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Efficacy of sucroferric oxyhydroxide treatment in Japanese hemodialysis patients and its effect on gastrointestinal symptoms

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Sucroferric oxyhydroxide (SFOH) is a non-calcium, iron-based phosphate binder indicated for the treatment of hyperphosphatemia in adult dialysis patients. Studies in Japan about the side effects of SFOH treatment indicate that the incidence of diarrhea (25%) is greater while that of constipation (2.9%) is lesser in comparison to that observed upon treatment with an existing phosphate binder. In the present study, the effect of treatment with a combination of the existing phosphate binders and SFOH on the serum phosphorus level and digestive symptoms was observed in hemodialysis patients with hyperphosphatemia, which is untreatable using only the existing phosphate binders. We evaluated the serum phosphorus levels and gastrointestinal symptoms (using the gastrointestinal symptom rating scale) of 6 patients (2 men, 4 women) before and 2, 4, 6, and 8 weeks after continuous administration. The serum phosphorus levels before and 2, 4, 6, and 8 weeks after combination treatment were 7.4±1.0 mg/dL, 5.9±1.3 mg/dL, 5.8±1.5 mg/dL, 5.8±1.4 mg/dL, and 5.8±1.3 mg/dL, respectively, with significant reduction in the levels being observed 2 weeks after administration ($p<0.05$) and persisting even 8 weeks after continuous administration. The constipation scores before and 2, 4, and 8 weeks after drug administration were 2.39±0.85, 2.34±1.93, 2.56±1.44, and 3.28±2.19, respectively, with no changes observed during the investigation period. The diarrhea scores before and 2, 4, and 8 weeks after drug administration were 2.22±0.91, 2.06±1.16, 1.28±0.39, and 1.06±0.13 respectively. The scores improved significantly, 4 weeks after drug administration ($p<0.05$), and the improvement persisted, even 8 weeks after continuous administration. Thus, by using a combination of the existing phosphate binders and SFOH, we were able to reduce the serum phosphorus level in patients with hyperphosphatemia, which is untreatable using the existing phosphate binder alone, with no sign of exacerbation of the gastrointestinal symptoms despite a few contradictory case reports.

1. Introduction

Hyperphosphatemia is highly prevalent in hemodialysis patients and is one of the most important risk factors for cardiovascular disease and mortality in these patients (Hruska et al. 2008). Appropriate control of phosphorus and calcium levels in chronic kidney disease patients undergoing hemodialysis is a new concept in the clinical management of chronic kidney disease-mineral and bone disorder and is intended to improve patient prognosis (Fukagawa et al. 2013). In most patients, dietary restrictions and thrice-weekly hemodialysis sessions are insufficient to reduce phosphate levels to the treatment goals. Thus, phosphate-binding agents, such as calcium-containing phosphate binders, lanthanum carbonate, ion-exchange resins, ferric citrate hydrate, and sucroferric oxyhydroxide (SFOH) are necessary for dialysis patients with hyperphosphatemia. In few cases, a single agent alone is unable to reduce the blood phosphorus concentration to desired levels, necessitating the administration of a combination of phosphate binders and thus increasing the pill burden. Phosphate binders have been reported to account for about half of all medication prescribed to hemodialysis patients (Chiu et al. 2009). This has prompted us to look for a drug having an excellent phosphorus-lowering effect in small doses. Additionally, phosphate binders cause several undesired gastrointestinal symptoms. Although the incidence rate of constipation with sevelamer treatment is reported to be only 7% overseas (Slatopolsky et al. 1999), the rate is much higher in Japan (Hatakeyama et al. 2013). While we had previously reported that switching from sevelamer to lanthanum carbonate significantly improved constipation symptoms (Suzuki et al. 2015), complaints of gastrointestinal symptoms from hemodialysis patients still persist.

