Scientific Research Publishing

Open Journal of Nephrology, 2024, 14, 324-333
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

Hyperkalemia in Patients on Peritoneal Dialysis: Clinical Use Experience with New Potassium-Binders

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How to cite this paper: Argentino, G., Iorio, M., Mele, A.A., Camocardi, A., Cascone, E.E., Liberti, M.E., Sagliocca, A., Pota, A., Russo, L., Sirico, M.L., Terzini, G., Cavasso, M., Mennillo, C., Nettuno, F., Genualdo, R., Surfaro, G. and Di Micco, L. (2024) Hyperkalemia in Patients on Peritoneal Dialysis: Clinical Use Experience with New Potassium-Binders. *Open Journal of Nephrology*, **14**, 324-333.
https://doi.org/10.4236/ojneph.2024.143030

Received: April 2, 2024
Accepted: August 23, 2024
Published: August 26, 2024

Abstract

Background: Patients with end-stage kidney disease (ESKD) on maintenance dialysis have a high risk of developing hyperkalemia. In addition to traditional approaches, a new option for the management of patients on dialysis includes the use of a potassium binder, sodium zirconium cyclosilicate (SZC). We evaluated the effect and safety of SZC in patients with chronic PD. **Objective:** To present a case series that illustrates the real-world use of new potassium-binders in hyperkalemic patients on peritoneal dialysis. **Methods:** This case series collected 9 patients on PD with baseline potassium values > 5.5 mmol/l and who were treated with SZC 5 g once a day. Data were collected at baseline and at 1, 2, and 3 months after initiation of treatment. **Results:** The median age of patients was 64.5 years and the median duration of observation was 90 ± 5 days. It was observed that median serum potassium decreased (5.8 mmol/l at baseline with a range of 5.8 mmol/L - 6.8 mmol/L versus 4.5 in the third month with a range of 3.6 mmol/L - 5.3 mmol/L) after SZC treatment. Adverse events were observed in 2 (22.2%). The unique adverse event was constipation and presented in 2 patients (22.2%). Constipation was mild and transient during the observation period. No adverse events of special interest were reported. **Conclusion**: Normokalemia was established and maintained in this series of patients treated with SZC. No episodes of hyper- or hypo-kalemia were observed. SCZ had a good safety profile and was well tolerated over 3 months.

Keywords

SZC, Sodium Zirconium Cyclosilicate, Hyperkalaemia, Peritoneal Dialysis

1. Introduction

Patients with end-stage kidney disease (ESKD) on maintenance dialysis have a high risk of developing hyperkalemia, generally defined as serum potassium concentrations of >5.0 mmol/l, and particularly in subjects undergoing maintenance haemodialysis [1] [2]. Patients undergoing peritoneal dialysis (PD) have a lower risk of developing hyperkalaemia than those on haemodialysis (HD) due to the continuous nature of PD treatment and the residual kidney function that is retained longer in patients on PD compared to those on HD [3].

In a meta-analysis of observational studies, hyperkalemia increased the risk of cardiovascular mortality by 1.4-fold in patients on dialysis. Taken together, these studies emphasize the importance of maintaining serum potassium concentrations within the normal range in patients on dialysis [4]. Furthermore, hyperkalemia is associated with an increased healthcare burden in patients with chronic kidney disease [5].

Currently, the key approaches in the management of hyperkalemia in patients with ESKD are dialysis, dietary potassium restriction, potassium binders, use of oral bicarbonate and avoidance of medications that increase the risk of hyperkalaemia [6] [7]. Other options for the management of patients on dialysis also include the use of a newer potassium binder agent, sodium zirconium cyclosilicate (SZC), which may reduce the risk of potentially life-threatening hyperkalaemia. Its use is approved in Haemodialysis patients and on non dyalisis day. As far as we know, while there are different studies on the use of SCZ in haemodialysis [8]-[12], there is no data in peritoneal dialysis.

