A Review of Sucroferric Oxyhydroxide for the Treatment of Hyperphosphatemia in Patients Receiving Dialysis

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ABSTRACT

Purpose: Sucroferric oxyhydroxide is the newest phosphate binder to receive US Food and Drug Administration approval for patients on dialysis. The purpose of this review is to critically evaluate the studies that have been conducted with this medication and determine where it may fit in the clinician's overall treatment plan for hyperphosphatemia in patients with chronic kidney disease.

Methods: Literature searches were performed in the PubMed database and www.ClinicalTrials.gov using the search terms sucroferric oxyhydroxide, and PA21 phosphate binder. Limits were set to include only clinical trials performed in human subjects.

Findings: Four completed clinical trials and 3 ongoing studies were identified. Completed clinical trials included Phase I, Phase II, and Phase III studies that all demonstrated the ability of sucroferric oxyhydroxide to lower serum phosphorus concentrations. One study compared sucroferric oxyhydroxide with sevelamer and reported no statistically significant difference in serum phosphorus–lowering ability. The ongoing trials are evaluating sucroferric oxyhydroxide for long term use, in peritoneal dialysis patients, and compared with calcium-based phosphate binders.

Implications: Sucroferric oxyhydroxide is an effective phosphate binder for chronic kidney disease patients receiving hemodialysis and may offer an advantage in terms of pill burden. Gastrointestinal side effects are similar to those of current phosphate binders. Advantages of other phosphate binders (ie, the lipid- and uric acid–lowering abilities of sevelamer) may outweigh the pill burden benefits of sucroferric oxyhydroxide. (*Clin Ther.* 2014;36:2082–2093)

Key words: PA 21, sucroferric oxyhydroxide, Velphoro.

INTRODUCTION

Hyperphosphatemia is a common complication for nearly all end-stage renal disease (ESRD) patients. As kidney function declines and eventually fails, the ability to excrete phosphorus is impaired.[1] Furthermore, hyperphosphatemia can have serious consequences for ESRD patients that include soft-tissue calcification (STC), cardiovascular calcifications, and valvular calcifications. Hyperphosphatemia is typically managed by limiting the dietary phosphate intake to 800 to 1000 mg/d and administering phosphate binders that bind additional phosphorus in the gastrointestinal tract, thereby preventing absorption and allowing it to be excreted in the feces.[1] There are several types of phosphate binders that are commonly classified into 2 main categories: calcium-containing phosphate binders and noncalcium-containing phosphate binders. Calcium-containing phosphate binders are typically less expensive but can cause hypercalcemia in some instances, thereby limiting their use in situations in which the patient may be at risk of STC. These binders include calcium carbonate and calcium acetate. Noncalcium-containing phosphate binders include aluminum hydroxide (Amphogel®*), which also carries the risk of aluminum toxicity, and the newer agents, sevelamer carbonate (Renvela®†) and lanthanum carbonate (Fosrenol®‡), which are more expensive compared with their calcium-containing counterparts. Sucroferric

*Trademark: Amphogel® (Wyeth-Ayerst, Radnor, Pennsylvania).

†Trademark: Renvela® (Genzyme Corporation, Cambridge, Massachusetts)

‡Trademark: Fosrenol® (Shire US Inc, Wayne, Pennsylvania).

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oxyhydroxide (Velphoro®§) is the newest noncalcium-containing phosphate binder that was approved by the US Food and Drug Administration (FDA) in 2014. It is an iron-based, chewable phosphate binder indicated for the reduction and control of the serum phosphorus concentration in patients with chronic kidney disease (CKD).[2,3] Serum phosphorus and calcium-phosphorus product concentrations in the gastrointestinal tract are lowered by sucroferric oxyhydroxide via a ligand exchange between its hydroxyl group and/or water and dietary phosphate. Sucroferric oxyhydroxide, when taken with meals, combines with dietary phosphate and forms a complex.[2,3] Dietary phosphate elimination is achieved by the removal of the bound phosphate in the feces.

This review examines this new phosphate binder compared with other phosphate binders on the market and discusses its potential role in current therapy. The efficacy of and drug interactions associated with sucroferric hydroxide were evaluated in 4 clinical trials. The results of these trials are presented and discussed.

METHODS

A PubMed search was conducted using the search terms "PA 21 phosphate binder" and "sucroferric oxyhydroxide" and limited to clinical trials in human subjects. Another search conducted of www.clinicaltrials.gov using the search term "PA 21 hyperphosphatemia" returned 3 other ongoing studies evaluating sucroferric oxyhydroxide for long-term use in hemodialysis (HD) patients, for use in peritoneal dialysis (PD) patients, and for use in HD patients with calcium carbonate.

RESULTS

Primary Literature Evaluating Sucroferric Oxyhydroxide in Patients With Chronic Kidney Disease Receiving Dialysis

The literature search returned 4 relevant clinical trials for evaluation. Three of them investigated the efficacy of sucroferric oxyhydroxide in HD patients (Table I). The main focus of the fourth study was investigating some of the more common drug–drug interactions of sucroferric oxyhydroxide. The results are presented in chronological order according to the publication date of the studies.

§Trademark: Velphoro® (Fresenius Medical Care, Waltham, Massachusetts.

A 2010 Phase I, open-label, single-arm study investigated the iron uptake after oral administration of 10 g/d of the sucroferric oxyhydroxide in 24 subjects aged 18 to 75 years of age after a single dose of radiolabeled sucroferric oxyhydroxide. The study population included 8 nondialysis-dependent chronic kidney disease (CKD) patients (stages 3–4), 8 maintenance HD patients, and 8 healthy subjects.[3] The iron uptake after oral administration of sucroferric oxyhydroxide was studied to identify any potential risk of iron overload.[3] The influence of the sucroferric oxyhydroxide on serum phosphorus concentration and on vitamin D metabolism was determined by measuring the intact parathyroid hormone concentration, 1,25(OH) D3 and 25(OH) D3 concentrations, respectively. The potential effects of the sucroferric oxyhydroxide on iron indices including serum ferritin, transferrin, and serum iron were additional objectives of this study. The safety and tolerability of sucroferric oxyhydroxide were assessed as well. Unlabeled doses of sucroferric oxyhydroxide were administered on days 1 to 6 followed by the radiolabeled dose on day 7 to CKD patients. Healthy subjects received the radiolabeled dose of sucroferric oxyhydroxide on day 1 followed by unlabeled doses on days 2 through 7. The daily dose of 10 g was recommended to be taken as a suspension in a 75 mL of water in 3 divided doses of 2.5 g, 5.0 g, and 2.5 g with breakfast, lunch, and dinner, respectively. The dosing schedule was decided on based on the assumption that the largest phosphate intake would occur with the midday meal. The blood and plasma Fe-59 were measured on days 8, 15, 22, 29, and 36 and on days 2, 8, 15, 22, and 29 for the CKD and healthy patients, respectively. Overall, the median uptake of Fe ranged from 0.04% (0–0.44%) in nondialysis-dependent CKD and maintenance HD subgroups and 0.43% (0.16%–1.25%) in healthy subjects. Statistically significant reductions in serum phosphate concentrations between predose and day 8 concentrations were observed ($P < 0.01$); however, there were no consistent changes in serum concentration of intact parathyroid hormone, 1,25 (OH) D3, and 25(OH) D3 concentrations. Similarly, no effect on iron indices was observed. The most commonly encountered adverse event was mild to moderate diarrhea, which was resolved by the end of study.

The second trial was a Phase II randomized, parallel-group, active-controlled, multicenter, open-label study