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Efficacy and Safety of Sucroferric Oxyhydroxide and Calcium Carbonate in Hemodialysis Patients

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Introduction: In this phase III, open-label, single-arm, multi-center 12-week study, we evaluated the efficacy and safety of combination therapy with sucroferric oxyhydroxide (PA21) and calcium carbonate for hemodialysis patients with hyperphosphatemia.

Methods: We enrolled 35 subjects aged ≥ 20 years with end-stage kidney disease and serum phosphorus 3.5–6.0 mg/dl who were undergoing hemodialysis 3 times weekly and taking calcium carbonate and sevelamer hydrochloride. Patients switched from sevelamer hydrochloride and calcium carbonate to sucroferric oxyhydroxide and calcium carbonate. Sucroferric oxyhydroxide was orally administered 3 times daily within 750 mg/d (250 mg per dose) to 3000 mg/d (1000 mg per dose), immediately before every meal, for 12 weeks. Calcium carbonate was orally administered 3 times daily after every meal. Outcomes were serum phosphorus concentration, safety, and satisfaction with bowel movements.

Results: Mean (SD) serum phosphorus concentrations were 5.01 (0.63) mg/dl at week 0 and 4.89 (1.14) mg/dl at the end of treatment, after patients switched from sevelamer hydrochloride to sucroferric oxyhydroxide. The incidence of adverse drug reactions was 31.4% (11/35), with diarrhea being the most frequent (31.4%). More sucroferric oxyhydroxide-treated patients were satisfied with their bowel movements. More patients with constipation, as well as those who experienced diarrhea, were satisfied with their bowel movements at the end of the study.

Conclusion: Combined administration of sucroferric oxyhydroxide and calcium carbonate at low doses was effective in maintaining serum phosphorus concentrations within the target range, and patients' gastrointestinal status improved. Sucroferric oxyhydroxide maintained its serum phosphorus-lowering effect with a decreased pill burden, and its concomitant administration with calcium carbonate was well tolerated.

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Patients with chronic kidney disease (CKD), especially those in the advanced stages and receiving hemodialysis, have a high propensity to develop hyperphosphatemia.[1] Indeed, the prevalence of hyperphosphatemia in end-stage kidney disease patients is approximately 50%.[2,3]

The propensity to develop heterotopic calcification of vascular and other soft tissues is mainly due to the increase in calcium-phosphate product in end-stage kidney disease.[4] Such a propensity has been identified in several observational studies as an important component of the cardiovascular risk in end-stage kidney disease[5,6] and an independent cardiovascular risk factor in CKD.[7,8] Some studies have attributed the high morbidity[4] and mortality[9,10] in this population to the development of coronary artery, cardiac valve, and lung calcifications, which may lead to the development of cardiovascular disease. This, together with other possible clinical implications of hyperphosphatemia in these patients, makes it necessary to prevent and manage hyperphosphatemia to maintain serum phosphorus levels within the normal range.[11]

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Despite dietary restrictions and dialysis, removal of excess phosphate might be insufficient to prevent hyperphosphatemia. Thus, patients with CKD undergoing hemodialysis usually require treatment with phosphate binders to enhance phosphate elimination. Treatment with phosphate binders is suggested in the Kidney Disease: Improving Global Outcomes (KDIGO) CKD–mineral and bone disorder (MBD) guideline.[11] In addition, it has been reported that 88% of dialysis patients are prescribed phosphate binders.[12] However, poor patient adherence to hyperphosphatemia therapy is common and is usually associated with a large daily pill burden.[13]

