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# Troches for Hyperphosphatemia: A Case-Series Study by a Unique Administration Style of Chewable Tablets of Sucroferric Oxyhydroxide during Hemodialysis Sessions

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**Abstract**

*Hyperphosphatemia is still one of critical issues in hemodialysis (HD) patients, phosphate binders, a main treatment to decrease serum phosphorus levels, also increases pill-burden to patients. To resolve this problem, we tried a troche (throat lozenges)-like administration style (troche therapy) of sucroferric oxyhydroxide (SFOH) during a HD session in a prospective case-series study. The patients were advised to keep chewable tablets containing 500 mg/tablet of SFOH in their oral cavities until the tablets were dissolving spontaneously, then to swallow their dissolved contents. According to patient tolerability, an administration dose was determined in each patient by an attending physician (one of co-authors). Six man and six woman with age of 62.1±22.4, resistant to routine therapies for hyperphosphatemia were enrolled with their informed consents. During one-year-observation period, three patients withdrew from the study due to drug-related causes, and four patients resigned the study due to drug-unrelated reasons. Other five patients continued the study over a year. Serum inorganic phosphorus (IP) levels were significantly reduced three months after starting SFOH (from 7.3±1.2 to 5.7±1.4 mg/dL, p. = 0.013, reduction rate 22.9±11.2%, p. = 0.009). Meanwhile, other phosphate binders were tapered in three patients and calcium carbonate was increased in one patient. Serum intact FGF23 levels were significantly reduced by 40.7±22.0% (p. = 0.042) and 47.8±25.7% (p. = 0.041) after three and four months, respectively. Log (intact FGF23) was well correlated with serum IP in total measured samples (r. = 0.762, p. < 0.0001, n. = 98). In conclusion, not only decrease serum phosphorus levels, but to reduce pill-burdens, the troche therapy of SFOH would be a possible and beneficial alternate to a conventional oral administration of PBs in some parts of hemodialysis patients.*

**Keywords:** *hyperphosphatemia, troche therapy, lozenges, pill-burden, polypharmacy, FGF23*

## Introduction

Hyperphosphatemia is one of serious concurrent problems in dialysis patients. However, hemodialysis (HD) with phosphate-restriction diet alone could not reduce serum inorganic phosphorus (IP) levels to satisfactory ranges in cases especially with exhausted residual renal function, because sufficient amount of IP contained in diet could never be removed by routine dialysis settings. Thus maintenance HD patients are obliged to receive quite a few phosphate binders (PBs) daily to prevent chronic kidney disease mineral and bone disorder (CKD-MBD). Consequently, PBs are known to be symbolic drugs of pill burden, or polypharmacy to dialysis patients, and adherence to PBs was inversely correlated with hyperphosphatemia [1, 2].

Sucroferric oxyhydroxide (SFOH) is one of non-absorbable PBs. Contrary to ferric citrate hydrate, iron ions of the drug content are more resistant to absorption in the gastro-intestinal (GI) tract. A newly developed chewable tablet of SFOH (P-tol®, Kissei Pharmaceutical Co, Nagano, Japan) is designed to chew before swallowing. However, the tablet is spontaneously disintegrating and dissolving within 15 minutes, unless chewing. This study utilized its unique character of the tablet, and an administration style of "troches" as mentioned below was evaluated in its feasibility and effectiveness.

Troches, or throat lozenges are popular family medicine against sore throat or cough not only in Western countries but in Japan. Therefore, this kind of administration style, "the troche therapy", would be acceptable to HD patients who must generally take so many pills every day. By administration of the drug during HD sessions, it will make easier to as certain the drug-adherence of each patient. Moreover, the troche therapy was expected to absorb IP not only in the GI tract, but in the saliva during dissolving phases of tablets in the oral cavity [3]. This therapy will also be beneficial in saving oral intake of water for taking medicine.

Based on the above reasons, we examined the tolerability and the effectiveness of the troche therapy of SFOH in a case-series study.

## Patients and Methods

Of approximately 170 maintenance HD patients at JA Toride Medical Center, we screened hyper phosphatemic patients with serum IP > 5.5 mg/dL, resistant to routine medical therapies including PBs. Among the patients, those who accepted the study protocol were included in the study with their informed consents. One or more chewable tablets of SFOH (500 mg / tablet) were orally administered to these patients during each HD session. The patients were advised not to chew tablets, and to keep them in their oral cavity until tablets were dissolving spontaneously, then to swallow the dissolved content. Initial doses of SFOH for each patient was determined by an attending physician in co-authors. The patients undertook HD in a bed-resting, supine position, and no meal was served during HD sessions. Dialysis settings affecting IP removal were not changed through the observation period.