We evaluated the effect and safety of SZC in patients with chronic PD and its potential benefits on serum potassium variations. We also hypothesized other potential benefits such as the more extensive use of mineralocorticoid receptor antagonists, vegetarian diet with an enhancement of peristalsis (a fundamental point in PD) and reduced use of other potassium binders with known side effects such as constipation.

2. Materials and Methods

2.1. Case Selection

We report data regarding 9 patients on PD with hyperkalaemia who were treated with SZC 5 g once a day. We considered hyperkalaemia as serum potassium levels > 5.5 mmol/l. Inclusion criteria were the following: age > 18 years; signed informed consent; patients with prevalent PD with a dialysis vintage > 6 months; baseline potassium values > 5.5 mmol/l. Exclusion criteria were current participation in an interventional study. The observation period was 3 months. We reported effects of SCZ on potassium stability and safety. The effect of SZC was evaluated by change from baseline in serum potassium and percentage of patients achieving target potassium levels.

2.2. Assessments and Data Collection

This case series retrospective analysis included patients who received SCZ from

September 2022 to December 2022. Data were collected from baseline and monthly until 3 months after initiation of treatment. We collected information on demographics, medical history, and comorbidities within the 3 months before SZC initiation from medical records and/or at baseline visits. Routine measurements and assessments (e.g. laboratory parameters) registered during routine follow-up visits were collected. Prior and concomitant adverse events were reported.

2.3. Data Analysis

For descriptive analysis, we reported continuous variables with their median values and categorical variables with Number (%), at baseline and after 3 months.

3. Results

The case series included 9 patients with a median age of 64.5 years (Table 1); mean duration of observation was 90 ± 5 days. Overall, none of the patients discontinued the drug. The dose of SZC during the observational period was 5 g once a day (1 sachet powder for oral suspension a day).

Table 1. Baseline demographic and clinical characteristics.

Parameter	Baseline (n = 9)	Month 3 (n = 9)
Age, years	65 (median)	
Male, n (%)	5 (55.56%)	
Body weight, kg	76.5 (median)	73.9 (median)
Primary cause of CKD, n (%)		
Diabetes	1 (11.11%)	1 (1.11%)
Hypertension	3 (33.33%)	3 (33.33%)
Other	2 (22.22%)	2 (22.22%)
Unknown	3 (33.33%)	3 (33.33%)
Peritoneal transport types at the PET	6 LA-t (66.67%) 3 HA-t (33.33%)	6 LA-t (66.67%) 3 HA-t (33.33%)
Oligoanuric patient N (%) < 150 ml/die	5 (55.56%)	5 (55.56%)
Concomitant medication use, n (%)		
ACE inhibitors	5 (55.56%)	6 (66.67%)
ARBs	3 (33.33%)	4 (44.44%)
MRAs	0 (0%)	3 (33.33%)
Diuretic use		
Loop	4 (44.44%)	4 (44.44%)
Thiazide	4 (44.44%)	3 (33.33%)

LA-t: low-average transporter; HA-t: high-average transporters.

Adverse events were observed in 2 patients (22.2%) (Table 2). The only adverse event was constipation (22.2%). However, constipation was mild and transient during the observational period. SZC treatment was associated with a reduction in median serum potassium level (5.8 mmol/l at baseline with a range of 5.8 mmol/L - 6.8 mmol/L versus 4.5 in the third month with a range of 3.6 mmol/L - 5.3 mmol/L) after SZC treatment (Figure 1).

Table 2. Adverse events during the observation period.

AE category	N (%)
Any AE	2 (22.2%)
Any AE with death as outcome	0
Oedema-related AE	0
Hypertension	0
Any AE leading to discontinuation of SZC	0

AE adverse event.

