CHALLENGES AND CONSIDERATIONS IN THE MANAGEMENT OF HYPERKALAEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Chairperson
David Goldsmith

Speakers
Johannes F. E. Mann, Martin H. de Borst

1. Renal Unit, Guy’s and St Thomas’ Hospital, London, UK
2. Department of Nephrology and Hypertension, Friedrich Alexander University Erlangen-Nürnberg and KfH Kidney Center, Munich-Schwabing, Germany
3. Division of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

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MEETING SUMMARY

Prof David Goldsmith opened the symposium by highlighting the objectives of the meeting. The education objectives of the symposium were to summarise the mechanisms that regulate potassium balance, specifically highlighting how these mechanisms are affected by inhibition of the renin-angiotensin-aldosterone system (RAAS); to examine the pathophysiology of hyperkalaemia and illustrate the impact on clinical outcomes; to evaluate current clinical evidence and outline key considerations that help determine the urgency; and to describe recent clinical trial data on investigational oral ion exchangers and the potential future role of these emerging therapies in clinical practice.

In the first presentation, Prof Johannes F. E. Mann discussed the predisposing factors of hyperkalaemia by presenting a case of a heart failure (HF) patient with Stage 3 chronic kidney disease (CKD), and also discussed the epidemiology and pathophysiology of hyperkalaemia. Dr Martin H. de Borst then discussed the current therapeutic options available for the outpatient treatment of hyperkalaemia, along with recent clinical data on novel treatments, in particular patiromer and zirconium cyclosilicate (known as ZS-9).
Pathophysiology and Risk of Hyperkalaemia

Professor Johannes F. E. Mann

Prof Mann presented the case of a male patient with known congestive HF and CKD Stage 3 (creatinine in the range of 2 mg/dL) to highlight the predisposing factors of hyperkalaemia. The patient was admitted with general muscular weakness, and his underlying diseases included ischaemic heart disease and Type 2 diabetes mellitus (T2DM). He was appropriately treated with ramipril, eplerenone, furosemide, bisoprolol, digoxin, and more recently hydrochlorothiazide plus amiloride (prescribed by his family physician). The patient’s laboratory results revealed a high serum potassium level (6.7 mmol/L), substantial metabolic alkalosis (pH: 7.53; HCO₃⁻: 33 mmol/L), recovery of serum creatinine to 4.3 mg/dL, and blood glucose 120 mg/dL. Although the patient’s serum potassium level was not exceedingly high and his prior electrocardiogram (ECG) was normal, ECG results at presentation showed a wide QRS complex (left bundle branch block) and a PQ interval at the higher end. As a result, the patient underwent dialysis, leading to a reduction in his serum potassium and ECG normalisation post-dialysis; this indicated that his hyperkalaemia was responsible for the observed left bundle branch block.

With regards to his medications, all were considered likely contributors to his hyperkalaemia, except for furosemide and hydrochlorothiazide. However, careful evaluation is required to ensure that discontinuation of any medications accounting for hyperkalaemia will not have an adverse impact on clinical outcome. For example, angiotensin-converting enzyme (ACE) inhibitors like ramipril have been shown to improve both survival in patients with HF and renal outcomes in patients with or without diabetes, while eplerenone also improves survival in HF patients. Additionally, the β-blocker, bisoprolol, has been associated with improved survival in patients with HF, including those with renal impairment. In contrast, the DIG study demonstrated that digoxin provided symptomatic improvements but had no effect on survival. Similarly, furosemide and amiloride do not contribute to improvement of survival nor do they preserve renal function. As a result, the discontinuation of furosemide, amiloride, and digoxin may be appropriate given that these agents are unlikely to contribute to his outcomes. Taken together, this case highlights two major predisposing factors for hyperkalaemia, the patient’s underlying diseases (i.e. congestive HF, CKD, ischaemic heart disease, T2DM) and the use of medications that may have interfered with potassium disposal. This is supported by a recent large, nested, case-control study, which identified renal failure, T2DM, and current use of potassium-sparing diuretics as significant risk factors for hyperkalaemia in patients with newly diagnosed HF.

