

Chronic Kidney Disease: Uraemic Toxins

CKJ Review

Iron-based phosphate binders: do they offer advantages over currently available phosphate binders?

Armando Luis Negri¹ and Pablo Antonio Ureña Torres²

¹Instituto de Diagnostico e Investigaciones Metabólicas, Universidad del Salvador, Buenos Aires, Argentina and ²Clinique du Landy, Service de Néphrologie-Dialyse, Saint Ouen, France

Correspondence to: Armando Luis Negri; E-mail: armando.negri@gmail.com

Abstract

Increased cardiovascular morbidity and mortality has been associated with the hyperphosphatemia seen in patients with end-stage chronic kidney disease (CKD). Oral phosphate binders are prescribed in these patients to prevent intestinal absorption of dietary phosphate and reduce serum phosphate. In prospective observational cohorts they have shown to decrease all-cause and cardiovascular mortality risk. Different problems have been associated with currently available phosphate binders as positive calcium balance and impaired outcomes with calcium-based phosphate binders or increased costs with non-calcium-based phosphate binders. Iron-based phosphate binders represent a new class of phosphate binders. Several iron-based phosphate binders have undergone testing in clinical trials. Ferric citrate (JTT-751) and sucroferric oxyhydroxide (PA21) are the two iron-based binders that have passed to the clinical field after being found safe and effective in decreasing serum phosphate. Iron from ferric citrate is partially absorbed compared to sucroferric oxyhydroxide. Ferric citrate usage could result in an important reduction in erythropoiesis-stimulating agent (ESA) and IV iron usage, resulting in significant cost savings. Sucroferric oxyhydroxide was effective in lowering serum phosphorus in dialysis patients with similar efficacy to sevelamer carbonate, but with lower pill burden, and better adherence. Ferric citrate may be more suited for the treatment of chronic hyperphosphatemia in CKD patients requiring iron supplements but its use may have been hampered by potential aluminum overload, as citrate facilitates its absorption; sucroferric oxyhydroxide may be more suited for hyperphosphatemic CKD patients not requiring iron supplementation, with low pill burden.

Keywords: chronic dialysis; hyperphosphatemia; iron-based phosphate binders

Introduction

Chronic kidney disease mineral bone disorder (CKD-MBD), present in dialysis patients, is a complex syndrome involving mineral and bone laboratory abnormalities, clinical and histological bone disease and cardiovascular calcifications associated with increased risk of cardiovascular morbidity and mortality [1]. Not all components of CKD-MBD are present in all patients at all times, but they are highly interrelated. Hyperphosphatemia is one of its most frequent components that have traditionally been managed with dietary restriction and phosphate binding in the gut, but the beneficial effects of phosphate reduction on mortality and cardiovascular outcomes in CKD stage 5D are still unknown. Studies analyzing prospective observational cohorts (DOPPS and COSMOS) have shown that phosphate binder administration decreases all-cause and

cardiovascular mortality risk [2, 3]. These association studies need to be confirmed by randomized controlled trials to prove the observed beneficial effect.

Advantages and disadvantages with currently available phosphate binders

Phosphate binders, both calcium-based and calcium-free, are recommended to lower serum phosphate and prevent hyperphosphatemia in CKD patients. Evidence supports that phosphate binders are equally efficacious in lowering serum phosphate concentrations if they are adequately titrated. Because of the absence of evidence of improved survival rate by any one of the calcium-free intestinal phosphate binders, and because of their more than 50–70-fold lower cost, the Kidney Disease Improving Global

Outcomes (KDIGO) guidelines has recommend the use of calcium-based phosphate binders as first-line treatment in CKD5D patients [4].

However, the new concept of CKD-MBD has clearly influenced clinical guidelines. KDOQI guidelines from the National Kidney Foundation recommended in 2003 that calcium-based phosphate binders should be avoided to treat hyperphosphatemia in the presence of cardiovascular calcifications [5]. In 2009, the KDIGO and other international guidelines reinforced and extended this recommendation by stating that it is reasonable to choose oral phosphate binder therapy taking into consideration other components of CKD-MBD: In the presence of vascular/valvular calcification, calcium-free phosphate binders should be preferred.

