKD and diabetes other common risk factors for hyperkalemia are acute kidney injury (AKI),cardiovascular disease and medications used in these conditions [2]. Medications most often associated with hyperkalemia are the inhibitors of the renin-angiotensin-aldosterone system (RAASi),which have to be discontinued frequently for causing hyperkalemia, despite their clinical benefit. Recently, novel hyperkalemia drugs were approved by the FDA [5-7]. In this mini-review pathophysiology, diagnosis and management of hyperkalemia are discussed with a special emphasis on these novel potassium binders.

Pathophysiology

Potassium is the most abundant intracellular cation and is critical in many physiological functions. Absorption of potassium from the gastrointestinal tract (GIT) is rapid and usually complete. Daily intake varies with diet. Common potassium-rich foods include fruits, potatoes, beans and grains. In contrast, high -fat diets usually contain low amounts of potassium.

Potassium concentrations are maintained between 3,5 and 5,5mmol/l by renal and extrarenal mechanisms. The major key effector is the energy-consuming enzyme Na^+/K^+/-ATPase located in the plasma membranes of cells, which pumps Na^+ out of and K^+ into the cell in a 3:2 ratio. The Na^+/K^+/ATPase helps to maintain the resting potential and avail transport, and helps to regulate cellular volume as well as intracellular calcium content.

Extra renal mechanisms are able to shift K^+ from extra-to intracellularly, but the excretion of potassium mainly occurs in the kidneys. Renal adaptive mechanisms allow the kidneys to maintain potassium homeostasis until the glomerular filtration rate (GFR) drops to less than 15ml/min/1,73m^2. Approximately 10% of the daily potassium intake is cleared by the gut. In the presence of renal failure the proportion of potassium excreted by the GIT can increase somewhat [8].

Handling of potassium in the nephron depends on passive and active mechanisms. Potassium is filtered in the glomerulus and almost completely reabsorbed n the proximal tubule and the loop of Henle. Excretion mainly occurs in the collecting duct [9]. Reabsorption and secretion occur simultaneously, and many modulators are important as diet, adrenal steroids and acid-base balance.

Aldosterone is a key regulator of renal potassium homeostasis and binds to the nuclear mineralocorticoid receptor (MR) within the distal tubule and the principal cells in the cortical collecting ducts (CDCs). It activates the basolateral Na^+/K^+/-ATPase thereby increasing Na^+ and water reabsorption into the blood and secretion of K^+ into the urine. Aldosterone also upregulates the amiloride sensitive sodium channels in the apical membranes of CDC and stimulates H^+ secretion by intercalated CDC cells, thereby influencing acid-base balance [10]. K^+ secretion can be partially counteracted by reabsorption in the intercalated cells in the cortical and outer medullary collecting tubules [11,12]. Vasopressin increases K^+ secretion in the medullary collecting duct while promoting antidiuresis [13].

Acid-base balance can affect the balance between cellular and extracellular potassium concentration. Acidosis increases the plasma K^+ concentration by inducing a net shift of K^+ from the cellular to the extracellular

compartment in exchange with H^+, also leading to a reduced tubular secretion of potassium.

Insulin is important in preventing a large change in extracellular K^+ concentration as it increases potassium uptake into liver and muscle cells by stimulating Na^+/K^+/-ATPase. Large increases in extracellular K^+ concentration (> 1,0-1,5mmol/l) stimulate insulin secretion, which promotes shift of excess K^+ into the intracellular compartment. Catecholamines (adrenaline, noradrenaline, dopamine) binding to beta-2-receptors on muscle cells stimulate Na^+/K^+/ATPase and cause increased shifts into cells. In patients with normal renal function large amounts of potassium are needed to achieve hyperkalemia, whereas in patients with impaired renal function especially when GFR< 15ml/min a slight increase in potassium intake can cause severe hyperkalemia [14].