The epidemiology of hyperkalaemia can be best described by its prevalence in large clinical trials of relevant patient populations (i.e. cardiovascular disease [CVD], diabetes, CKD). In the HOPE trial evaluating RAAS inhibition with ramipril in >9,000 patients at high cardiovascular risk over approximately 4.5 years, the incidence of hyperkalaemia (serum potassium ≥5.0 mmol/L) in the ramipril and placebo arms were 8.7% and 6.5%, while 1.2% and 0.7% of patients had serum potassium ≥5.5 mmol/L, respectively. Substantial rates of hyperkalaemia were also reported in the ONTARGET trial of >25,000 high-risk patients with CVD or diabetes, with serum potassium ≥5.0 mmol/L being observed in 3.7% and 5.7% of patients in the ramipril and ramipril plus telmisartan treatment arms, respectively; serum potassium ≥5.5 mmol/L was reported in 1.6% and 2.7% of patients, respectively. It should be noted that active study treatment was administered to all patients during the run-in phase of both studies, which resulted in approximately 1% of patients being excluded from both studies due to hyperkalaemia; this may in part account for the high incidence of hyperkalaemia in the placebo arm of the HOPE trial. The findings of these two studies highlight the increased risk of hyperkalaemia following RAAS inhibition in the cardiology setting, particularly during intensive blockade with dual therapy.

The prevalence of hyperkalaemia is high in the nephrology setting, as demonstrated by data from the RENAL trial, which evaluated losartan versus placebo in >1,000 patients with T2DM and nephropathy. In the overall RENAL population, 30.6% of patients had serum potassium ≥5.0 mmol/L, comprising 38.4% of patients in the losartan and 22.8% in the placebo arms; serum potassium ≥5.5 mmol/L was reported in 10.8% and 5.1% of patients, respectively. Importantly, the incidence of hyperkalaemia was high in the placebo arm of this study despite patients not being allowed concomitant use of RAAS inhibitors, indicating that both diabetes and renal impairment...
distal tubules is a critical step to its excretion given the nephron. The secretion of potassium via the kidneys in the distal tubules of the nephron. Potassium disposal is regulated by aldosterone and the nervous system through ATPase, which is upregulated by the sympathetic nervous system. Potassium uptake from the blood into the intracellular space is followed by uptake into cells. Potassium in the gastrointestinal tract, with 98% of the body's potassium being stored intracellularly. Potassium in the diet is absorbed via the gastrointestinal tract. A transient increase in serum potassium levels of >1 mmol/L as a result of local potassium release in a tourniquet-clenching technique during phlebotomy resulted in hyperkalaemia. The findings of these studies emphasise the challenges faced by clinicians when treating patients at high cardiovascular and/or renal risk. Although pharmacological RAAS inhibition carries a risk of hyperkalaemia, one must consider if the major renal and cardiovascular benefits of inhibiting the RAAS outweighs the risk of hyperkalaemia.

An important issue in the management of hyperkalaemia is to determine if there is a threshold at which hyperkalaemia is considered dangerous, warranting prompt intervention. This issue was addressed in a recent study that analysed data from >50,000 ambulatory CKD patients (eGFR <60 mL/min/1.73 m²) having serum potassium >5.5 and >6.0 mmol/L (14.9% and 4.7%, respectively). Furthermore, data from the ONTARGET trial indicated that elevated urinary albumin increases the risk of hyperkalaemia, particularly in the presence of low eGFR, with >10% of patients with macroalbuminuria and eGFR <60 mL/min/1.73 m² having serum potassium levels in excess of 5.5 mmol/L. The findings of these studies emphasise the challenges faced by clinicians when treating patients at high cardiovascular and/or renal risk. Although pharmacological RAAS inhibition carries a risk of hyperkalaemia, one must consider if the major renal and cardiovascular benefits of inhibiting the RAAS outweighs the risk of hyperkalaemia.