A recent meta-analysis has combined data from randomized trials to update the effect of calcium-based versus calcium-free phosphate binders on all-cause mortality in patients with CKD as the primary outcome [6]. Analysis of the 11 randomized trials (4622 patients) that reported an outcome of mortality showed that patients assigned to calcium-free binders (sevelamer and lanthanum carbonate) had a 22% reduction in all-cause mortality compared with those assigned to calcium-based phosphate binders (odds ratio 0.78, 95% CI 0.61–0.98). However, further studies are needed to identify if the reduction in mortality is due to reduced cardiovascular mortality (probably in relation to decreased progressive arterial calcification) and to assess whether mortality differs by type of calcium-free phosphate binder.

In addition to this important aspect of phosphate binder therapy, there are other aspects that should be considered. The first aspect is the potential for gastrointestinal (GI) absorption of the active moieties that could be harmful or beneficial in the body. The second aspect is whether the phosphate binders can bind not only phosphate but also harmful or useful substances in the gut. The third aspect is the compliance to phosphate binder therapy. Finally, the fourth aspect is the effect of different phosphate binders on FGF23 serum levels.

Absorption of active moieties, even if minor, could give rise to concern due to accumulation and eventual toxicity as has been seen in the past with aluminum-based phosphate binders. In the case of lanthanum, there were concerns regarding its potential accumulation in blood, liver and bone. However it has been shown experimentally and clinically that lanthanum accumulation in these organs is minimal [7]. Magnesium, absorbed from magnesium carbonate-containing phosphate binders, could act as an anti-arrhythmic and could have important inhibitory actions on vascular calcification, although definitive evidence on cardiovascular protection is sparse [8, 9]. Observational studies in dialysis patients have suggested that low serum magnesium levels are associated with cardiovascular morbidity such as mitral annular calcification, peripheral arterial calcification, increased carotid intima-media thickness and increased mortality risk [10, 11]. On the other hand, higher serum magnesium levels have been linked to lower parathyroid hormone (PTH) levels resulting in low turnover bone disease.

Sevelamer binds several compounds in the gut apart from phosphate such as cholesterol, urate and uremic toxins. Thus, it could have pleiotropic effects apart from reducing serum phosphate [12]. It also binds liposoluble vitamin such as vitamins D and K. However, their clinical implications remain to be established.

Phosphate binders that account for about one-half of the daily pill burden patients in hemodialysis take leading

to frequent non-adherence. In a recent study, the median pill burden by type of phosphate binders was sevelamer mono-therapy, 9 (interquartile range IQR, 6), calcium mono-therapy, 9 (IQR, 3), lanthanum mono-therapy, 6 (IQR, 3) and combination therapy, 13 (IQR 10) ($P < 0.001$ for trend) [13]. For several phosphate binders, the number of pills taken daily, and the GI side effects are the major causes of decreased compliance.

Several prospective studies in populations of pre-dialysis CKD [14], incident [15] and prevalent [16] ESRD on hemodialysis and kidney transplant recipients [17] demonstrate that elevated circulating FGF23 levels are independently associated with an increased risk of cardiovascular events and mortality. It was originally thought that FGF-23 was only a biomarker of deranged phosphate balance and toxicity. However, recent studies have now shown that FGF-23 can have direct effect on the heart producing left ventricular hypertrophy [18, 19]. This suggests that elevated FGF-23 may be a novel mechanism of adverse outcomes in CKD. Thus the effect of different phosphate binders on circulating FGF23 levels could have important implications on morbidity and mortality in CKD patients. Non-calcium-based phosphate binders have been shown to decrease FGF23 while calcium-based phosphate binders not. A recent study showed that there was a negative relationship between iron administration and serum intact FGF23 level in a dialysis population, in contrast to what is seen for the general population. So, if high levels of FGF23 are harmful, iron therapy may have a beneficial effect on cardiovascular events and mortality in dialysis patients by reducing FGF23 levels [20].

Iron-based phosphate binders

Iron-based phosphate binders represent a new class of phosphate binders recently introduced. Several iron-based phosphate binders have undergone testing in clinical trials: Ferric Citrate (JTT-751, Zerenex[®]), Sucroferric oxhydroxide (PA21- Velphoro[®]), Fermagate, SBR759 and PT20. Fermagate (Iron-magnesium hydroxycarbonate) and SBR759 development are currently on hold (Table 1).