Sucroferric oxyhydroxide (PA21) is a noncalcium, iron-based phosphate binder found to be efficacious and noninferior to sevelamer hydrochloride (hereinafter referred to as sevelamer) in decreasing serum phosphorus concentrations with a lower pill burden in dialysis patients with hyperphosphatemia in recent short- and long-term phase III studies.[14–16] Several phosphate binders are currently on the market. In particular, calcium carbonate has been used worldwide for decades because of its high efficacy, tolerability, and low cost.[17] However, the calcium carbonate dosage is restricted because of its calcium loading and the associated risk of arterial calcification.[4,5] Thus, calcium carbonate is frequently used in combination with other phosphate binders, both in Japan and worldwide.[18,19] In fact, its use in combination with sevelamer was recommended in the Japanese Society for Dialysis Therapy (JSDT) Guidelines for the Management of Secondary Hyperparathyroidism in Chronic Dialysis Patients in 2006.[20] More recently, in the revised 2012 JSDT CKD-MBD guidelines, the combination of calcium-containing phosphate binders and non-calcium-containing phosphate binders has been indicated to control serum phosphorus and calcium concentrations.[21] In addition, many dialysis patients, especially Japanese patients, experience constipation caused by water restriction. Available phosphate binders are frequently associated with constipation, nausea, and/or vomiting,[22] whereas in the previous studies of sucroferric oxyhydroxide, diarrhea was frequently reported.[14–16] Based on the above results, we conducted this exploratory study to evaluate the efficacy and safety of switching from combination therapy with sevelamer and calcium carbonate to sucroferric oxyhydroxide and calcium carbonate for 12 weeks, as well as to evaluate the gastrointestinal status of hemodialysis patients with hyperphosphatemia.

METHODS

Study Design

This was a phase III, open-label, single-arm, multicenter, 12-week exploratory study, commencing on 29 April 2013. The clinical trial was registered in ClinicalTrials.gov under the identifier NCT01850641. The study protocol was approved by the ethical review boards of all participating centers, and written informed consent was obtained from all individual participants included in the study. All study procedures were conducted according to the latest version of the Declaration of Helsinki.

The study comprised 2 periods. During the 2-week observation period, patients completed previous treatment with calcium carbonate and sevelamer without undergoing any changes in their doses. During the 12-week treatment period, sucroferric oxyhydroxide and calcium carbonate were administered orally.

Treatment and Dosages

Sucroferric oxyhydroxide was administered in the form of a brown chewable oral tablet containing 250 mg of iron. Commercially marketed calcium carbonate, in both tablet and powder presentations, was used in routine practice at study sites. During the observation period, sevelamer was commercially available in 250-mg tablets, which was the presentation routinely used at all study sites. Sucroferric oxyhydroxide was orally administered 3 times daily immediately before every meal, within a dose range of 750 mg/d (250 mg per dose) to 3000 mg/d (1000 mg per dose). Calcium carbonate was orally administered 3 times daily immediately after every meal at the same dose given in the observation period, with no change in the dosage regimen throughout the treatment period. Dose reduction of calcium carbonate was allowed when the serum phosphorus concentration decreased to < 3.4 mg/dl despite the administration of 750 mg/d sucroferric oxyhydroxide. The amounts of sucroferric oxyhydroxide and calcium carbonate taken were recorded in a diary, and treatment adherence was checked at every visit by the investigator.

If necessary, the investigator adjusted the sucroferric oxyhydroxide dose based on the predialysis serum phosphorus concentration at the beginning of the previous week to maintain the serum phosphorus concentration in the range of 3.5 to 6.0 mg/dl. After week 2, the investigator adjusted the dose as follows: if the serum phosphorus concentration was ≥ 6.1 mg/dl, the sucroferric oxyhydroxide dose was increased by 750 mg/d; if the serum phosphorus concentration was between 3.5 and 6.0 mg/dl, the dose was maintained; and if the serum phosphorus concentration was ≤ 3.4 mg/dl, the dose was reduced by 750 mg/d. No dose change was allowed for 2 consecutive weeks during this study. The dosage of vitamin D receptor activators and calcimimetics was not changed throughout the study period wherever possible.

Concomitant use of the following drugs was prohibited during the study period: any phosphate binders other than calcium carbonate that were concomitantly used with sucroferric oxyhydroxide in this study; any drugs containing aluminum, magnesium, or calcium that have a phosphate-binding action (apart from hyperkalemia drugs); niceritrol, colestimide, or any other drugs having an effect on serum phosphorus concentrations; any oral iron agents; or any study drugs other than sucroferric oxyhydroxide. The use of i.v. iron was permitted if the investigator considered it necessary.

Participants

The study inclusion criteria were as follows: patients with chronic renal failure $\geq$ 20 years of age at the time that informed consent was obtained, with a serum phosphorus concentration between 3.5 and 6.0 mg/dl at the initiation of the observation period (week -2) or at the beginning of week -1, undergoing stable hemodialysis 3 times weekly for $\geq$ 12 weeks prior to week -2 and who were planned to continue on the same hemodialysis schedule, and were taking only calcium carbonate and sevelamer as phosphate binder agents for $\geq$ 4 weeks before week -2 without changes in dose.