Pseudohyperkalaemia as a result of the tourniquet-and-fist-clenching technique during phlebotomy can best describe the pathophysiology of hyperkalaemia. In this small study, the application of a tourniquet in addition to fist clenching resulted in a transient increase in serum potassium levels by >1 mmol/L as a result of local potassium release due to contraction of the forearm muscles. Potassium in the diet is absorbed via the gastrointestinal tract, with 98% of the body's potassium being stored intracellularly. Potassium uptake from the blood into the intracellular space is regulated by the ion transporter, sodium-potassium ATPase, which is upregulated by the sympathetic nervous system through β-receptors and insulin. Potassium disposal is regulated by aldosterone and occurs through the kidneys in the distal tubules of the nephron. The secretion of potassium via the distal tubules is a critical step to its excretion given that potassium is freely filtered and fully reabsorbed in the proximal tubules. This step requires the presence of sufficient sodium levels and energy provided by sodium-potassium ATPase, which removes sodium and drives potassium into the cell and the urine. Therefore, impaired renal potassium excretion is key to the pathophysiology of hyperkalaemia.

One example of pharmacological interference of the mechanism involved in renal potassium disposal is volume depletion due to intensive diuretic therapy in chronic heart failure patients, which results in substantial increases in proximal tubular sodium reabsorption, leading to reduced delivery of sodium into the distal tubule cells via the epithelial sodium channel, thus decreasing potassium secretion. Other drugs that interfere with the epithelial sodium channel include amiloride, triamterene, trimethoprim, tacrolimus, and cyclosporine. Given that aldosterone is a major regulator of potassium excretion, drugs or diseases (e.g. diabetes, hyporeninaemic hypoaldosteronism) that result in low aldosterone levels can lead to decreased expression of the sodium channel. Finally, digitalis compounds are a potent inhibitor of sodium-potassium ATPase and β-blockers interfere with this pump. Therefore, there are multiple ways where drugs, including RAAS inhibitors, can interfere with potassium excretion in the kidneys. Insulin deficiency, β-blocker therapy and the presence of CKD can also decrease the activity of sodium-potassium ATPase in cells outside of the kidney, thus reducing the cellular uptake of potassium.

Current and Emerging Options for Outpatient Treatment of Hyperkalaemia

Doctor Martin H. de Borst

Dr de Borst opened his presentation by referring to Prof Mann’s case study to discuss approaches to the acute management of hyperkalaemia. Initial management of the patient would likely include a calcium infusion and a combined insulin-glucose infusion, which both have a rapid onset of effect. However, these acute interventions are short-lasting, and hyperkalaemia will eventually reoccur. As previously mentioned, starting haemodialysis is another approach with a rapid effect. Following these strategies, a current possibility would be the use of an ion exchanger, such as sodium polystyrene sulphonate (SPS) or a calcium-containing...
alternative (CPS) available in some countries, which has an onset of effect of 2–4 hours with a duration of action of 4–6 hours. Additional interventions that may also be initiated in the acute setting based on the specific properties of this patient include fluid supplementation to manage dehydration, diuretic therapy, correction of metabolic acidosis with bicarbonate supplementation, and salbutamol or fludrocortisone to promote rapid potassium excretion. Lastly, close monitoring of the patient is required, potentially in the intensive care unit, involving the monitoring of ECG and laboratory results.

The chronic management of hyperkalaemia involves three major approaches: management of potassium intake, metabolism, and excretion (Figure 1). Potassium intake can be managed by dietary restriction of potassium-rich fruits (e.g. bananas, apples, mangoes). However, avoiding these foods on a daily basis may not always be beneficial as they may also contain vitamins, fibre, and other nutrients that are essential for a healthy diet. Indeed, findings of the international PURE study in >100,000 individuals from the general population demonstrated that a very low potassium intake using the surrogate measure of 24-hour potassium excretion may also be associated with an increased risk of death or cardiovascular events. Furthermore, the U-shaped association of serum potassium levels with mortality in the CKD population indicated that both very high (≥6 mmol/L) and very low (<3.5 mmol/L) serum potassium levels significantly increased mortality risk, suggesting that high and low intake of potassium should be avoided. Therefore, although the management of potassium intake may be appropriate in most patients at risk of hyperkalaemia, careful consideration must be undertaken before prescribing daily restriction of potassium in the diet.