Ferric citrate (JTT-751—ZERENEX[®])

Ferric citrate is approved for anemia management in ESRD in Japan and has recently been approved by the US Food and Drug Administration as an oral treatment for hyperphosphatemia in CKD. The summary of published studies seen in Table 2.

Animal studies. Normal rats fed a diet containing 0.3, 1 or 3% ferric citrate (JTT-751) for 7 days had increased fecal phosphorus excretion with reduced phosphorus absorption and urinary phosphorus excretion. After feeding CRF rats (induced by a 0.75% adenine diet) for 35 days with ferric citrate (1 or 3%) in the dietary admixture, serum phosphorus levels, calcium-phosphorus product and calcium content in the aorta were reduced. Serum intact PTH levels and the incidence and severity of parathyroid hyperplasia were also decreased. This was also associated with a reduction in femoral bone fibrosis, porosity and osteoid formation [26].

Table 1. Main characteristic of iron-based intestinal phosphate binders

Name	Composition	Recommended daily dose	Mean daily number of pills	Main side effects	Pros/Cons	Pharmaceutical company
VELPHORO PA21	Sucroferric oxyhydroxide	1500 mg	Three pills per day	Discolored feces diarrhea, nausea	Iron not absorbed	Vifor (Fresenius)
ZERENEX JTT-751	Ferric citrate coordination complex	6000 mg	Six pills per day	Discolored feces diarrhea, nausea	Iron absorbed risk Al absorpt higher ferritin	Keryx Bio-pharmaceuticals
ALPHAREN Fermagate SBR-759 PT20	Iron-magnesium hydroxycarbonate Polymeric iron (III) Ferric oxide adipate	3000 mg	Three pills per day	Discolored feces gastrointestinal	Elevation in serum Mg levels	Shire Novartis Phosphate therapeutics

Table 2. Summary of published trials with ferric citrate

Author/journal year	Study phase	Subjects enrolled	Comparator	Duration	Main results
Yokoyama K Am J Nephrol 2012 [21]	Dose-response	192	Placebo	28 days	Pi decrease is dose dependent up to 6 g/day Pi decreased -2.16 with 3 g/day; Pi < 5.5 in 50% with 3 g/day
Dwyer JP Am J Kid Dis 2013 [22]	Dose-response	151	None	28 days	FC 6 g/day decrease Pi -1.9 ± 1.7 mg/dL and 8 g/day, -2.1 ± 2.0 mg/dL
Yokoyama K Nephrol Dial Transp 2014 [23]	III	230	Sevelamer HC 3–9 g/day	12 weeks	Pi -0.82 mmol/L with FC and -0.78 with sevelamer (non-inferiority) with sig. increase in ferritin and transferrin sat
Lee CT Nephrol 2014 [24]	III	166	Placebo	8 weeks	Pi decrease with 4 and 6 g/day; increase in ferritin and transferrin sat
Lewis JB JASN 2014 [25]	III	441	Active control and Placebo	52 weeks	Pi -2.2 mg/dL compared to Placebo and similar to active control but higher mean iron parameters with less IV iron

Clinical studies. A phase-2, open-label study was conducted in hemodialysis patients to evaluate the short-term safety, tolerability and iron absorption of ferric citrate when used as a phosphate binder. Fifty-five subjects were enrolled in two periods. Subjects discontinued their previous binders and started 4.5 g/day of ferric citrate (period 1) or 6 g/day (period 2) and were titrated for 4 weeks to maintain phosphorus between 3.5 and 5.5 mg/dL. Ferric citrate was well tolerated. The subjects' mean dose of ferric citrate was 7.1 ± 2.4 g/day at the end of 4 weeks. Mean phosphorus was 5.9 ± 1.4 mg/dL at baseline on their previous phosphate binder and was not significantly different at 4 weeks on ferric citrate (5.4 ± 1.4 mg/dL). GI adverse events included stool discoloration (69%), constipation (15%) and bloating (7%). Mean iron parameters (ferritin, iron and iron saturation) increased significantly at the end of follow-up [27].