The main study exclusion criteria were as follows: patients with a corrected serum calcium concentration of $\leq$ 7.5 mg/dl or $>$ 11.0 mg/dl at week -2; with a serum intact parathyroid hormone (PTH) concentration $>$ 800 pg/ml at week -2; patients with a history of hemochromatosis or other iron accumulation disorders or patients who had a serum ferritin concentration of $>$ 800 ng/ml or transferrin saturation (TSAT) of $>$ 50% at week -2; patients with severe gastrointestinal disorder or a history of severe digestive tract procedure based on the investigator's diagnosis; patients with history of pronounced brain or cardiovascular disorder; and patients with severe hepatic disorders.

The main criteria for discontinuation of patients were as follows: development of any adverse event (AE) that would make study continuation difficult; any serum phosphorus concentration $<$ 3.0 mg/dl or $>$ 10.0 mg/dl in 2 consecutive weeks; any corrected serum calcium concentration $\leq$ 7.5 mg/dl or $>$ 11.0 mg/dl; and any serum ferritin concentration $>$ 800 ng/ml during the treatment period.

Baseline Evaluations

Demographic characteristics (i.e., age and sex) as well as baseline clinical characteristics (i.e., primary diseases, hemodialysis method and duration, dose of phosphate binders used during the observation period, and previous use of erythropoietin-stimulating agents and iron preparations), among other information, were recorded.

Efficacy End Points

Efficacy was evaluated based on the following parameters: serum phosphorus concentration, corrected serum calcium concentration, and serum intact-PTH concentration.

Safety End Points

Safety was assessed based on the following parameters: development of AEs and development of adverse drug reactions (ADRs; coding by MedDRA); laboratory tests (including iron-related parameters); and status of defecation (number of days with bowel movements and days of taking laxatives, constipation condition, and satisfaction level with bowel movements). The number of bowel movements per day and days on which patients took laxatives were recorded in their diaries. Patients' satisfaction with their constipation condition and satisfaction with their bowel movements were self-evaluated using questionnaires. Five categories evaluated the patients' satisfaction with their constipation condition: (i) not at all bothersome; (ii) bothers me very little; (iii) somewhat bothersome; (iv) bothers me quite a lot; and (v) could not tolerate. Similarly, 5 categories were used to evaluate patients' satisfaction with their bowel movements: (i) very much satisfied; (ii) satisfied; (iii) can say neither; (iv) dissatisfied; and (v) very much dissatisfied.

Statistical Analysis

All statistical analyses were conducted with SAS 9.3 (SAS Institute Inc., Cary, NC). A sample size of 30 subjects was established for the 12 weeks of treatment based on feasibility and likelihood that this number of patients would yield sufficient data regarding the efficacy and safety of sucroferric oxyhydroxide in combination with calcium carbonate. The sample size was not calculated by statistical methods.

For efficacy end points, summary statistics of measurement at each evaluation time point and the change from week 0, and the 95% confidence interval of the mean were calculated. Achievement rates for the target range of the JSDT (3.5–6.0 mg/dl) and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) (3.5–5.5 mg/dl)[23] were also calculated.

For AEs and ADRs, the number of patients with events and event incidences were calculated. The AEs and ADRs were analyzed, excluding the discoloration events caused by the iron contained in sucroferric oxyhydroxide, such as feces discoloration. For laboratory test parameters and number of days with bowel

movements and days of taking laxatives, summary statistics were calculated for measurements at each evaluation point. The numbers of patients satisfied with their constipation condition and bowel movements were also analyzed at week 0 and at the end of treatment. Because this was an exploratory study, statistical tests for normality of data distribution or for comparison from baseline to the end of the study treatment were not performed.

RESULTS

Patient Demographic and Clinical Baseline Characteristics

A total of 35 patients were enrolled to treatment. Of these, 30 patients (85.7%) completed the 12-week treatment, and 5 patients (14.3%) discontinued. The reasons for discontinuation were serum phosphorus decrease (n = 1), serum calcium increase (n = 2), ferritin increase (n = 1), and personal reasons (n = 1). All 35 patients were included in both the full analysis set and the safety set. The demographic and clinical baseline characteristics of patients are shown in Table 1. Patients had a mean (minimum–maximum) age of 63.7 years (46–82 years) and 60.0% were male. The median (Q1–Q3) length of time on dialysis was 89 months (45–147 months).