SFOH is a non-calcium, iron-based phosphate binder indicated for the treatment of hyperphosphatemia in adult dialysis patients. SFOH is effective in lowering serum phosphorus in hemodialysis patients, with similar efficacy to that of sevelamer, a lower pill burden, and better adherence (Floege et al. 2014). A study in Japan on the side effects of SFOH treatment indicate that the incidence of diarrhea (25 %) is greater while that of constipation (2.9 %) is lesser in comparison to that observed upon treatment with an existing phosphate binder (Koiwa et al. 2016). Since these are the results of washing out the existing phosphate binder and prescribing SFOH independently, it is unclear whether the observed efficacy and changes in digestive symptoms are really due to the combination of the existing phosphate binders and SFOH. In the present study, the effect of treatment with a combination of the existing phosphate binders and SFOH on the serum phosphorus level and digestive symptoms was observed in hemodialysis patients with hyperphosphatemia, which is untreatable using only the existing phosphate binders.

2. Investigations and results

2.1. Changes in biochemical parameters

Of the 6 patients who received continuous dosages of the phosphate binders for 8 weeks, 5 patients had 750 mg of SFOH while the remaining patient had 250 mg of the drug. The SFOH dosage was changed to 1500 mg for 3 patients, 500 mg for 2, and 250 mg for the remaining 1 patient, 8 weeks after the start of drug administration. The serum phosphorus levels before and 2, 4, 6, and 8