Three phase-3 prospective randomized trials have been published recently in hemodialysis patients comparing ferric citrate efficacy and safety in phosphate control. The first study investigated the dose-response and safety of ferric citrate (JTT-751) among Japanese hemodialysis patients. This was a multicenter, randomized, placebo-controlled, double-blind, parallel-group, comparative study that included a total of 192 subjects with serum phosphorus (P) levels between 6.1 and 10.0 mg/dL [21]. Patients were randomized to receive ferric citrate (1.5, 3 or 6 g/day) or placebo treatment for 28 days. Serum P levels were significantly reduced in a dose-dependent manner up to 6 g/day. In the full analysis set, the mean change in serum P

level at week 4 was 0.04, -1.28 , -2.16 and -4.10 mg/dL in the placebo, 1.5-, 3- and 6-g/day groups, respectively. Overall, a reduction in serum P levels to ≤ 5.5 mg/dL was achieved in 2.5, 16.7, 50.0 and 92.6% of subjects, in the placebo, 1.5-, 3- and 6-g/day groups, respectively. The most common adverse events were mild and GI in nature. In 25 patients, treatment was discontinued due to increased transferrin saturation $\geq 50\%$; however, this was not considered to be a safety issue [21].

The second was a prospective, multicenter, open-label, randomized clinical trial performed in 151 maintenance hemodialysis patients with hyperphosphatemia. A fixed dose of ferric citrate was taken orally as a phosphate binder for up to 28 days (1, 6 or 8 g/day). The primary outcome was the dose-response of ferric citrate on serum P level; secondary outcomes were safety and tolerability. Mean baseline phosphorus levels were above 7 mg/dL in all groups. Phosphorus levels decreased in a dose-dependent manner (mean change at the end of treatment, -0.1 ± 1.3 mg/dL in the 1-g/day group, -1.9 ± 1.7 mg/dL in the 6-g/day group and -2.1 ± 2.0 mg/dL in the 8-g/day group). The mean difference in reduction in P levels between the 6- and 1-g/day groups was 1.3 mg/dL (95% CI 0.69–1.9; $P < 0.001$). The most common adverse event was stool discoloration [22].

In a third Phase-3, multicenter, open-label, parallel-group study, a total of 230 patients with a serum phosphorus ≥ 1.97 and < 3.23 mmol/L were randomized to ferric citrate (doses between 1.5 and 6.0 g/day) or sevelamer hydrochloride (doses between 3.0 and 9.0 g/day) for 12 weeks. The primary outcome was change in serum P from

baseline to end of treatment. Secondary outcomes included the changes in corrected serum calcium and intact PTH. The changes in ferritin, transferrin saturation and erythropoiesis-stimulating agent (ESA) dose were additional outcomes. Changes in serum P at the end of treatment were -0.82 mmol/L in the JTT-751 group and -0.78 mmol/L in the sevelamer group, establishing non-inferiority of ferric citrate to sevelamer. Corrected serum calcium increased and PTH decreased from baseline within both groups; changes between groups were similar. GI disorders were the most common adverse events in both groups; the incidence of diarrhea was higher in ferric citrate, while constipation occurred frequently in the sevelamer group. Treatment with ferric citrate resulted in significant relative increases in serum ferritin and transferrin saturation [23].

In another prospective, double-blind, placebo-controlled, randomized trial study carried out in five hospitals in Taiwan, 166 hemodialysis patients completed the 56-day study. Serum phosphorus levels declined while serum ferritin level/transferrin saturation increased significantly in both ferric citrate 4 and 6 g/day groups ($P < 0.05$ for 4 and 8 weeks). Most adverse events were mild to moderate and were comparable among the three groups [24].

In another sequential, randomized trial, 441 subjects on dialysis were randomized to ferric citrate or active control in a 52-week active control period followed by a 4-week placebo control period, in which subjects on ferric citrate who completed the active control period were re-randomized to ferric citrate or placebo. The primary analysis compared the mean change in phosphorus between ferric citrate and placebo during the placebo control period. A sequential gatekeeping strategy controlled study-wise type 1 error for serum ferritin, transferrin saturation, and intravenous iron and erythropoietin-stimulating agent usage as pre-specified secondary outcomes in the active control period. Ferric citrate better controlled phosphorus compared with placebo, with a mean treatment difference of -2.2 ± 0.2 mg/dL (mean $\pm$ SEM) ($P < 0.001$). Active control period phosphorus was similar between ferric citrate and active control, with comparable safety profiles. Subjects on ferric citrate achieved higher mean iron parameters [ferritin = 899 ± 488 ng/mL (mean $\pm$ SD); transferrin saturation = $39 \pm 17\%$] versus subjects on active control [ferritin = 628 ± 367 ng/mL (mean $\pm$ SD); transferrin saturation = $30 \pm 12\%$; $P < 0.001$ for both]. Subjects on ferric citrate received less intravenous elemental iron (median = 12.95 mg/week ferric citrate; 26.88 mg/week active control; $P < 0.001$) and less erythropoietin-stimulating agent (median epoetin-equivalent units per week: 5306 units/week ferric citrate; 6951 units/week active control; $P = 0.04$). Hemoglobin levels were statistically