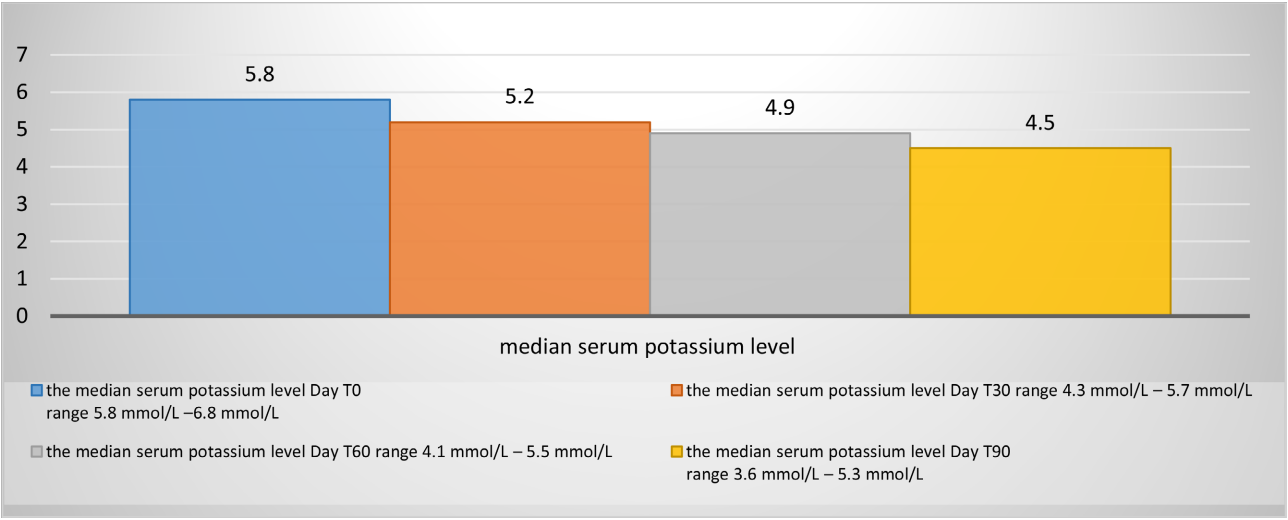

Figure 1. The median serum potassium level at the start of treatment with SZC and reduction in median serum potassium level after treatment.

4. Discussion

Patients undergoing PD have a lower risk of developing hyperkalaemia than those on HD because of the continuous nature of the dialysis treatment and since residual kidney function is retained longer with PD compared to HD [13]. The rate of potassium removal with PD is much slower but equally or more effective than HD due to the continuous nature of treatment. The average potassium clearance is approximately 17 ml/min in patients on intermittent PD and 7 ml/min in those on continuous ambulatory PD [14]. Moreover, patients on PD often receive high-dose diuretics, leading to increased urinary potassium excre-

tion. On the other hand, patients with chronic kidney disease have a higher potassium-related risk of cardiovascular mortality leading to increased healthcare burden [13] [14].

In patients with residual kidney function, renin-angiotensin-aldosterone system inhibitors (RAAS-i) are known to cause hyperkalaemia by blocking aldosterone secretion and impairing kidney excretion of potassium (**Figure 2**) [8]; however, these drugs are recommended in patients undergoing dialysis to manage cardiovascular disease and also to prevent peritoneal fibrosis [15]. The addition of the mineralocorticoid receptor antagonist (MRA) spironolactone to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy in patients on PD has been shown to decrease the rate of change in left ventricular mass index and prevent left ventricular hypertrophy [16]-[18].

In our small series, the use of the potassium binder allowed the introduction of spironolactone in 3 patients who were already treated with a RAAS-i without the appearance of hyperkalaemia and with an increase in urinary volume.