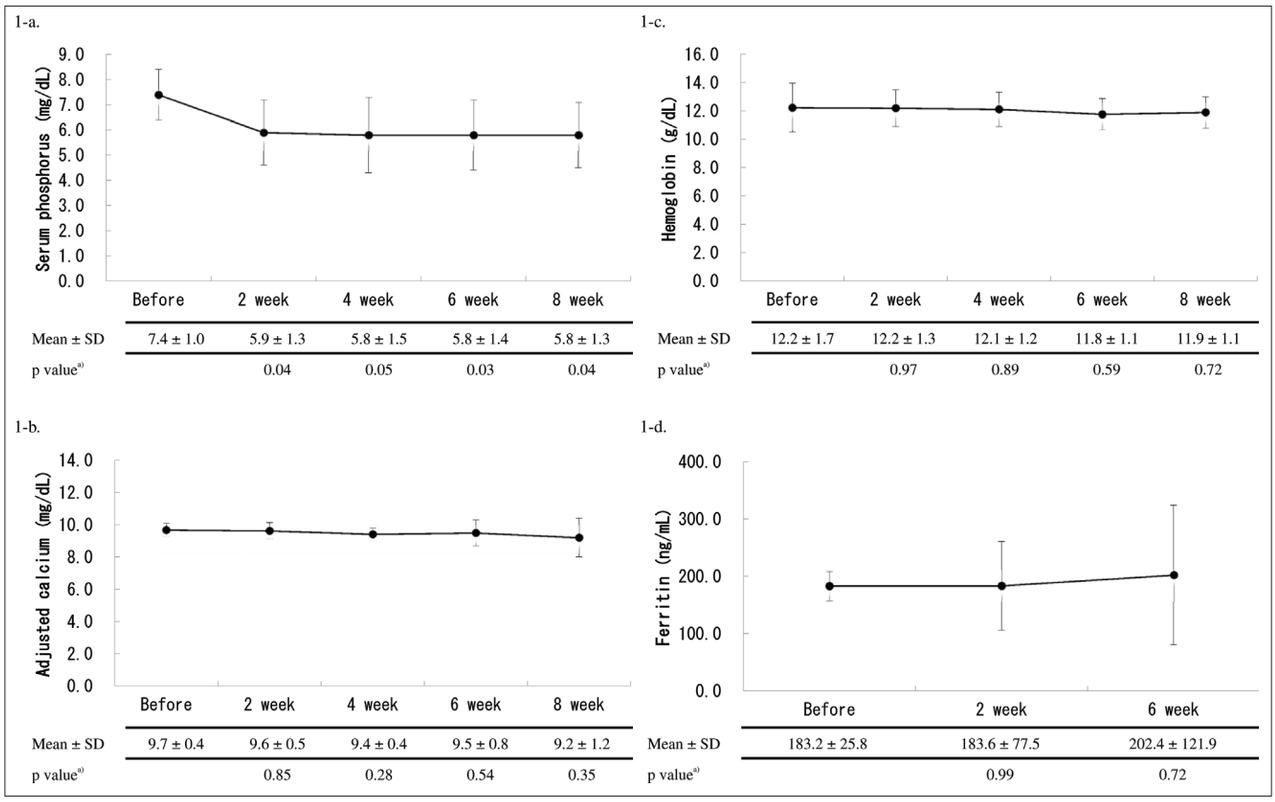

Fig. 1: Changes in laboratory values during the investigation period. a. Serum phosphorus level (n = 6, week before the beginning of hemodialysis); b. Adjusted calcium level (n = 6, week before the beginning of hemodialysis); c. Hemoglobin level (n = 6, week before the beginning of hemodialysis); d. Ferritin level (n = 6, week before the beginning of hemodialysis). [a)]p values were compared to those before administration and calculated using the Wilcoxon signed rank test

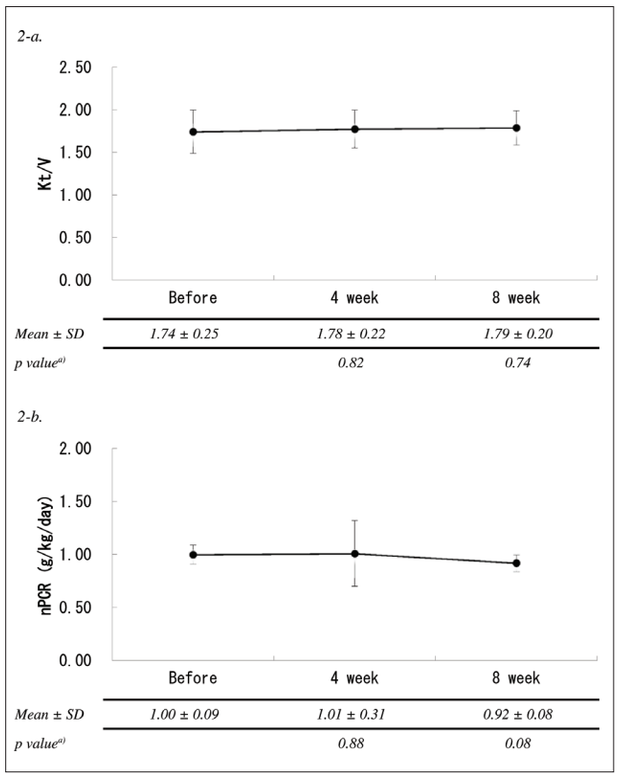

Fig. 2: Changes in Kt/V and nPCR during the investigation period. a. Kt/V (n = 6, week before the beginning of hemodialysis); b. nPCR (n = 6, week before the beginning of hemodialysis). [a)]p values were compared to those before administration and calculated using the Wilcoxon signed rank test

weeks after drug administration were 7.4±1.0 mg/dL, 5.9±1.3 mg/dL, 5.8±1.5 mg/dL, 5.8±1.4 mg/dL, and 5.8±1.3 mg/dL, respectively, with significant reduction in the levels being observed 2 weeks after administration ($p<0.05$) and persisting even 8 weeks after continuous administration (Fig. 1a). We could not find any changes in the corrected calcium (Fig. 1b), hemoglobin (Fig. 1c), or ferritin levels (Fig. 1d), before and after drug administration. Thus, there was no indication that the iron load was affected by SFOH.

Similarly, no change was observed in the Kt/V and nPCR values before and after drug administration (Fig. 2) and therefore, there was no indication that the lowering of serum phosphorus levels during the investigation period was affected by the amount of dialysis and oral intake of diet.

2.2. Evaluation of gastrointestinal symptoms

The total GSRS scores before and 2, 4, and 8 weeks after drug administration were 1.81±0.49, 1.89±1.01, 1.78±0.92, and 1.87±1.03, respectively, with no change observed during the investigation period (Fig. 3a).