higher on ferric citrate. Thus, ferric citrate is an efficacious and safe phosphate binder that increases iron stores and reduces intravenous iron and erythropoietin-stimulating agent use while maintaining hemoglobin [25].

Pharmacoeconomic studies. A cost-effective study from a managed-care perspective by Mutell *et al.* [28] demonstrated the potential for cost savings with the use of ferric citrate compared with other phosphate binders in that study, monthly ESA cost was projected to be reduced by 8.15%, and IV iron cost by 33.2%. A Monte Carlo simulation demonstrated a reduction of US\$160 per month in overall dialysis cost per patient with the use of ferric citrate. In another study, the projected cost reduction for ESA and iron for ESRD, based on the use of ferric citrate as a phosphate binder agent was modeled. They found that ferric citrate usage could result in a 20% reduction in ESA usage and 40% reduction in IV iron usage, resulting in 0.9–1.1 billion USD savings [29]. Presently, IV iron and ESAs are part of the bundled dialysis payment in the US, while phosphate binders are paid by private insurers, Medicare part D or the patient. Thus, the cost savings would be for the dialysis units while the cost of phosphate binder therapy (ferric citrate) would be for other payers.

Ferric citrate may be more suited for chronic treatment of hyperphosphatemia in CKD patients requiring iron supplements but its use may produce negative effects as the increased risk of aluminum absorption due to the presence of citrate in the salt [30].

Sucroferric oxhydroxide (PA21—Velphoro®)

Sucroferric oxhydroxide is an iron-based calcium-free chewable phosphate binder developed by Vifor Pharma recently approved by the US FDA for the treatment of hyperphosphatemia of CKD patients on dialysis. In June 2014, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion recommending marketing authorization for this iron phosphate binder. The summary of published studies seen in Table 3.

Animal studies. The efficacy of PA21, Sucroferric oxhydroxide, was evaluated in controlling calcium/phosphate disorders and preventing vascular calcifications in uremic rats. Rats with adenine-diet-induced CRF were randomized to receive PA21 0.5, 1.5 or 5% or CaCO₃ 3% in the diet for 4 weeks, and were compared with uremic and non-uremic control groups. After 4 weeks of phosphate

Table 3. Summary of published trials with sucroferric oxhydroxide

Author/journal year	Study phase	Subjects enrolled	Comparator	Duration	Main results
Wuthrich RP Clin JASN 2013 [31]	Dose finding	154	Sevelamer HC	6 weeks	Sevelamer 4.8 g/day Pi -1.06 ± 1.35 mg/dL; PA21 5.0 g/day Pi -1.08 ± 2.12 mg/dL
Floege J Kidney Int 2014 [32]	III	1055 hemo and peritoneal dialysis	Sevelamer carbonate	24 weeks 8 weeks titration 4 weeks no dose change 12 weeks maintenance	At 12 weeks PA21 Pi -0.71 mmol/L versus -0.78 sevelamer (non-inferiority) PA21 3 tablets versus sevelamer 8 tablets

binder treatment, serum P was reduced with CaCO₃ 3%, PA21 1.5% and PA21 5% compared to CRF controls. Intact PTH was strongly reduced in the PA21 5% and CaCO₃ 3% CRF groups to a similar extent versus CRF controls. A lower serum fibroblast growth factor 23 concentration was observed in the PA21 5%, compared with CaCO₃ 3% and CRF, control groups. PA21 5% CRF rats had a lower vascular calcification score compared with CaCO₃ 3% CRF rats and CRF controls [33].