As mentioned before diabetes mellitus and cardiovascular disease can cause hyperkalemia directly or indirectly and often cluster with CKD. Diabetes mellitus can be associated with hyporeninemic hypoaldosteronism, resulting in decreased tubular potassium secretion [15,16]. The use of cardiovascular classes has become one of the major causes of hyperkalemia in clinical practice. Among these,beta-2-receptor blockers inhibit renin production and hampers potassium redistribution to the intracellular space [17], heparin inhibits aldosterone production [18] and digitalis glycosides block Na^+/K^+/ATPase and hence impair collecting duct potassium secretion [19]. However, the magnitude of the increase in serum potassium attributable to them is typically only 0,2-0,5mmol/l [20,21].

More relevant are the RAASi e.g. angiotensin converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors and mineralocorticoid receptor antagonists [3]. Hyperkalemia attributable to these medications is uncommon in patients without CKD (<2%), but the incidence rises to 5% with dual RAASi therapy and to 10% in patients with CKD [2,22-25]. Only 8% of patients newly started on a RAASi maintained treatment therefore [26].

Diagnosis

Hyperkalemia can be classified according to serum potassium into mild (5,5-6,5mmol/l), moderate (6,5-7,5mmol/l) and severe (>7,5mmol/l) hyperkalemia. Hyperkalemia is rarely associated with symptoms. Occasionally patients complain of palpitations, nausea, muscle pains, or paraesthesia. However, moderate and especially severe hyperkalemia can lead to disturbances of cardiac rhythm, which can be fatal [27,28]. ECG monitoring is mandatory in patients with serum potassium >6,5mmol/l. ECG changes may present as non-specific repolarization abnormalities 'peaked T-waves' and QRS widening as well as depression of ST-segment.

Management

1. If there is severe hyperkalemia, start ECG monitoring.

-Ca-gluconate 10% can be used in patients to stabilize membrane potential, except in digoxin-intoxicaton.

2. Identify and immediately eliminate sources of potassium intake.

-Review prescriptions and stop oral or parenteral potassium supplements.

-Stop all drugs that might cause or aggrevate hyperkalemia.

-Check on potassium-rich foods in patients with CKD.

3. Increase potassium shift from extra-to intracellular space.

-Dextrose and/or insulin infusion.

-Beta-adrenergic agonists (salbutamol, reproterol) stimulate potassium shift from extra-to intracellular space.

-Sodium bicarbonate, preferably given to patients who are acidotic.

4. Increase potassium excretion.

-Loop diuretics as e.g. furosemide.

-Ion-exchange resins

-Renal replacement therapy (RRT) is the ultimate measure in severe hyperkalemia.

Ion-Exchange Resins (Kayexalate, Resonium)

For over 50 years the only potassium binder that was available in the U.S. was sodium polysterene sulfonate and it was mainly used in the context of acute hyperkalemia [29]. The approval of sodium polysterene sulfonate in 1961 for treatment of hyperkalemia was based on a clinical trial involving 32 azotemic patients, and showing a significant decrease of 0,9mmol/l n serum potassium over 24hours [30]. The efficacy of sodium polysterene sulfonate as an acute intervention for hyperkalemia has also been shown in a small retrospective analysis of 154 hyperkalemic patients with mean serum potassium of 5,9mmol/l in whom serum potassium decreased by 0,7-1,1mmol/l in response to the binder therapy [29]. Sodium polysterene sulfonate is an acute intervention but its onset of action takes several hours. In emerging situations it should be used in conjunction of other interventions with shorter onset of action [31].

The use of sodium polysterene sulfonate as a chronic intervention for hyperkalemia has never been approved, although the off-label application is common. In an observational study of 14 patients treated with sodium polysterene sulfonate, hyperkalemia was successfully corrected and controlled [32]. Notwithstanding the lack of larger clinical trials, the effectiveness of sodium polysterene sulfonate towards hyperkalemia management is generally accepted. There are some case reports describing severe upper and lower GIT injuries following its administration, but these are rare [33,34]. Insufficient data about the efficacy and safety of sodium polysterene sulfonate, the lack of an indication for its use in chronic hyperkalemia and the poor tolerance of this medication has led to two new potassium binders for chronic hyperkalemia therapy.