Blood samples were obtained before the first dialysis session of the third week of each month, and Serum IP, calcium (Ca), and biologically active full-length FGF23 (intact FGF23) were measured through the observation periods. Serum IP and Ca were measured by the auto-analyzer system (ARCHITECT PLUS, Canon Medical System, Tochigi, Japan). Intact PTH was measured by the established electro-chemiluminescence immuno assay (ECLIA). Intact FGF23 was measured by the established ELISA [4].

A statistical analysis of obtained data through one year period was done by Excel and R [5]. Because the study design encompassed arrangement of medication including PBs other than SFOH which could affect serum IP and intact FGF23 levels, we conducted repeated measures analysis of variance (rmANOVA), and subsequently compared the data at each measured time-point by Bonferroni method. The correlation of serum IP and intact FGF23 levels was examined by Pearson's correlation coefficient analysis. Data were described as mean±sample standard deviation (SD), unless otherwise specified. Based on the above statistical analysis, p. less than 0.05 was considered significant.

The study was approved by the ethical committee of JA Toride Medical Center (No. 302), and registered on University Hospital Medical Information Network (UMIN) with UMIN000031337.

## Results

Twelve patients were enrolled in this study after their informed consents were obtained. The characteristics of the patients were summarized in Table 1.

**Table 1.** *Patient characteristics*

| Case | Gender | Age | Cause of ESRD | Dialysis period (month) | Initial serum IP (mg/dL) | Treatments | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Phosphate binders (g/day) | | Vitamin D analogues (μg/week) | Ca-mimetis (μg/week) |
| | | | | | | Ca binders | Non-Ca binders | | |
| 1 | M | 76 | CGN | 139 | 5.9 | CaC 1.0 , CaL 4.0 | FeCit 0.25 | 1,25VitD 0.5 x 3 | Etelcalcetide 5 x 3 |
| 2 | F | 50 | CGN | 24 | 9.9 | CaC 3 | bixalomer 1.5 | 1,25VitD3 0.5 x 3 | – |
| 3 | F | 44 | DKD | 36 | 7.5 | CaC 4.5 CaL 9.0 | bixalomer 1.5 | – | – |
| 4 | M | 78 | DKD | 64 | 6.4 | CaC 4.5, Cal3 | – | – | – |
| 5 | F | 58 | CGN | 57 | 6.7 | CaC 4 | FeCit 2.5 | – | Etelcalcetide 5 x 3 |
| 6 | M | 52 | AKI | 78 | 6.7 | CaC 6.0 | FeCit 0.25 sevelamer 7.5 | – | – |
| 7 | M | 61 | DKD | 90 | 8.1 | CaC 3.0 | Bixalomer 2.0 | – | – |
| 8 | M | 72 | CGN | 94 | 6.3 | CaC 2.0 | Sevelamer 4.5 | – | – |
| 9 | M | 66 | RCC | 14 | 5.8 | CaC 1.5 | – | – | – |
| 10 | F | 50 | CGN | 286 | 8.6 | CaC 1.6 | – | 1αVitD 0.25 x 7 | – |
| 11 | F | 70 | CGN | 490 | 7.8 | CaC 3.0 | sevelamer 2.25 | OCT 10 x 2 | – |
| 12 | F | 68 | AKIP | 250 | 7.7 | – | – | – | – |
| mean | | 62 | | 135 | 7.3 | | | | |

*ESRD: end stage renal disease; CGN: chronic glomerulonephritis; DKD: diabetic kidney disease; AKI: acute kidney injury; RCC: renal cell carcinoma; AKIOP: acute kidney injury on pregnancy; CaC: calcium carbonate; CaL: calcium lactate; CKD-MBD: chronic kidney disease mineral and bone disorder; FeCit: ferrous citrate; VitD: vitamin D; OCT: oxacacitol*

Their age was 62.1±22.4 (50 - 78) year old, and the HD period was 135.2±276.1 (14 - 490 months. The initial serum IP level was 7.3±1.2 (5.8 – 9.9) mg/dL. All patients underwent HD thrice a week. The patients except for case 12 had received one or more PBs on the study registration (Table 2).