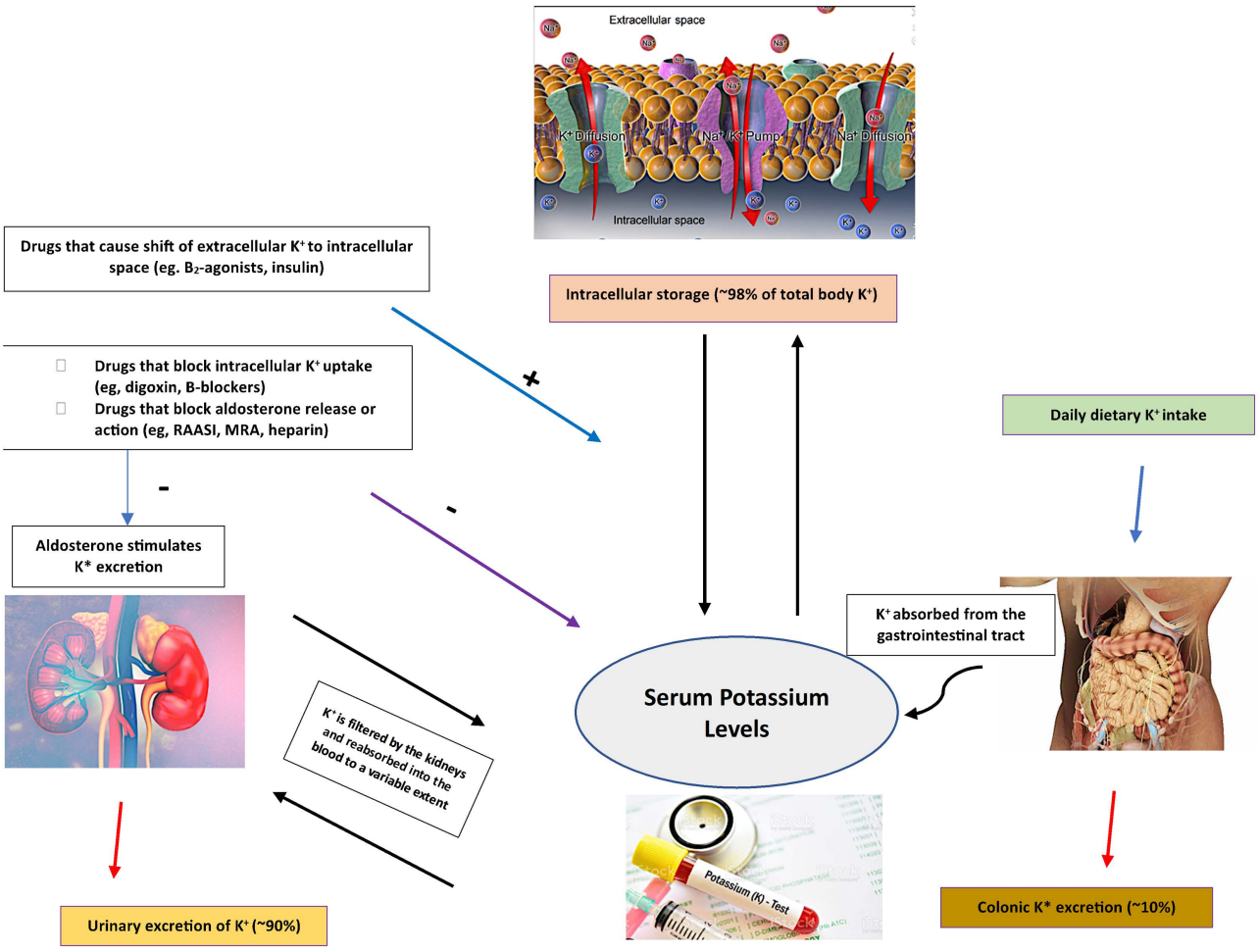

Figure 2. Schematic representation of the mechanisms controlling serum potassium (K^+) concentrations. Serum K^+ is reduced by drugs that affect intracellular potassium uptake and increased by drugs that block intracellular uptake through inhibition of Na^+/K^+ ATPase transporters. The elimination of K^+ is stimulated by aldosterone, which increases the excretion of sodium and water in the distal tubule. Drugs that result in inhibition of aldosterone secretion or its action will therefore lead to an increase in K^+.