With itemized scores, the constipation scores before and 2, 4, and 8 weeks after drug administration were 2.39±0.85, 2.34±1.93, 2.56±1.44, and 3.28±2.19, respectively, with no changes observed during the investigation period (Fig. 3b). The diarrhea scores before and 2, 4, and 8 weeks after drug administration were 2.22±0.91, 2.06±1.16, 1.28±0.39, and 1.06±0.13, respectively. The scores improved significantly, 4 weeks after drug administration ($p<0.05$), and the improvement persisted, even 8 weeks after continuous administration (Fig. 3c). The acid reflux scores before and 2, 4, and 8 weeks after drug administration were 1.58±1.02, 1.75±1.41, 1.42±0.80, and 1.67±0.98, respectively, with no changes observed during the investigation period (Fig. 3d). The indigestion scores before and 2, 4, and 8 weeks after drug administration were

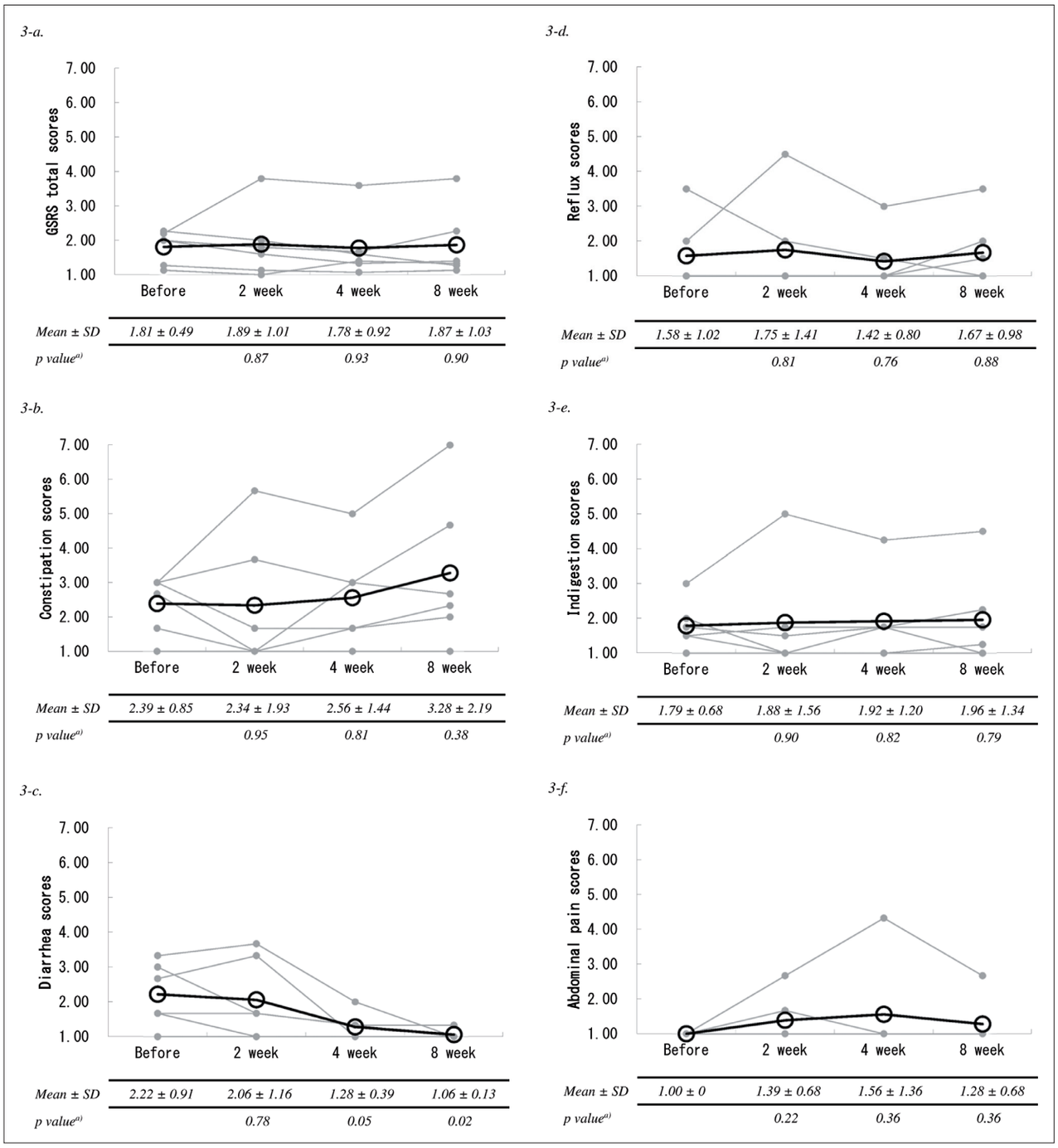

Fig. 3: Changes in each GSRS score during the investigation period. a. GSRS total scores (n = 6); b. Constipation scores (n = 6); c. Diarrhea scores (n = 6); d. Reflux scores (n = 6); e. Indigestion scores (n = 6); f. Abdominal pain scores (n = 6). Black line is average score, Gray line is personal score. ^{a)}p values were compared to those before administration and calculated using the Wilcoxon signed rank test
GSRS: Gastrointestinal Symptom Rating Scale

1.79±0.68, 1.88±1.56, 1.92±1.20, and 1.96±1.34, respectively, with no changes observed during the investigation period (Fig. 3e). The abdominal pain scores before and 2, 4, and 8 weeks after drug administration were 1.00±0, 1.39±0.68, 1.56±1.36, and 1.28±0.68, respectively, with no changes observed during the investigation period (Fig. 3f). SFOH, which is a chewable, oral intake pill, requiring adequate biting before intake, caused vomiting at the beginning of drug administration in 2 patients (33.3 %) who complained of nausea likely attributable to their excessive biting habit. This was resolved by breaking the chewable pills to small pieces before oral intake.

3. Discussion

The dependence on an increased number of drugs has lowered the quality of life of hemodialysis patients with hyperphosphatemia (Slatopolsky et al. 1999). SFOH has proven to be non-inferior to sevelamer in lowering serum phosphorus level and the pill burden (Floege et al. 2014). Increased serum phosphorus levels are associated with increased mortality rates in hemodialysis patients (Block et al. 2004). The level of serum phosphorus can be decreased by increasing the amount of dialysis along with dietary restrictions and medication. While phosphate binders have been utilized for therapy, there are some cases where a single agent