**Table 2.** *Prescribed number of tablet containing 500 mg of sucroferric oxyhydroxide during the study period*

| month / case | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | off | | | | | | | | | | |
| 2 | 2 | 2 | 2 | 2 | 2 | off | | | | | | | |
| 3 | 2 | 2 | 3 | 4 | 4 *a | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 4 | 1 | 1 | 2 | 2 | 2 | off | | | | | | | |
| 5 | 1 | 1 | 2 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 2 |
| 6 | 1 | 1 | 3 | 4 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 7 | 1 *b | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 |
| 8 | 1 | 2 | 2 | 2 *c | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | 1 | 1 | 1 *d | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | off |
| 10 | 1 | off | | | | | | | | | | | |
| 11 | 1 | 1 | 1 | 1 | 1 | off | | | | | | | |
| 12 | 1 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | off | | | | |
| mean (T) | 1.2 | 1.4 | 2 | 2.2 | 2.4 | 2.9 | 2.9 | 2.9 | 2.7 | 2.7 | 2.7 | 2.8 | 3.2 |
| n. | 12 | 11 | 10 | 10 | 10 | 7 | 7 | 7 | 6 | 6 | 6 | 6 | 5 |

*a: Bixalomer was reduced from 1.5 to 0.75 g/day; b: Two gram per day of bixalomer was discontinued; c: Sevelamer was reduced from 4.5 to 3.75 g/day; d: Calcium carbonate was increased from 1.5 to 3.0 g/day; T: tablet*

Case 12 had a difficulty in prescription of any PBs, because she had received more than 10 drugs daily against concurrent clinical problems, such as liver cirrhosis.

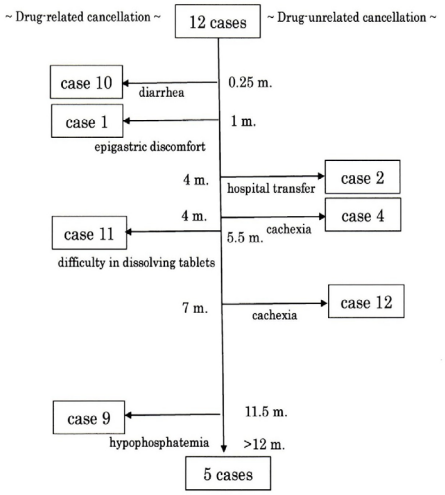


**Figure 1.** *Actual studied period of each patient*

m.: month

As shown in Figure 1, seven patients discontinued the trial within a year, and other five patients continued the trial for longer than a year. One patient (case 10) resigned the study one week after starting the therapy, because of diarrhea. One another patient (case 1) also resigned the study after one month, because of epigastric discomfort. Case 11 had complained of a difficulty in dissolving tablets in the oral cavity, and withdrew from the study after 5.5 months from the initiation of the study. Four patients discontinued the study due to reasons unrelated to the therapy. Other five patients continued the trial for longer than a year. The administration dose for each patient was summarized in Table 2. The mean initial dose was 1.2 T (600 mg) in each dialysis session (1.8 g/week), and the averaged maximum dose was 3.2 T (1600 mg) per HD session or 4.8 g/week.

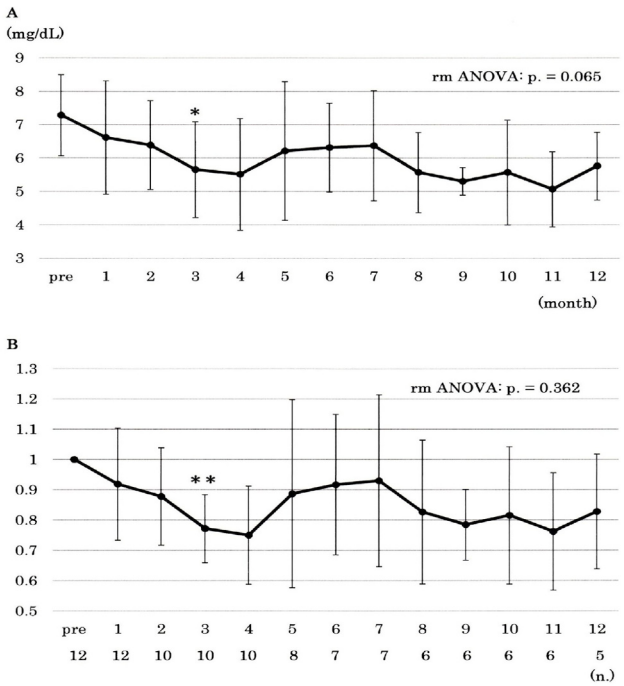


**Figure 2.** *Serum inorganic phosphorus levels before and after administration of sucroferric oxyhydroxide and its relation to serum FGF23 levels*

**A. Serum IP levels**

*: p. = 0.013 compared with serum IP levels before starting the troche therapy

**B. Relative IP levels**

Each relative value was obtained by the measured value divided by the value before starting the troche therapy in each patient. Arrangement of other PBs during the initial four months (see Table 2 in detail) may cause a transient elevation of serum IP levels at five months after starting the troche therapy.