Table 1. Patient baseline and demographic characteristics (N = 35)

Characteristic	Values
Age, yr, mean (SD)	63.7 (8.0)
Sex, n (%)	
Male	21 (60.0)
Female	14 (40.0)
Primary disease, n (%)	
Diabetic nephropathy	10 (28.6)
Chronic glomerulonephritis	20 (57.1)
Nephrosclerosis	3 (8.6)
Polycystic kidney disease	1 (2.9)
Unknown	1 (2.9)
Dialysis vintage, mo, median (Q1–Q3)	89 (45–147)
Mode of dialysis, n (%)	
Hemodialysis	31 (88.6)
Hemodiafiltration	4 (11.4)
Previous use of erythropoietin-stimulating agent, n (%)	30 (85.7)
Previous use of iron preparations, n (%)	3 (8.6)
Calcium carbonate, mg/d, mean (SD)	2221 (1009)
Sevelamer hydrochloride, mg/d, mean (SD)	2400 (1322)
Serum phosphorus, mg/dl, mean (SD)	5.01 (0.63)
Corrected serum calcium, mg/dl, mean (SD)	9.39 (0.50)
Intact parathyroid hormone, pg/ml, median (Q1–Q3)	161 (100 – 250)
Frequency of laxative use, n (%)	
Partial use	7 (33.3)
Everyday use	14 (66.7)

Q1, 25th percentile; Q3, 75th percentile.

Efficacy

The mean (SD) serum phosphorus concentration was 5.01 (0.63) mg/dl at week 0 and 4.89 (1.14) mg/dl at the end of treatment after patients switched from sevelamer treatment to sucroferric oxyhydroxide. The mean serum phosphorus concentrations were within the control target range (≥ 3.5 mg/dl, ≤ 6.0 mg/dl) throughout the treatment period (Figure 1).

The protein catabolic rate and Kt/V did not fluctuate throughout the study period (Table 2). The daily dose of sucroferric oxyhydroxide at the end of treatment was 750 mg/d and 1500 mg/d in 91.4% and 8.6% of the patients, respectively. The phosphorus concentration was maintained in more than 90% of the patients by administration of 1 sucroferric oxyhydroxide tablet per dose when concomitantly administered with calcium carbonate. None of the patients received a dose of 2250 mg/d or 3000 mg/d during the study period. The compliance rate for taking sucroferric oxyhydroxide was 99.24%.

The mean (SD) dose of sevelamer during the observation period was 2400 (1322) mg/d. Thereafter, the medication was switched to sucroferric oxyhydroxide, and the mean dose of sucroferric oxyhydroxide at the end of treatment was 814 (213) mg/d. The number of tablets taken notably decreased from 9.6 (5.3) sevelamer tablets to 3.3 (0.9) sucroferric oxyhydroxide tablets. The mean dose of calcium carbonate decreased from 2221 (1009) mg/d during the observation period to 2043 (1060) mg/d at the end of treatment. It was predetermined that the patients whose serum phosphorus concentration reached ≤ 3.4 mg/dl underwent dose reduction of calcium carbonate, despite the sucroferric oxyhydroxide dose of 750 mg/d. In this study, 3 patients underwent calcium carbonate dose reduction from week 3 onward, and eventually, a total of 7 patients (20.0%) underwent dose reductions before the end of treatment.

The serum phosphorus target concentration of JSDT (3.5–6.0 mg/dl) was achieved after administration of the study drug in ≥ 80% of the patients from week 5 onward and in 77.1% at the end of treatment. The KDOQI serum phosphorus target concentration (3.5–5.5 mg/dl) was achieved in 65.7% of patients at the end of treatment.

The mean corrected serum calcium level and the median serum intact PTH level are shown in Table 2. Overall, no notable changes were observed in the concentrations of mean corrected serum calcium and median serum intact PTH from week 0 to the end of treatment.

