Patiromer Decreases Serum Potassium and Phosphate Levels in Patients on Hemodialysis

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Abstract
Background: Persistent hyperkalemia (serum potassium (K) ≥5.5 mEq/l) is a common condition in hemodialysis (HD) patients, is associated with increased mortality, and treatment options are limited. The effect of patiromer, a gastrointestinal K binder, on serum K was examined in HD patients. *Methods:* Six hyperkalemic HD patients (5 anuric) were admitted to clinical research units for 15 days (1 pretreatment week and 1 patiromer treatment week) and they received a controlled diet with identical meals on corresponding days of pretreatment and treatment weeks. Phosphate (P) binders were discontinued on admission. Patiromer, 12.6 g daily (divided 4.2 g TID with meals), was started on the Monday morning following the last pretreatment week blood sampling. Serum and 24-hour stool samples were collected daily. *Results:* Mean ± SE serum K decreased (maximum change per corresponding day, 0.6 ± 0.2 mEq/l, p = 0.009) and fecal K increased 58% on patiromer compared with the pretreatment week. During the pretreatment week, 69.0, 47.6, and 11.9% of patients' serum K values were ≥5.5, ≥6.0, and ≥6.5 mEq/l, respectively. This was reduced to 38.1% (p = 0.009), 11.9% (p < 0.001), and 2.4% (p = 0.2) on patiromer. Following P binder discontinuation, the long interdialytic interval mean ± SE serum P numerically increased from 5.8 ± 0.4 to 7.0 ± 0.5 mg/dl (p = 0.06). On patiromer, P decreased from 7.0 ± 0.5 to 6.2 ± 0.5 mg/dl (p = 0.04). While on patiromer, fecal P numerically increased by 112 ± 72 mg/day (17%; p = 0.1792; range –148 to 344 mg/day). No patient discontinued patiromer because of adverse events (AEs); none had serious AEs. *Conclusions:* In 6 hyperkalemic HD patients, patiromer decreased serum K and P levels and increased fecal K.

Introduction

Hyperkalemia is a common condition found in chronic hemodialysis (HD) patients, being present in nearly 20% of routine laboratory results from large dialysis providers [1]. While often viewed as acute or episodic, these increases in serum potassium (K) appear to reflect oscil-

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lations above a persistent hyperkalemia baseline [2]. Numerous observational studies in HD patients have reported an association between elevated K levels and increased morbidity and mortality [1, 3]. The increased event rate, and particularly sudden death, observed in the HD population is not evenly distributed over the 7-day week but is clustered toward the end of the long interdialytic interval and the immediate post dialysis period [4]. These data raise the possibility that hyperkalemia occurring during the long interdialytic interval and the acute decreases in the serum K concentrations induced by the HD procedure may play a role in the increased event rate and mortality seen in HD patients.

Patiromer is an FDA-approved, sodium-free, nonabsorbed K-binding polymer shown to reduce serum K levels in patients with chronic kidney disease (CKD), with and without heart failure [5–8]. Patiromer exchanges calcium (Ca) for K in the gastrointestinal tract, primarily in the colon where active K secretion occurs, the pKa of patiromer is optimal for ion exchange, and the polymer has the longest residence time [9–11]. This phase 2 study was performed early in the clinical development program following studies in healthy volunteers. The primary objective of this study was to assess the efficacy of patiromer in reducing the serum K in HD patients and to evaluate the safety and tolerability of patiromer in this patient population.

Methods

The study protocol was reviewed and approved by an institutional review board (Copernicus Group, Research Triangle Park, N.C., USA) and written informed consent was obtained from each patient prior to enrollment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in accordance with International Conference on Harmonization/ Good Clinical Practice guidelines.