**: p. = 0.009 compared with serum IP levels before starting the troche therapy

As depicted in Figure 2A. serum IP levels were significantly reduced from 7.3±1.2 mg/dL before the troche therapy to 5.7±1.4 mg/dL after three months (p. = 0.013 by Bonferroni method). Reduction rate of serum IP was also significant (Figure 2B; -22.9% after three months, p. = 0.009). During the initial four months period, PBs other than SFOH were tapered in three patients, and calcium carbonate was increased in one patient (Table 2). Consequently, serum IP levels were transiently elevated, then, controlled below the initial level, although entire time course was not statistically changed by administration of SFOH (p. = 0.065 by rmANOVA). Serum Ca levels were not changed during the observation period (8.9±0.7 mg/dL before the study and 8.8±0.8 mg/dL after 12 months, p. = 0.510 by rmANOVA). Serum intact PTH levels were not also changed (305.3±344.4 pg/mL before the study and 227.0±156.7 pg/mL after 12 months, p. = 1.00 by rmANOVA).

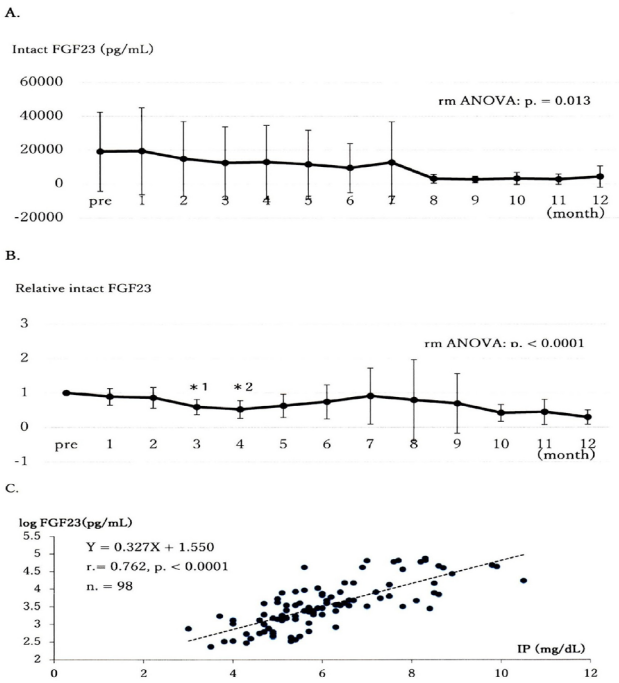


**Figure 3.** *Serum intact FGF23 levels before and after administration of sucroferric oxyhydroxide*

**A. Serum intact FGF23 levels**

**B. Relative intact FGF23 levels**

Each relative value was obtained by the measured value divided by the value before starting the troche therapy in each patient. Since serum intact FGF23 levels in case 7 were missing during 0 – 4 month, total data of intact FGF23 in case 7 were deleted in counting relative intact FGF23 levels.

*1: p. = 0.042 and *2: p. = 0.041 compared with serum IP levels before starting the troche therapy

**C. Measured serum IP and logarithmic conversion of intact FGF23**

Serum intact FGF23 levels were affected and tend to be reduced by the troche therapy (p. = 0.01 by rmANOVA), although no significant difference was identified between each observation point before and after administration of SFOH (Figure 3A). Meanwhile, reduction rates of intact FGF23 were significant at three (-40.7±22.0%, p. = 0.042) and four months (-47.8±25.7%, p. = 0.041) after starting SFOH, compared with those before administration of SFOH (Figure 3B). Because individual intact FGF23 levels were widely distributed, only the reduction rate might show such significant differences. Log (intact FGF23) and IP levels were well correlated in total samples (Figure 3C; r. = 0.762, p. < 0.0001). Relative changes of intact FGF23 from the initial point were also correlated with relative changes of serum IP (r. = 0.585, p. < 0.0001).