alone is unable to sufficiently lower the serum phosphorus level. In such cases, a combination of phosphate binders is required, but there is insufficient data to determine the optimal combination. In the present study, the patients whose serum phosphorus level could not be lowered to the target level by using existing phosphate binders, were administered an additional dose of SFOH. As a result, the serum phosphorus levels significantly decreased, 2 weeks after the start of administration, without increasing the amount of dialysis and dietary restrictions. The target level of 3.5-6.0 mg/dL, as per the guideline in our country (Fukagawa et al. 2013), could not be achieved in all the cases at the start of the drug administration, but the success rate improved to 75%, 2 weeks after the administration with a decrease in the serum phosphorus levels. Thus, administering a dose of SFOH along with the existing phosphate binders has a synergistic effect on the serum phosphorus level. However, as SFOH contains iron, iron overload becomes a concern. However, the change in serum ferritin level due to SFOH is comparable to that due to another iron-containing phosphate binder such as ferric citrate hydrate (Negri et al. 2015). Further, an increase in serum ferritin level has not been recognized even in our current study, and thus, SFOH seems to have little impact on the dynamics of iron.

Diarrhea is a major side effect that is frequently reported one week after the start of SFOH administration and gradually disappears without requiring any changes to the therapeutic strategy (Floege et al. 2014). In case of the existing phosphate binders, a relatively large proportion of Japanese patients complain of constipation symptoms (Hatakeyama et al. 2013). It is, however, unclear, how the combination of existing phosphate binders and SFOH affects the gastrointestinal symptoms in Japanese patients. In this study, we investigated the effect on gastrointestinal symptoms upon the administration of SFOH to hemodialysis patients who were already on another phosphate binder. There were no changes in the itemized scores except for the diarrhea score and no cases where the continuation of an oral intake became difficult owing to the side effect. The diarrhea score significantly improved, 4 weeks after the start of drug administration ($p<0.05$), with the improvement persisting even after 8 weeks (Fig. 3c). There were no modifications made to the amount of drugs prescribed for constipation during the investigation period, but the possibility of some patients adjusting the amount on their own persists. While an objective evaluation of the improvement in symptoms should include the effect of laxatives, the amount and type of constipation drugs and the time of administration are patient-specific (Table), thus making it difficult to evaluate the corresponding effects. Hemodialysis patients usually complain of constipation and are therefore highly likely to take excessive doses of oral laxatives, leading to repeated occurrences of constipation and diarrhea. In this study, whether a reduction in the amounts of laxatives was actually realized remains unclear. However, it seems to be a primary factor in the mechanism by which SFOH administration leads to an improvement in the diarrhea score.