Safety

The incidence of AEs was 80.0% (28 of 35 patients), and the incidence of ADRs was 31.4% (11 of 35

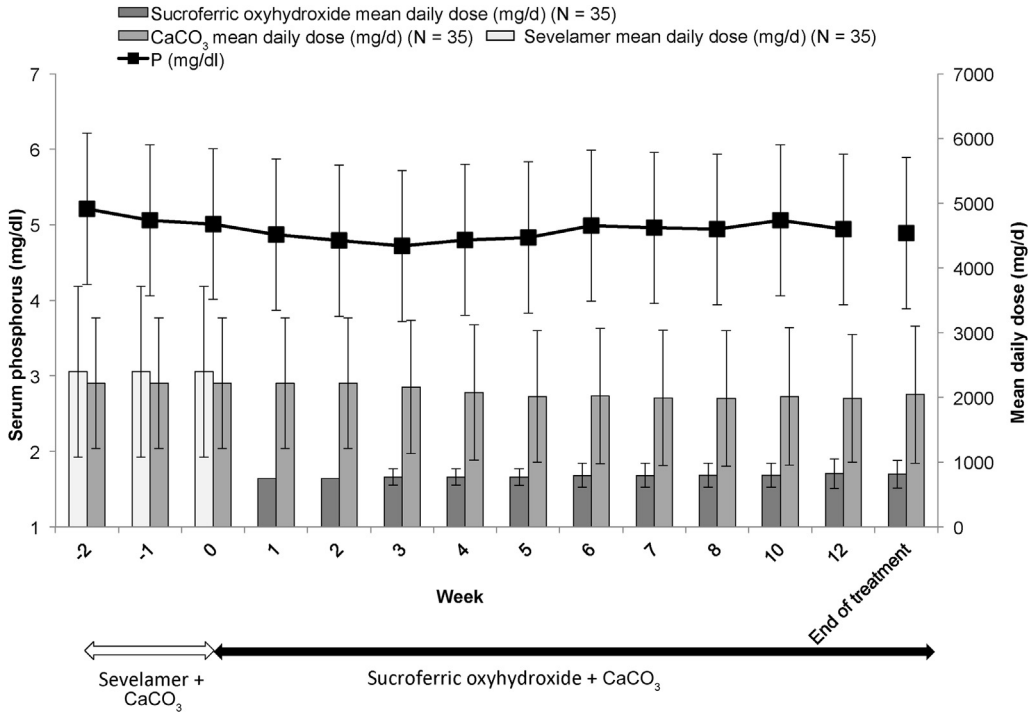

Figure 1. Time-course changes in mean serum phosphorous concentration and mean daily doses of sevelamer and $CaCO_3$ during the observation period, and sucroferric oxyhydroxide and $CaCO_3$ during the treatment period. $CaCO_3$, calcium carbonate.

patients). The most frequently observed ADR was diarrhea, with an incidence of 31.4% (Table 3). All ADRs were mild. No deaths or AEs leading to study withdrawal were observed. One case of acute hepatitis was reported as a serious AE; however, this case was not considered related to the study drug, based on the clinical course of the patient.

Regarding laboratory tests, no propensity for increase was observed in the ferritin level; meanwhile, TSAT and hemoglobin level tended to increase. The mean changes from baseline to the end of treatment for ferritin, TSAT, and hemoglobin levels are shown in Table 4.

No major changes were observed in the number of days with bowel movements per week (Table 5). The number of patients satisfied with bowel movement status increased from 21 patients at week 0 to 28 patients at the end of treatment. More specifically, the number of satisfied patients increased from 11 patients at week 0 to 17 patients at the end of treatment among those with concurrent constipation, and from 9 to 10 patients among those who experienced diarrhea (Table 5). The number of days of laxative use per week decreased slightly from week 0 to the end of treatment (Table 5). Approximately one-half of the patients (47.6%) who ordinarily used laxatives decreased the dose of the laxative used or changed to a milder agent at the end of treatment. The number of patients who did not experience constipation increased from 15 patients at week 0 to 26 patients at the end of treatment. The numbers of patients who did not experience constipation increased from 8 patients at week 0 to 14 patients at the end of treatment among patients with concurrent constipation, and increased from 9 to 11 patients among those who experienced diarrhea (Table 5).