Six patients were enrolled and admitted to the clinical research unit at 2 sites (Minneapolis, Orlando) on a Sunday and they remained confined throughout the 2-week study (1 pretreatment week and 1 patiromer treatment week). Patients received 3 times per week HD and were required to have a serum K ≥5.5 mEq/l and a Kt/V ≥1.2 for entry into the study. All patients were on a stable dialysis prescription, including a stable dialysate K prior to admission and remained on that same prescription throughout the study. All patients were dialyzed on a Monday–Wednesday–Friday schedule and received treatment approximately the same time of day throughout the study. On admission, patients were placed on a K-, magnesium (Mg)-, Ca-, and Na-controlled diet throughout the study period with identical meals on corresponding days of the pretreatment and patiromer treatment weeks. It was essential that dietary intake remained unchanged from the time of screening through the end of study participation. No food or drink other than that provided by the Clinical Research Unit was consumed during the entire study period. On average, the daily K-, Mg-, Ca-, and Na-controlled diet provided the following micronutrients (mean ± SE): K 2,760 ± 60 mg, Na 2,692 ± 93 mg, Ca 619 ± 22 mg, Mg 225 ± 27 mg. Any unconsumed food was recorded.

P binders, Ca supplements, and the polymer-based medications colesevelam and colestipol were discontinued on admission and along with commercially available K-binding resins were not allowed during the study period. No subject had received sodium polystyrene sulfonate (SPS) in the 30 days preceding study entry. All treatments were administered in the Clinical Research Unit under the supervision of clinical personnel.

Serum chemistries were measured on a daily basis (pre-HD on HD days). Serum bicarbonate was not measured during the course of the study. Only 1 patient produced more than 200 ml of urine per day and the ionic content of the urine was not analyzed. Twenty-four-hour stool samples were collected during the entire confinement period. Each 24-hour fecal collection was homogenized and aliquots were then analyzed for K, Na, Ca, Mg, and P. Change from baseline in fecal ion excretion was evaluated by comparing the mean daily fecal excretion of the ion during the patiromer treatment week (Tuesday–Monday) versus the pretreatment week (Tuesday–Monday). Serum measurements were performed at the MedTox Laboratory (St. Paul, Minn., USA) and fecal analyses at the Battelle Toxicology Northwest (Richland, Wash., USA).

Electrocardiograms (ECGs) were performed in triplicate daily with the patient resting and prior to the morning patiromer dose. On HD days, triplicate ECGs were performed prior to HD, at the mid-dialysis time point, and 1 h post HD.

Patiromer, at a total daily dose of 12.6 g/day, was administered as 4.2 g TID with meals starting on the Monday morning of week 2.

Statistics

Originally, it was planned that 12–24 patients would be assessed, but due to difficulty in the enrolling process, the study was stopped after assessment on 6 patients was completed. Due to the limited number of patients, the statistical inference testing results were conducted only for descriptive purposes. Descriptive statistics were summarized as mean ± SE for continuous variables or as proportions for categorical variables unless specified otherwise. The protocol had a one-day run-in period on the diet, which is why the values on the first Monday of treatment was not analyzed; rather Tuesday–Monday values of the pre-patiromer week was compared to the Tuesday–Monday values of the patiromer treatment week. The changes on the corresponding days between pretreatment week and the patiromer treatment week in serum potassium and phosphate concentrations were analyzed by paired t test using SAS (version 9.4). The proportions of patients in each defined potassium range between the pre-treatment and the patiromer treatment week were analyzed by Fisher's exact test.

Results

Six patients enrolled and completed all study activities. One patient was enrolled in error with a screening K of 5.1 mEq/l but remained in the study. The mean ± SD age was 50 ± 4 (range 44–55) years. Five patients were male