The chronic management of hyperkalaemia may also require the correction of coexisting metabolic abnormalities. The presence of metabolic acidosis may be corrected by sodium bicarbonate supplementation, which has also been previously shown to retard CKD progression and renal function loss. Additionally, the correction of hyperglycaemia will have a beneficial impact on serum potassium levels. Furthermore, medications that influence potassium homeostasis should be reassessed to determine if their use may be temporarily or permanently discontinued. While RAAS inhibitors (ACE inhibitors and angiotensin II receptor blockers) and mineralocorticoid receptor antagonists can increase the risk of hyperkalaemia, the discontinuation of these drugs may not be appropriate as they provide long-term preservation of renal function. Other medications contributing to hyperkalaemia that should be reassessed include diuretics, antibiotics, non-steroidal anti-inflammatory drugs, β-blockers, heparin, digitalis, calcineurin inhibitors, and potassium-containing supplements.

Figure 1: Chronic management of hyperkalaemia.
SPS: sodium polystyrene sulphonate; ZS-9: sodium zirconium cyclosilicate; EMA: European Medicines Agency.
With regards to the excretion of potassium, treatment with diuretics in patients with fluid overload and/or hypertension may promote renal potassium excretion, but this approach is limited in patients with advanced CKD. Mineralocorticoid stimulation with drugs such as fludrocortisone may promote intestinal potassium excretion, but is offset by the potential complication of sodium retention. As previously mentioned, SPS is a resin ion exchanger commonly used to treat hyperkalaemia, along with the alternative CPS; these two compounds promote intestinal potassium excretion by exchanging potassium for sodium (SPS) or calcium (CPS). To date, the clinical data for SPS in the management of hyperkalaemia are limited to early open-label studies reporting reductions in serum potassium of >1 mmol/L.\(^{20,21}\) and a recent small randomised controlled trial reporting a reduction in potassium of 1.04 mmol/L (95% CI: -1.37 to -0.71) in outpatients with CKD and mild hyperkalaemia (5.0–5.9 mmol/L).\(^{22}\) Safety data did not reveal clear differences in tolerability between SPS and placebo in this study.\(^{22}\) However, the taste of SPS may be an important tolerability issue, making its long-term use less than ideal in this setting. Therefore, additional strategies targeting the excretion of potassium are needed.

Two novel drugs were recently developed for the treatment of hyperkalaemia. Patiromer is a spherical non-absorbed polymer that exchanges potassium for calcium, while ZS-9 is a non-absorbed oral powder that acts as a potassium selective ion trap.\(^{23,24}\) Patiromer was recently approved by the US Food and Drug Administration (FDA) for the treatment of hyperkalaemia, but ZS-9 has yet to receive FDA approval; neither agent has been approved by the European Medicines Agency (EMA).

Two recent clinical trials evaluated the efficacy and safety of patiromer in the CKD setting. The short-term efficacy of patiromer was evaluated in the 2-part, pivotal OPAL-HK trial (N=237).\(^{25}\) CKD patients who were using RAAS inhibitors and had a potassium of 5.1 to <6.5 mmol/L were initially treated with patiromer for 4 weeks. Serum potassium levels were significantly reduced by approximately 1 mmol/L from 5.6 to 4.6 mmol/L at Week 4. Furthermore, a target potassium level of 3.8 to <5.1 mmol/L was achieved by 76% of patients during the initial treatment phase. A total of 107 patients reached the target potassium level and were subsequently randomised to patiromer or placebo for 8 weeks in Part 2 of the trial. During this phase, recurrent hyperkalaemia was reported in 60% of placebo recipients, compared with 15% of patiromer recipients, at Week 8.

The long-term treatment effects of patiromer were evaluated for 52 weeks in the Phase II, open-label AMETHYST-DN trial (N=306),\(^{26}\) which randomised patients with T2DM and kidney disease (eGFR: 15 to <60 mL/min/1.73 m\(^2\); serum potassium: >5.0 mmol/L) to one of three patiromer dosages, titrated to reach serum potassium <5.1 mmol/L; all patients received RAAS inhibitors before and during treatment. A reduction from baseline in serum potassium was observed at Week 4, which persisted through Week 52; however, patiromer withdrawal resulted in the return of serum potassium to approximately 5.0 mmol/L. Safety data in both patiromer clinical trials indicated that gastrointestinal adverse events (AEs; constipation, diarrhoea, and nausea) were the most common events, occurring in approximately 3–5% of patients; hypomagnesaemia was also reported in approximately 7% of patients from the AMETHYST-DN trial.\(^{25,26}\)