Table 2. Phosphorus concentration, corrected calcium level, intact PTH level, PCR, and Kt/V (at week 0 and at the end of treatment) and changes from baseline in all patients

Timepoint	Serum phosphorus concentration, mg/dl N = 35	Corrected serum calcium level, mg/dl N = 35	Serum intact-PTH level, pg/ml, N = 35	PCR, g/kg per day N = 35	Kt/V N = 35
Week 0	5.01 (0.63)	9.39 (0.50)	161 (100 – 250)	0.889 (0.116)	1.549 (0.27)
End of treatment	4.89 (1.14)	9.52 (0.88)	138 (82 – 236)	0.874 (0.151)	1.519 (0.27)
Change from baseline	−0.13 (1.11)	0.13 (0.77)	−3 (−77 to 49)	−0.005 (0.159)	−0.031 (0.094)

K, dialyzer clearance of urea; PCR, protein catabolic rate; PTH, parathyroid hormone; Q1, 25th percentile; Q3, 75th percentile; t, time; V, volume of distribution of urea.
Data in the table are presented as mean (SD) except for intact PTH, which is presented as median (Q1–Q3).

Table 3. Adverse events with an incidence above 5% and adverse drug reactions above 2%, excluding discoloration events

Event	Sucroferric oxyhydroxide + calcium carbonate N = 35
Adverse events, n (%)	28 (80.0%)
Diarrhea	14 (40.0)
Nasopharyngitis	10 (28.6)
Dermatitis contact	2 (5.7)
Hemorrhage subcutaneous	2 (5.7)
Back pain	2 (5.7)
Wound	2 (5.7)
Adverse drug reactions, n (%)	11 (31.4)
Diarrhea	11 (31.4)
Defecation urgency	1 (2.9)

DISCUSSION

Generally, the type of phosphate binder and treatment regimen (monotherapy or combination therapy) used is determined according to each patient's condition. In the present study, we enrolled hemodialysis patients who had received combination therapy with sevelamer hydrochloride and calcium carbonate to evaluate the efficacy and safety of sucroferric oxyhydroxide administered concomitantly with calcium carbonate for 12 weeks after switching from sevelamer hydrochloride and calcium carbonate. As a result, sucroferric oxyhydroxide, at low doses and with decreased pill burden, was able to maintain serum phosphorus concentrations within the control target range by the JSDT[21] and was well tolerated after switching the treatment from sevelamer and calcium carbonate to sucroferric oxyhydroxide and calcium carbonate.

The serum phosphorus concentration was controlled in most patients with the lowest dose of sucroferric oxyhydroxide when concomitantly used with calcium carbonate. The number of tablets of phosphate binder required decreased when patients switched from sevelamer to sucroferric oxyhydroxide; thus, the pill burden for patients decreased. A decreased pill burden is associated with a greater quality of life and improved patient adherence to treatment among hemodialysis patients with hyperphosphatemia.[13] As a consequence, lowering the pill burden may lead to risk mitigation for secondary hyperparathyroidism, renal osteodystrophy, and cardiovascular disease. Although the timing of sucroferric oxyhydroxide intake differed from that of

Table 4. Measured values and changes in iron-related parameters

Parameter/timepoint	Sucroferric oxyhydroxide + calcium carbonate N = 35
Serum ferritin levels, ng/ml, median (Q1–Q3)	
Week 0	57.5 (27.7–146.0)
End of treatment	73.8 (38.2–183.0)
Change from baseline	13.4 (−8.6 to 37.0)
Serum transferrin saturation, %, mean (SD)	
Week 0	24.39 (7.76)
End of treatment	27.72 (8.27)
Change from baseline	3.33 (9.62)
Hemoglobin, g/dl, mean (SD)	
Week 0	10.61 (1.02)
End of treatment	11.22 (1.19)
Change from baseline	0.60 (1.15)

Q1, 25th percentile; Q3, 75th percentile.

Table 5. Status of constipation and satisfaction with the status of bowel movement.

Parameter/timepoint	Sucroferric oxyhydroxide + calcium carbonate
Days with bowel movement, mean (SD) (N = 35)	
Week 0	5.83 (1.52)
EOT	6.09 (1.40)
Days with laxative use, mean (SD) (n = 21)	
Week 0	5.90 (1.73)
EOT	4.55 (2.65)
Laxative use at the end of treatment, n (%) (n = 21)	
No change	11 (52.4)
Decreased use or changed to milder agent	10 (47.6)