Phosphate-binding capacity studies. The iron-based agent PA21 has high phosphate-binding capacity *in vitro*. Phosphate adsorption and Fe release were assessed under conditions simulating administration of PA21 on an empty stomach and full stomach across a pH range to which PA21 would be exposed during passage through the GI tract. PA21 showed a robust phosphate-binding capacity over the entire physiologically relevant pH range. The high binding capacity at low pH indicates that phosphate binding could begin in the stomach. In that experimental setting, the maximal bound phosphate to Fe ratio was 0.47 mmol P/mmol Fe. The largest amount of Fe release was observed at the lowest pH without phosphate and was much lower in the presence of phosphate. These results are in line with the formation of iron phosphate at low pH, as indicated by X-ray photoelectron spectroscopy and thermodynamic calculations. Fe release was minimal ($\leq 0.35\%$) across pH 2.5–8.5. These studies demonstrate that PA21 has potent phosphate-binding capacity and low iron release over a physiologically relevant pH range in the GI tract [34].

Iron absorption studies. A study was undertaken to investigate the uptake of iron after oral administration of PA21 in order to identify any potential risk of iron overload in the clinical setting, and to assess the effect of PA21 on serum P levels prior to larger trials over a longer treatment period. An open-label, Phase I study was undertaken in which PA21 10 g/day was administered for 7 days to 8 non-dialysis-dependent CKD patients (Stages 3–4), 8 maintenance hemodialysis patients and 8 healthy subjects. In addition, a single dose of radiolabeled PA21 was administered to determine iron uptake. Median iron uptake (range) was 0.06% (0.008–0.44%), 0.02% (0–0.04%) and 0.43% (0.16–1.25%) in the non-dialysis-dependent CKD patients, hemodialysis patients and healthy subjects, respectively [35].

Clinical studies. A randomized, active-controlled, multicenter, open-label, dose-finding study was undertaken at 50 clinical sites in Europe and the United States. Hemodialysis patients were randomized to receive PA21 at dosages of 1.25, 5.0, 7.5, 10.0 or 12.5 g/day or sevelamer-HCl 4.8 g/day for 6 weeks. The primary efficacy endpoint was the change in serum P concentration from baseline. There were 154 participants who were randomized and received the study drug. All groups except PA21 1.25 g/day showed a significant decrease in serum P. Mean decreases in serum P in PA21 10 g/day and 12.5 g/day were -2.00 ± 1.71 mg/dL and -1.69 ± 1.81 mg/dL, respectively. A similar decrease to sevelamer-HCl (-1.06 ± 1.35 mg/dL)

was seen with PA21 5.0 g/day (-1.08 ± 2.12 mg/dL) and 7.5 g/day (-1.25 ± 1.21 mg/day). Overall, 60.9% of participants randomized to PA21 and 57.7% randomized to sevelamer-HCl reported ≥ 1 adverse event. The most frequent adverse events were hypophosphatemia (18.0%) and discolored feces (11.7%) for the pooled PA21 dose groups, and diarrhea, hypophosphatemia and hypotension (each 11.5%) for sevelamer-HCl. Discontinuation due to adverse events occurred at a similar rate in PA21-treated (21.1%) and sevelamer-HCl-treated (23.1%) participants. PA21 5–12.5 g/day significantly reduces serum phosphorus in hemodialysis patients. The 5 g/day and 7.5 g/day dosages showed similar efficacy to 4.8 g/day of sevelamer-HCl [31].

The efficacy of PA21 was compared with that of sevelamer carbonate in an open-label, randomized, active-controlled phase III study. Seven hundred and seven hemo- and peritoneal dialysis patients with hyperphosphatemia received PA21 1.0–3.0 g per day and 348 received sevelamer 4.8–14.4 g per day for an 8-week dose titration, followed by 4 weeks without dose change, and then 12 weeks maintenance. Serum phosphorus reductions at week 12 were -0.71 mmol/L with PA21 and -0.79 mmol/L with sevelamer, demonstrating non-inferiority of, on average, three tablets of PA21 versus eight of sevelamer. Efficacy was maintained to week 24. Non-adherence was 15.1% (PA21) versus 21.3% (sevelamer). The percentage of patients that reported at least one treatment-emergent adverse event was 83.2% with PA21 and 76.1% with sevelamer. A higher proportion of patients withdrew owing to treatment-emergent adverse events with PA21 (15.7%) versus sevelamer (6.6%). Mild, transient diarrhea, discolored feces and hyperphosphatemia were more frequent with PA21; nausea and constipation were more frequent with sevelamer. After 24 weeks, 99 hemodialysis patients on PA21 were re-randomized into a 3-week superiority analysis of PA21 maintenance dose in 50 patients versus low dose [250 mg per day (ineffective control)] in 49 patients. The PA21 maintenance dose was superior to the low dose in maintaining serum phosphorus control. Thus, PA21 was effective in lowering serum phosphorus in dialysis patients, with similar efficacy to sevelamer carbonate, a lower pill burden and better adherence [32].