There are several limitations of this study. First, our sample size was small, which can obscure the results of the present study. In addition, an evaluation for the constipation drugs could not be carried out. However, we were able to reduce the serum phosphorus level in patients with hyperphosphatemia, which is untreatable using the existing phosphate binders, by treatment with a combination of the existing phosphate binders and SFOH. The effectiveness of the combination therapy is also established by the lack of exacerbation of the gastrointestinal symptoms despite a few contradictory case reports. Further, there is a possibility of reducing the episodes of side effects through effective adjustment of laxative dosages from the very start of administration. Therefore, we concluded that appropriate instructions for medications are very important.

Table: Demographic profile of the subjects

	All
Total patient no.	6
Age (Y), mean ± SD	69.0 ± 7.0
Sex (M/F)	2/4
Hemodialysis vintage (M), mean ± SD	242.3 ± 98.2
Use of phosphorus agents	
Precipitated calcium carbonate	5 (83.3)
Lanthanum carbonate	6 (100)
Bixalomer	2 (33.3)
Use of vitamin D_3 analogs	
Oral alfacalcidol	1 (16.7)
Intravenous maxacalcitol	2 (33.3)
Use of erythropoietin	
Darbepoetin alfa	2(33.3)
Use of cathartic drugs	
Sennoside	3 (50.0)
Powdered rhubarb	3 (50.0)
Suppository compounding sodium bicarbonate and sodium phosphate	1 (6.3)
Use of cinacalcet	0 (0)

Data provided are the number (%) of patients, unless otherwise indicated.

4. Experimental

4.1. Study patients

We included outpatients undergoing dialysis who were already receiving a combination of phosphate binders and were prescribed SFOH later, at Kainan Hospital. We did not set definite exclusion criteria such as age, sex, or dialysis duration. The characteristics of the 6 subjects (2 men, 4 women) are shown in the Table. The investigation was conducted over an 8-week period from January to August 2016 after starting SFOH administration. During the period of study, dosages of the phosphate binders were unchanged while SFOH doses were adjusted based on clinical laboratory test results. Prescriptions of medication for constipation were also unchanged during the investigation period.

4.2. Evaluation method

Gastrointestinal symptoms were evaluated before and 2, 4, and 8 weeks after drug administration using the Japanese version of the gastrointestinal symptom rating scale (GSRS) (Svedlund et al. 1988). GSRS is a score table where the occurrence of five gastrointestinal symptoms including acid reflux, abdominal pain, indigestion, diarrhea, and constipation is converted into 15 questions for evaluation. We measured the following four parameters: serum phosphorus level (mg/dL) via a biochemical examination, adjusted calcium level (mg/dL) determined using Payne's formula, and serum hemoglobin level (g/dL). All measurements were taken before the start of drug administration, and at 2, 4, 6, and 8 weeks after administration, on the first day of the following week, prior to the next dialysis treatment. In addition, because SFOH contains iron, the serum ferritin level (ng/dL) was also examined before the start of drug administration, and at 2 and 6 weeks later, on the first day of the following week, prior to the next dialysis treatment. Further, the adequacy of dialysis treatment was assessed via calculation of the normalized protein catabolic rate (nPCR), measured in terms of g/(kg. day), and urea clearance (Kt/V), which were examined within 2 weeks before SFOH administration, and at 4 and 8 weeks later, on the first day of the following week.

4.3. Statistical methods

Data were examined using the Wilcoxon signed rank test, and risk rates less than 5% were considered statistically significant.

4.4. Consideration of medical ethics

This research was approved by the Institutional Ethics Review Board after consideration of the appropriate medical ethics. We adequately protected each patient's privacy, and obtained oral and written consent.

Conflicts of interest: None declared.

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