Constipation condition, n	All (N = 35)	Patients concurrent constipation[a] (N = 22)	Patients experienced diarrhea[b] (N = 14)
(i) Not at all bothersome			
Week 0	15	8	9
EOT	26	14	11
(ii) Bothers me very little			
Week 0	14	10	3
EOT	5	4	1
(iii) Somewhat bothersome			
Week 0	2	0	1
EOT	2	2	1
(iv) Bothers me quite a lot			
Week 0	4	4	1
EOT	2	2	1
(v) Could not tolerate			
Week 0	0	0	0
EOT	0	0	0

Satisfaction with bowel movement, n	All (N = 35)	Patients concurrent constipation[a] (n = 22)	Patients experienced diarrhea[b] (n = 14)
(i) Very much satisfied/ (ii) Satisfied			
Week 0	21	11	9
EOT	28	17	10
(iii) Can say neither			
Week 0	8	6	3
EOT	5	4	2
(iv) Very much dissatisfied/ (v) Dissatisfied			
Week 0	6	5	2
EOT	2	1	2

EOT, end of treatment.
[a]Patients who had constipation at the initiation of the observation period.
[b]Patients who experienced diarrhea during the treatment period.

calcium carbonate intake, the compliance rate for taking sucroferric oxyhydroxide in this study was high (99.24%).

Calcium carbonate is a low-cost phosphate binder used worldwide, and it is frequently used with other phosphate binders because of dose restriction. Calcium loading caused by overdose of calcium carbonate is reported to be associated with possible occurrences of hypercalcemia, suppression of parathyroid function, and vascular calcification.[4,5] In the current study, because a dose reduction of calcium carbonate was permitted only when the serum phosphorus level was under the lower end of the normal range ($\leq$ 3.4 mg/dl) despite the administration of the minimum daily dose of sucroferric oxyhydroxide, the amount of calcium carbonate decreased only by approximately 10% after administering sucroferric oxyhydroxide. In addition, the corrected serum calcium level was stable throughout the study period. In clinical practice, there are no such limitations, and thus, the amount of calcium carbonate could be reduced further by increasing the sucroferric oxyhydroxide dose when used in combination with calcium carbonate. As a result, calcium carbonate dose reduction is possible for the purpose of alleviating calcium-loading and lowering serum calcium levels.

Although diarrhea was the most frequent ADR, the number of days with bowel movement per week did not change notably, and patient satisfaction with bowel habits improved throughout the study. Thus, we consider that the onset of diarrhea is unlikely to impair the daily life of patients treated with sucroferric oxyhydroxide. It is possible to prevent diarrhea by reducing the laxative dose or switching to a laxative with a milder action. Indeed, the number of days with laxative use decreased, and approximately one-half of the patients changed their dose or the type of laxatives used during the treatment. In addition, treatment with sucroferric oxyhydroxide improved bowel status in patients with constipation. Many patients receiving dialysis have concurrent constipation caused by various factors such as dialysis modality-based lifestyle, water restriction, and phosphate binders,[24] and most patients prefer alternatives to prevent constipation. Therefore, treatment with sucroferric oxyhydroxide may alleviate complaints about constipation and laxative use, and thereby improve the quality of life for CKD patients. No other gastrointestinal ADRs, such as constipation and nausea, which are frequently reported with other phosphate binders, were observed in this study.

No propensity for an increase in ferritin concentration was observed, but a slight tendency toward an increase in TSAT and hemoglobin concentration was observed in this study. When comparing these results with those obtained with 12-week sucroferric oxyhydroxide monotherapy in our previous study in a similar patient population (median change in ferritin level, mean changes in TSAT and hemoglobin of 13.4 ng/ml, 3.33%, and 0.60 g/dl in the present study, respectively, vs. 33.6 ng/ml, 6.97%, and 0.86 g/dl in the previous monotherapy study, respectively),[16] the ranges of the changes in the present study were smaller. The differences in iron parameter fluctuations between these studies may be attributable to the fact that most of the patients in the present study continued treatment at the initial dose of sucroferric oxyhydroxide because of concomitant administration with calcium carbonate.

The findings of the present study should be considered in light of several limitations. First, this was an open-label study without a control group, and thus was subject to the introduction of bias. Second, only Japanese patients were included, which limits the generalizability of the results to other populations. Third, the study had a relatively small sample size; and finally, the study period was short. However, these results are worth publishing, because they indicate that the combined use of sucroferric oxyhydroxide and calcium carbonate enabled a decrease in the amount of calcium carbonate taken. Furthermore, the combination therapy with sucroferric oxyhydroxide and calcium carbonate obviously reduced pill burden compared with combination therapy with sevelamer and calcium carbonate.