ZS-9 has been evaluated in two randomised, double-blind, placebo-controlled, Phase III trials. The HARMONIZE trial evaluated the short-term efficacy of ZS-9 therapy for 28 days in 258 patients with hyperkalaemia (potassium ≥5.1 mmol/L).\(^{27}\) During an initial 48-hour open-label phase, ZS-9 reduced serum potassium from 5.6 mmol/L at baseline to 4.5 mmol/L at 48 hours; analysis by patient subgroup demonstrated the consistent short-term potassium-lowering effect of ZS-9 (approximately 1 mmol/L) in patients with CKD, HF, diabetes, and those receiving RAAS inhibitors. During the randomised phase, ZS-9 was associated with significant dose-dependent reductions in potassium levels from Days 8–29, compared with placebo.

In the second Phase III trial by Packham et al.\(^{28}\) (N=753), initial treatment with ZS-9 at four dosages also effectively reduced serum potassium levels in a dose-dependent manner at 48 hours in patients with hyperkalaemia (5.0–6.5 mmol/L), with sustained normokalaemia (3.5–4.9 mmol/L) observed through 12 days of maintenance therapy in both the 5 and 10 g ZS-9 arms, which remained significant versus placebo; however, withdrawal of ZS-9 resulted in the return of serum potassium levels similar to that of the placebo arm.\(^{28}\)
Safety data from the two ZS-9 studies indicated that treatment during the short-term period was well-tolerated, with AE rates of 7.8% and 12.9% in the HARMONIZE trial and the Packham et al. study. The incidence of AEs increased during the maintenance phases of both studies (29.4% and 25.1%, respectively), but rates were similar to that of placebo. As with patiromer, gastrointestinal complaints (diarrhoea and constipation) were the most notable side effects in both studies; however, a high incidence of oedema was reported in the 15 g ZS-9 arm (14%) of HARMONIZE.

To date, the current treatment options for hyperkalaemia, particularly in the outpatient setting, are suboptimal and hyperkalaemia limits the optimal dosing of renoprotective therapy. The introduction of novel agents, such as patiromer and ZS-9, is likely to improve the management of hyperkalaemia, which may enable renoprotective therapy to be optimised in the long-term. Clinical trials of these novel compounds have established their short-term efficacy and safety, and long-term data appears to warrant further investigation. However, head-to-head studies comparing these agents with SPS are lacking, and there has been discussion on possible interactions with the uptake or bioavailability of other medications. Nevertheless, patiromer and ZS-9 represent a new and emergent therapeutic paradigm in the management of hyperkalaemia. Future research should focus on the potential clinical implications of these novel compounds when used in conjunction with RAAS inhibitors. Will management of hyperkalaemia with patiromer or ZS-9 improve the safety of RAAS inhibitors, allowing these agents to be used at higher dosages or as combination therapy, and will this lead to improvements in clinical outcomes?

Conclusions

Hyperkalaemia is a common complication in many patient populations, including those with CVD, diabetes, and CKD. In particular, patients with renal impairment and the concomitant use of drugs that may increase serum potassium levels (i.e. RAAS inhibitors) or interfere with potassium disposal (i.e. amiloride) are associated with an increased risk of hyperkalaemia. A critical aspect to the pathophysiology of hyperkalaemia involves impaired potassium excretion, highlighting the need for agents that target this key pathway. Current treatment options for the chronic management of hyperkalaemia are suboptimal. Although dietary restriction can manage potassium intake, this may interfere with a healthy diet. Furthermore, strategies targeting potassium excretion, such as SPS, appear to be efficacious, but are poorly tolerated and thus less ideal for long-term treatment. The need for new agents to effectively treat hyperkalaemia has seen the recent development of two novel therapies, patiromer and ZS-9, which have both demonstrated acceptable short-term efficacy and safety, along with promising long-term data. Their incorporation into clinical practice will represent a new treatment paradigm in the management of hyperkalaemia, thus allowing optimal dosing of renoprotective therapy with RAAS inhibitors in patients with CKD or those at high renal risk.

REFERENCES

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