Table 1. Patient demographic and characteristic information

	Patient number					
	02–001	02–003	02–005	02–010	02–016	03–008
Demographic						
Age, years	48	55	45	50	53	44
Gender	Male	Male	Female	Male	Male	Male
Race	Black	Black	Black	Black	White	White
BMI, kg/m^2	20.4	22.5	29.7	25.4	31.1	31.9
BP systolic, mm Hg	106	130	138	110	117	152
BP diastolic, mm Hg	70	70	88	53	68	98
Pulse, bpm	66	80	94	71	84	90
Laboratory results						
Baseline K (pre-HD Monday), mEq/l	5.7	7.0	5.1*	5.6	7.9	6.2
Baseline Ca, mg/dl	8.7	8.9	9.8	9.3	8.9	8.4
Baseline P, mg/dl	5.4	4.7	5.2	5.2	7.5	6.5
Dialysis vintage, months	22.0	71.2	80.7	261.1	46.1	>95.5
ACEi/ARB use (yes/no)	Yes	Yes	Yes	No	No	No
HD prescription						
Dialysis time, min	210	210	210	240	240	240
Filter type	CT190G	CT190G	Polyflux 17R	Polyflux 210H	CT190G	F180
Dialysate K, mEq/l	1.5	1.5	3	3	1.5	2
Dialysate Ca, mEq/l	2.5	2.5	2.2	2.5	2.5	2.5
Dialysate bicarbonate, mEq/l	38	38	38	38	38	Not listed
Dry weight, kg	66.2	61	72.3	75.6	94.5	95.5
HD medications						
Paricalcitol, µg	3 TIW	4 TIW	7 TIW	9 TIW	2 TIW	0
Epoetin alfa, units	4,400 TIW	3,300 TIW	9,900 TIW	4,400 TIW	2,200 TIW	0
P binders	Ca acetate	Ca acetate	Ca acetate	Sevelamer	Not listed	Ca acetate

ACEi = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; TIW = 3 times a week.

* Patient enrolled in error with K <5.5 mEq/l.

and 4 were black. Additional demographic information is shown in table 1. All 6 patients had extensive comorbid illnesses. Concomitant medical conditions present in all 6 patients at the time of the study in addition to end-stage renal disease (ESRD) included hyperkalemia, hyperparathyroidism, anemia, and hyperphosphatemia. In addition, 4 patients had concurrent hypertension. Patients were on multiple medications but were on stable doses for at least 15 days prior to the start of the study and throughout the study. Four patients received a beta-blocker, 2 an angiotensin-converting enzyme inhibitor, and 1 an angiotensin receptor blocker.

After 1 day of treatment, the serum K numerically decreased on patiromer versus the pretreatment week by 0.3 ± 0.3 mEq/l (p = ns; n = 6) when comparing the corresponding days of the week. The maximum difference was achieved at day 7 where the patiromer treatment serum K was 0.6 ± 0.2 mEq/l lower than the value on the corresponding pretreatment day (p = 0.009; n = 6; fig. 1). Online supplemental figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000451067) shows individual subjects' serum K values over time and demonstrates the variability of serum K in HD patients, while online supplemental figure 2 shows the average serum K values for the patiromer treatment week versus the pretreatment week by treatment day. During the pretreatment week, 69.0, 47.6, and 11.9% of patients' daily serum K values were ≥5.5, ≥6.0, and ≥6.5 mEq/l, respectively. These proportions were reduced to 38.1% (p = 0.008), 11.9% (p < 0.001), and 2.4% (p = 0.2), respectively, on patiromer (fig. 2). While on patiromer, fecal K excretion increased by 359 ± 113 mg/day (58%; equivalent to 64.4 ± 20.3 mEq/week) over the pretreatment week (p = 0.02; range 110–739 mg/day), while fecal Ca increased by 1.3 ± 0.1 g/day (172%; p < 0.01; range 0.7–1.5 g/day), fecal Na