In conclusion, in this study, the combined administration of sucroferric oxyhydroxide and calcium carbonate at low doses was effective in maintaining serum phosphorus concentrations within the target range and was well tolerated. Although diarrhea was observed, the gastrointestinal status of patients improved. Sucroferric oxyhydroxide, a new phosphate binder alternative, is considered to be useful for safely maintaining its serum phosphorus-lowering effect with a small pill burden while concurrently used with calcium carbonate, a widely used phosphate binder.

DISCLOSURE

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REFERENCES

1. Hruska KA, Mathew S, Lund R, et al. Hyperphosphatemia of chronic kidney disease. *Kidney Int*. 2008;74:148–157.
2. Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*. 2005;67:1179–1187.
3. Kimata N, Albert JM, Akiba T, et al. Association of mineral metabolism factors with all-cause and cardiovascular mortality in hemodialysis patients: the Japan dialysis outcomes and practice patterns study. *Hemodial Int*. 2007;11:340–348.
4. Guérin AP, London GM, Marchais SJ, Métivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant*. 2000;15:1014–1021.
5. London GM, Guérin AP, Marchais SJ, et al. Arterial media calcification in end-stage renal diseases: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*. 2003;18:1731–1740.
6. Raggi P, Boulay A, Chasan-Taber S, et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol*. 2002;39:695–701.
7. Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol*. 2005;16:520–528.
8. Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS Waves 1, 3, and 4 Study. *J Am Soc Nephrol*. 2005;16:1788–1793.
9. Ganesh SK, Stack AG, Levin NW, et al. Association of elevated serum PO(4), Ca × PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol*. 2001;12:2131–2138.
10. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
11. KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Introduction and definition of CKD–MBD and the development of the guideline statements (PDF). *Kidney Int*. 2009;76(suppl 113):S3–S8.
12. Lopes AA, Tong L, Thumma J, et al. Phosphate binder use and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS): evaluation of possible confounding by nutritional status. *Am J Kidney Dis*. 2012;60:90–101.
13. Chiu YW, Teitelbaum I, Misra M, et al. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol*. 2009;4:1089–1096.
14. Floege J, Covic AC, Ketteler M, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. *Kidney Int*. 2014;86:638–647.
15. Floege J, Covic AC, Ketteler M, et al. Long-term effects of the iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients. *Nephrol Dial Transplant*. 2015;30:1037–1046.
16. Koiwa F, Yokoyama K, Fukagawa M, et al. Efficacy and safety of sucroferric oxyhydroxide compared with sevelamer hydrochloride in Japanese haemodialysis patients with hyperphosphataemia: a randomised, open-label, multicentre, 12-week phase III study. *Nephrology*. 2017;22:293–300.
17. Coladonato JA. Control of hyperphosphatemia among patients with ESRD. *J Am Soc Nephrol*. 2005;16(suppl 2):S107–S114.
18. Ogata H, Koiwa F, Shishido K, et al. Combination therapy with sevelamer hydrochloride and calcium carbonate in Japanese patients with long-term hemodialysis: alternative approach for optimal mineral management. *Ther Apher Dial*. 2005;9:11–15.
19. Cannata-Andía JB, Fernández-Martín JL, Locatelli F, et al. Use of phosphate-binding agents is associated with a lower risk of mortality. *Kidney Int*. 2013;84:998–1008.
20. Guideline Working Group, Japanese Society for Dialysis Therapy. Clinical practice guideline for the management of secondary hyperparathyroidism in chronic dialysis patients. *Ther Apher Dial*. 2008;12:514–525.
21. Fukagawa M, Yokoyama K, Koiwa F, et al. Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. *Ther Apher Dial*. 2013;17:247–288.
22. Palmer SC, Gardner S, Tonelli M, et al. Phosphate-binding agents in adults with CKD: a network meta-analysis of randomized trials. *Am J Kidney Dis*. 2016;68:691–702.
23. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Available at: http://www2.kidney.org/professionals/kdoqi/guidelines_bone/guide3.htm. Accessed July 28, 2017.
24. Wu MJ, Chang CS, Cheng CH, et al. Colonic transit time in long-term dialysis patients. *Am J Kidney Dis*. 2004;44:322–327.