Patiromer (Veltassa)

Patiromer is a non-absorbable polymer which exchanges potassium with calcium and was approved in 2015 by the FDA for the treatment of hyperkalemia. The randomized controlled clinical trials which tested the efficacy and safety of patiromer have enrolled in excess over 500 patients total, and have shown that elevated levels of potassium were lowered effectively and normokalemia was maintained up to 52 weeks, even while RAASi therapy was maintained [6,35-37]. The mean decrease in serum potassium with patiromer in the different studies was 0,5-1,0mmol/l with larger decreases seen in patients with higher serum potassium levels. The most common adverse events with patiromer administration were constipation, hypomagnesemia, diarrhoea, nausea, abdominal discomfort and flatulence. Serious adverse effects were rare, and the rare observed fatalities were reportedly unrelated to patiromer use.

Agarwal *et al.* will define the ability of patiromer to facilitate the use of spironolactone, an effective antihypertensive therapy for resistant hypertension and chronic kidney diseases (CKD) in the upcoming AMBER trial (n=290)-[38]. Kloner *et al* showed in the open-label TOURMALINE that patiromer, a sodium-free, non-absorbed potassium binder, lowers serum potassium similar when given with or without foods. Patiromer was effective and generally well tolerated in this study, whether or not patients were taking RAAS inhibitors [39].

Zirconium Cyclosilicate (Lokelma)

Sodium zirconium cyclosilicate (Lokelma) has recently been approved by the FDA [7]. Lokelma is an oral sorbent that is highly selective to trap potassium ions throughout the GI tract [40]. Because of its high selectivity zirconium cyclosilicate may bind potassium in the upper GI tract where the amount of potassium is high but the concentration is low [41]. The HARMONIZE study had an open-label acute treatment phase (10g zirconium cyclosilicate thrice daily for 48 hours) in 258 patients with serum potassium > 5,1mmol/l and a second phase in those who achieved normal potassium in the first phase (92%), who were randomized to chronic treatment (placebo, and 5g,10g or 15g per day of zirconium cyclosilicate)- [42].

Zirconium cyclosilicate exerted its potassium lowering effect relatively quickly, with a median time to potassium normalization of 2,2 hours, and showed a dose-response relationship in the chronic treatment phase. The overall adverse event rates were similar across the different groups, except for edema and hypokalemia and a suggestion of increased risk of urinary tract infections [42].

In another randomized, double-blind, placebo-controlled trial 753 patients with serum potassium levels of 5,0-6,5mmol/l were assigned to 3 different doses of zirconium cyclosilicate thrice daily for 48 hours versus placebo [41]. Serum potassium decreased by a mean of 0,73mmol/l in patients receiving 10g zirconium cyclosilicate. After the initial 48hours, 543 patients who achieved normokalemia were randomized to the original zirconium cyclosilicate dose administered once daily versus placebo for 12 days. In this chronic phase, significantly more patients receiving 5g and 10g zirconium cyclosilicate maintained normokalemia compared with placebo [41].

Conclusion

More than 50 years after the introduction of sodium polysterene sulfonate as a potassium binder in hyperkalemia, two novel hyperkalemia drugs have entered the market. Their principal advantage is that they enable patients to continue RAASi treatment in CHF, diabetes mellitus and CKD. Patiromer may have an additional benefit over zirconium cyclosilicate because it is sodium-free. Both of these novel potassium binders have tested well as safe and efficacious drugs in clinical trials pending FDA approval.

They may result in a change in our therapeutic paradigm, by favouring the chronic use of a potassium binder over discontinuation of RAASi therapy or strict restrictions of dietary potassium. Whether the effects of such a novel strategy will also result in improved long-term clinical outcomes should be investigated in future large scale trials as e.g. the AMBER trial [38].

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