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Fig. 1. Serum K values over time during the pretreatment week and the patiromer treatment week. HD treatments are indicated by arrows. All patients were admitted to the research unit on a Sunday and started on the controlled diet Monday AM.
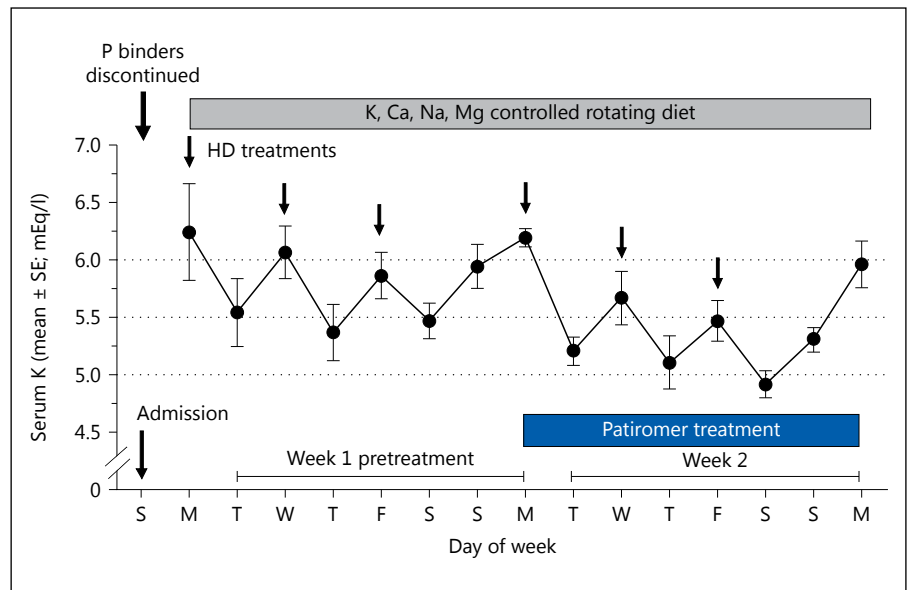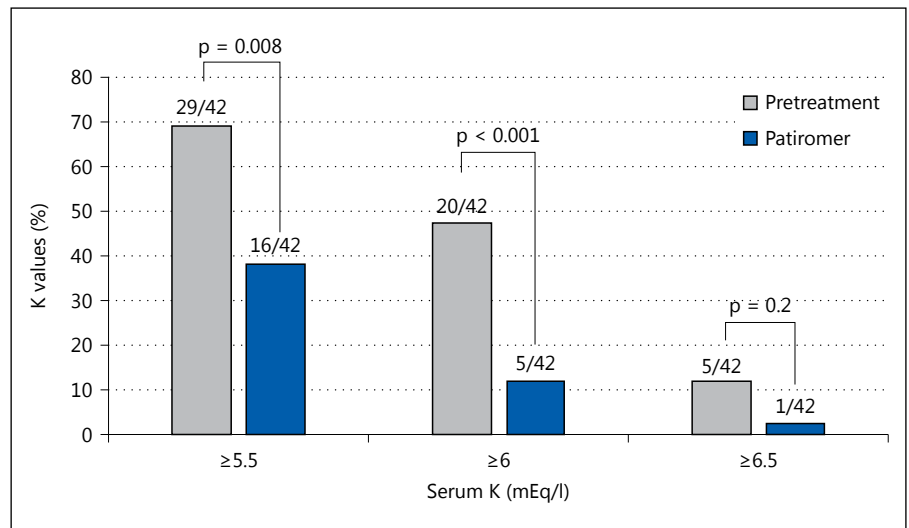

Fig. 2. The proportion of serum K concentrations above the corresponding K value.

numerically increased by 60 ± 35 mg/day (57%; p = 0.1434; range –10 to 223 mg/day), fecal Mg numerically increased by 42 ± 24 mg/day (21%; p = 0.1429; range –37 to 110 mg/day), and fecal P numerically increased by 112 ± 72 mg/day (17%; p = 0.1792; range –148 to 344 mg/day) (n = 6 for each).

Serum Ca remained within the normal range throughout the study (fig. 3). Serum P increased during the pretreatment week following the discontinuation of P binders. The long interdialytic serum P numerically increased from (mean ± SE) 5.8 ± 0.4 to 7.0 ± 0.5 mg/dl (p = 0.06). During the patiromer treatment week, the long interdia-

lytic serum P decreased from 7.0 ± 0.5 mg/dl to 6.2 ± 0.5 mg/dl (p = 0.04; fig. 3). Online supplemental figure 3 demonstrates that ongoing exposure to patiromer increases the separation between the serum P curves during the patiromer treatment versus the pre-patiromer treatment week.