According to the US National Academy of Sciences, the recommended daily adequate intake of potassium for healthy adults is 3400 mg in men and 2600 mg in women. For most people, intake of fruits and vegetables supplies most dietary potassium [19]. The Dietary Approaches to Stop Hypertension diet, which is rich in fruits and vegetables, low in fat, and has a target potassium intake of ~ 2238 mg/1000 kcal, has been shown to reduce blood pressure and the progression of chronic kidney disease. A plant-based diet also supplies a high fibre content, antioxidants, and trace elements, and has acid-neutralization properties that may prevent further kidney damage in patients with reduced rates of glomerular filtration [20]. Furthermore, studies in patients with HD suggest that increased fruit and vegetable intake is associated with a lower risk of all-cause mortality over 12 months and a lower risk of non-cardiovascular and all-cause mortality over 3 years [2] [21]. Obviously, a high intake of fruit and vegetables is associated with high dietary potassium.

In patients undergoing maintenance HD, high dietary potassium intake has been associated with increased 5-year mortality rates [22]. In fact, the National Kidney Foundation recommends restriction of dietary potassium intake to approximately 2000 mg/day in patients with chronic kidney disease [22]. The restrictive dialysis diet is complicated, often challenging to adhere to, and may lead to deterioration in nutritional status and health-related quality of life. Limiting potassium-rich foods, including fruits and vegetables, legumes, and grains, may increase the risk of cardiovascular disease in patients with chronic kidney disease. The recent Kidney Disease Improving Global Outcomes guidelines recommend the development of educational materials regarding the potassium content of foods that promote a low-potassium plant-based diet to be used at the clinician's discretion in patients in whom a reduction in high-potassium foods is clinically indicated [22]. Furthermore, the recommended increased protein intake in patients with ESRD can lead to a higher intake of potassium and phosphorus, an increased risk of metabolic acidosis, and a greater need for increased fluid intake [23].

The use of this new binder allowed all nine patients to take even more freely foods of plant origin, without the appearance of hyperkalaemia. Moreover, we observed a reduction in laxative administration (widely used to regulate intestinal transit, which is important in PD) [24]-[26].

No values out of the normal range in serum bicarbonate levels were reported during the maintenance phase. The mechanism of increased serum bicarbonate following treatment with SZC has not been fully elucidated. With a pore diameter of ~3.0 Å for SZC, it is possible that ammonium (2.98 Å), in addition to potassium (2.96 Å), has a high affinity for SZC. By binding to SZC, ammonium reabsorption from the gastrointestinal tract may be decreased, resulting in reduced urea synthesis and a lower consumption of bicarbonate within the liver [27] [28].

In our series, no patients showed signs or symptoms of oedema, though its occurrence was not expected. Similarly, in our patients constipation occurred

with the same frequency observed in a similar study of SZC in the patients with chronic kidney disease [28] [29]. The risk of clinically significant hypokalaemia in subjects treated with SZC is generally low and can be managed by careful monitoring and adequate medical care. We did not observe hypokalaemia in our patients [30].

The principal limitation of our study is the small sample size that affects its statistical power and generalizability.

However, this case series is the first published data on the use of SZC in patients undergoing PD. Our clinical use experience showed that SZC had a good safety profile and was well tolerated over 3 months. Normokalaemia (K levels < 5.5 mmol/l) was established and maintained with SZC in this population. There are several issues associated with the effective management of hyperkalaemia in dialysis patients [31]. The key approaches to managing hyperkalaemia are monitoring and restriction of dietary potassium intake, optimization of the dialysis prescription, and modification of medications that increase serum potassium concentrations [32]. The use of SZC in haemodialysis has been shown to normalize potassium levels, but it is used once daily only on non dyalisis days to reduce the risk of hypokalaemia. We used SZC in our patients' dialysis without observing hypokalemia and modifying diet and other drugs potentially affecting potassium levels. Thus, the availability of a new oral potassium binder may potentially reduce the need for a highly restricted diet in patients with ESRD, avoid the discontinuation of drugs such as RAASi and MRA, and reduce the risk of potentially life-threatening hyperkalaemia [33]-[35]. SZC appears to be a useful option for the treatment of hyperkalaemia, and long-term studies evaluating its safety and efficacy in patients undergoing dialysis are warranted.

Acknowledgements

The authors would like to thank the patients, their families, and all HCPs involved in this study.

Author Contributions

All authors have contributed to the concept and design of the manuscript and commented on all previous versions of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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