## Discussion

The troche therapy was introduced to 12 patients, and five of them had continued the therapy longer than a year. Meanwhile, three patients discontinued the study due to drug-related reasons, and four patients resigned the study by incidental problems unrelated to the study.

According to the international observation study, DOPPS [2], about half of 5262 HD patients in 12 countries received six or more pills of PBs per day, and similar proportion (45%) of the patients reported skipping these PBs at least once in the past month. Moreover, non-adherence to PBs was associated with hyperphosphatemia (> 5.5 mg/dL) and hyperparathyroidism (PTH > 600 pg/mL). A similar inverse correlation of adherence to PBs with hyperphosphatemia was also found in HD patients in the U.S.A. [1]. Therefore, improving adherence to PBs is quite an important issue in management of HD patients. Moreover, such efforts is expected to avoid medical costs being wasted.

In general medicine, troches are rare administration styles of drugs, which are indicated only to oral fungal infection [6] or to anti-aging, hormone replacement therapy [7]. Meanwhile, troches are popular styles of family medicine against sore throat and cough even in Japan. Therefore, it was expected to be an acceptable alternate by most dialysis patients who must receive so much drugs including PBs. In fact, only one patient gave up the troche therapy by a difficulty in dissolving tablets in the oral cavity after repeated efforts for 5.5 months. Since salivary excretion rate has been reported to be reduced in some parts of dialysis patients [8], it might be better to evaluate salivary excretion and oral condition of patients before starting the troche therapy.

"Troches" of SFOH are expected to adsorb IP of the saliva, as reported in the previous study using chitosan gum [3], although the absolute amount of IP removed from the saliva was not determined in this study. The concentration of IP in the saliva was reported to be increased in dialysis patients, and almost ten times higher than that of the serum. Considering 500 – 700 mL of saliva is daily excreted, at least 366 mg of inorganic phosphorus is delivered to the GI tract [9]. Moreover, HD itself increases salivary excretion [10]. Chitosan gum failed in significant reduction of serum IP levels. However, one more beneficial point in this "troche therapy" is that dissolved SFOH also adsorbs IP in the GI tract after swallowed, which might contribute to more reduction of phosphorus reserve of patients. Consequently, compared to regular oral administration of SFOH, in which 750 mg/day (5.25 g/week) of SFOH reduced serum IP levels by 1.84 mg/dL [11], the troche therapy was supposed to have comparable efficacy, since 1100 mg/HD session (3.3 g/week) of SFOH reduced serum IP levels by 1.63 (7.28 → 5.65) mg/dL at three months after starting the therapy (Table 2 and Figure 2).

As shown in Figure 3C, serum intact FGF23 levels were mostly determined by serum IP levels, a similar finding to the previous report in HD patients [12], although individual differences are not negligible as reported previously [13]. Increased iron-supply by SFOH was also expected to suppress serum intact FGF23 levels. However, there was rather positive correlation of intact FGF 23 levels with available serum ferritin levels (r. = 0.33, p. = 0.002 by simultaneous sampling of 81 data from all patient) in this study, although serum ferritin was not included in the study protocol. Contrary to ferric citrate hydrate, a time course of serum ferritin level in cases receiving SFOH were quite variable [14]. Therefore, the observed relationship of serum ferritin and intact FGF23 was far from conclusive, and should be ascertained in the future trial. Moreover, clinical significances of serum intact FGF23 levels have been controversial in association with cardiac or infectious complications [15]. Thus prospective careful follow

up will be needed in the patients under the troche therapy to clarify the actual role of intact FGF23 in patient survival.

In five patients who completed the troche therapy for one year observation period, two patients resigned the troche therapy, because of elevation of their serum ferritin levels; 514.3 ng/mL at 17th month in one case and 461.4 ng/mL at 19th month in another case. One patient discontinued the therapy due to developing hypotension during HD sessions at 25th month to avoid aspiration of SFOH. Other two patient have continued the troche therapy for 20 and 25 months at present.

Since this study was small-sized trial, and only five of 12 patients completed the study period of one year, the obtained results were not conclusive in evaluation of effectiveness of the troche therapy of SFOH. However, the results showed the troche therapy was tolerable and reasonable at least in some cases of maintenance HD patients. The authors expect more extensive studies both in patients and periods, to reach a final conclusion.

In summary, since the troche therapy, proposed in this study exhibited several benefits over routine oral administration of PBs, it should be noted as a potential alternate administration style of SFOH.

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