Safety

No patient discontinued the study because of adverse events (AEs) and there were no serious AEs. One patient had a serum Ca as high as 11.0 mg/dl prior to patiromer treatment. On treatment with patiromer, the highest se-

Fig. 3. Serum Ca and P over time in both the pretreatment week and during the patiromer treatment week. All P binders were stopped on the Sunday of admission. * p = 0.04 compared to the Monday (M) value just prior to the start of the patiromer treatment week.
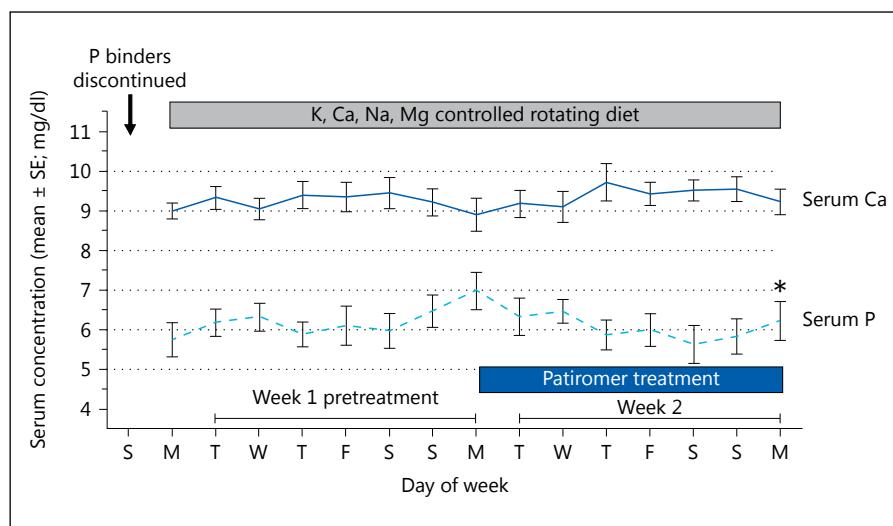
rum Ca in this patient was 10.8 mg/dl. No patient had a serum Ca level during the patiromer treatment week that was above the levels observed in the pretreatment week. No patient developed a serum K <4.0 mEq/l on patiromer (lowest recorded serum K = 4.2 mEq/l). Serum Mg remained in the normal range and no patient developed clinical symptoms of hypomagnesemia (lowest serum Mg = 1.3 mEq/l). There were no individual clinically significant abnormal ECG findings and no AEs associated with ECG abnormalities at any time point during the study. However, all patients had abnormal ECG findings at multiple time points in the study that were judged not to be clinically significant and that are expected for individuals on HD.

Discussion

In this metabolic study, daily administration of patiromer reduced the levels of both mean serum K and serum P in 6 hyperkalemic HD patients. Patiromer treatment decreased the proportion of days that patients were hyperkalemic compared with the pretreatment week. Despite the serum K variability in individual subjects, the differences in mean serum K between the treatment period and the pre-treatment period occurred early and were generally sustained throughout the treatment period, although the difference narrowed over the long interdialytic interval suggesting ongoing K redistribution or accumulation. A larger and longer-duration study allowing for dose titration is needed to further investigate the full effect of patiromer on serum K in this patient population. No patient

discontinued the study for AEs and there were no serious AEs. Until recently, treatment options for hyperkalemia in HD patients were limited to dietary K restriction, low-K dialysate, additional dialysis, or intermittent SPS. All of these options have significant limitations in adequately dialyzed patients. Lower dialysate K concentrations increase the risk of arrhythmias or sudden death [12, 13] and higher sodium intake has been associated with increased interdialytic weight gain and mortality [14]. Furthermore, use of SPS has been associated with increased interdialytic weight gain and higher serum phosphate, bicarbonate and sodium concentrations in HD patients [15].

The finding from this study provides preliminary evidence that daily patiromer, even when administered at a low dose (as discussed below), can remove more K than what is achieved by lowering the dialysate K by 1 mEq/l for 3 treatments/week [16] and suggests that patiromer may be an alternate and potentially safer therapy than lowering the dialysate K concentration for dialysis patients with hyperkalemia. As K normally fluctuates in patients with CKD [2], the possibility of minimizing these fluctuations and providing safer dialysis with patiromer deserves further study. Studies using patiromer in conjunction with a more physiologic K dialysate are also needed to determine if arrhythmic events during and post dialysis can be decreased by following such an approach.

In this study, P binders were stopped at the time of admission to the clinical research center and serum P levels were increased during the pre-treatment week. When patiromer was given with meals instead of the phosphate binder, the serum P level decreased. The numeric increase in stool P is supportive of a potentially clinically

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meaningful effect. The reduction in serum P level seen in these patients with the increasing separation with ongoing treatment (online suppl. fig. 3) is in agreement with earlier studies in healthy volunteers showing that patiromer decreased gastrointestinal phosphate absorption as measured by a decrease in urine P on a controlled diet [17]. The reduction in serum P level seen in this study may be due to the gastrointestinal binding of P by the Ca released from patiromer, leading to less gastrointestinal P absorption.

The mean serum Ca level remained within the normal range in these ESRD patients on patiromer. The 1 patient with mild hypercalcemia was hypercalcemic during the pretreatment period and the peak serum Ca level in this patient on patiromer was lower than the peak Ca level during the pretreatment period. The increase in stool Ca during the patiromer treatment week demonstrates that the vast majority of the Ca in patiromer appears in the stool bound to the polymer as previously reported [10]. This is consistent with the understanding that the main site of Ca-K exchange is in the colon where the efficiency of Ca absorption is minimal [18]. This is also in agreement with studies in healthy controls, where changes in urine calcium were used as a measure of intestinal ion absorption, which demonstrated that about 73 mg of calcium is absorbed from a daily dose of 25.2 g dose of patiromer [17].

The finding that the levels of stool Na and Mg increased, support data that patiromer binds Na and Mg within the gastrointestinal tract as measured by a decrease in these ions in the urine excreted by healthy adults who are given patiromer [17]. The changes in stool Na are such that it suggests that patiromer may bind Na in the gastrointestinal tract as previously reported [17]. Although numerically small, decreased Na absorption could be beneficial in this patient population where interdialytic weight gain and ultrafiltration volume have been associated with adverse outcomes [19, 20]. While the level of serum Mg is often within the normal range in HD, some patients have increased serum levels [21]. While the risk or benefits of increased serum Mg in HD patients is controversial [22], these findings suggest that serum Mg should be monitored in HD patients treated with patiromer [5].

This study has a few important limitations. Most notably is the small sample size (n = 6) of this study with short treatment duration. In addition, serum potassium concentrations vary within a patient. Larger and a longer-duration studies with a randomized controlled design in HD patients are needed to confirm the findings in this study and to ensure tolerability in this patient population. Another limitation of the current study was the non-randomization of the control and treatment weeks. The potential bias of this methodology was somewhat limited by the use of the clinical research center. An important strength of this study is the controlled dietary conditions, along with the consistency of its results (e.g., a decrease in serum K accompanied by an increase in stool K, the latter most probably ruling out any dietary confounding factor). Furthermore, only 1 dose strength of patiromer was tested in this study. The dose tested, 12.6 g/day, is half of the FDA-approved maximum dosage. While the dose tested limits our ability to assess tolerability of higher doses in this population, it suggests that greater K and P removal could be achieved with greater doses of patiromer. The increase toward baseline in the serum K on the Monday after the last dose of patiromer probably reflects the ongoing K burden in these patients and highlights the need for studies of longer duration with potential dose escalations. Finally, in this study, patiromer was administered 3 times per day and all P binders were stopped on admission. As patiromer is approved for once-per-day dosing [5], the optimal use of P binders in conjunction with patiromer treatment needs further study. This study suggests that P binders used 2 times per day with meals along with patiromer with the third meal might be a reasonable strategy to maintain adequate P control while allowing for safe and effective lowering of K levels.

In conclusion, the ability of patiromer to decrease serum K and P levels and increase fecal K, and potentially fecal P and Na in HD patients suggests that patiromer may have beneficial effects on multiple aspects of abnormal mineral metabolism in HD patients. The unique ability of patiromer to both lower serum K and bind gastrointestinal P, without increasing the daily Na load to HD patients, suggests it could play an important role in the care of HD patients.

Disclosure Statement

D.A.B. reports personal fees from Relypsa, Amgen, Sanofi, Aventis/Genzyme, Tricida, Fresenius Medical Care, and OPKO Health; he also reports stock options in Relypsa and Tricida. P.R.

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