CKD patients often have multiple comorbidities that may necessitate the daily use of several types of medication. Therefore, the potential pharmacokinetic drug-drug interactions between sucroferric oxyhydroxide and selected drugs commonly taken by dialysis patients were investigated. Five Phase I, single-center, open-label, randomized, three-period crossover studies in healthy volunteers investigated the effect of a single dose of sucroferric oxyhydroxide 1 g (based on iron content) on the pharmacokinetics of losartan 100 mg, furosemide 40 mg, omeprazole 40 mg, digoxin 0.5 mg and warfarin 10 mg. Pharmacokinetic parameters [including area under the plasma concentration-time curve (AUC) from time 0 extrapolated to infinite time ($AUC_{0-\infty}$) and from 0 to 24 h (AUC_{0-24})] for these drugs were determined: alone in the presence of food; with sucroferric oxyhydroxide in the presence of food; 2 h after food and sucroferric oxyhydroxide administration. Systemic exposure based on $AUC_{0-\infty}$ for all drugs, and AUC_{0-24} for all drugs except omeprazole (for which AUC_{0-8} h was measured), was unaffected to a clinically significant extent by the presence of sucroferric

oxyhydroxide, irrespective of whether sucroferric oxyhydroxide was administered with the drug or 2 h earlier. There is a low risk of drug–drug interactions between sucroferric oxyhydroxide and losartan, furosemide, digoxin and warfarin. There is also a low risk of drug–drug interaction with omeprazole (based on $AUC_{0-\infty}$ values). Therefore, sucroferric oxyhydroxide may be administered concomitantly without the need to adjust the dosage regimens of these drugs [36].

Finally, it should be noted that the use of Velphoro in diabetic patients, in particular in those treated by peritoneal dialysis, could interfere with capillary glucose tests and induce false results, since some of the saccharides contents of Velphoro could be metabolized to glucose, fructose and maltose.

Conclusion

Both ferric citrate and Sucroferric oxyhydroxide are effective phosphate binders, non-inferior to currently used phosphate binders. Ferric citrate may be more suited for the treatment of chronic hyperphosphatemia in CKD patients requiring iron supplements but its use may have been hampered by potential aluminum absorption. Sucroferric oxyhydroxide may be more suited for hyperphosphatemic CKD patients not requiring iron supplementation and its major benefit would be a low pill burden.

Conflict of interest statement. None declared.

References

1. Cozzolino M, Ureña-Torres P, Vervloet MG et al. On Behalf of the CKD-MBD Working Group of ERA-EDTA. Is chronic kidney disease-mineral bone disorder (CKD-MBD) really a syndrome? *Nephrol Dial Transplant* 2014; 29: 1815–1820
2. 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
3. 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
4. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease. *Am J Kidney Dis* 2003; 42(suppl): S1–S201
5. Kidney disease improving global outcomes (KDIGO) CKD-MBD work group. KDIGO clinical guidelines for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease mineral and bone disorder (CKD-MBD). *Kidney Int* 2009; 113: S1–S130
6. Jamal SA, Vandermeer B, Raggi P et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet* 2013; 382: 1268–1277
7. Zhang C, Wen J, Li Z et al. Efficacy and safety of lanthanum carbonate on chronic kidney disease-mineral and bone disorder in dialysis patients: a systematic review. *BMC Nephrol* 2013; 14: 226
8. Lutsey PL, Alonso A, Michos ED et al. Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr* 2014; 100: 756–764
9. Hruby A, O'Donnell CJ, Jacques PF et al. Magnesium intake is inversely associated with coronary artery calcification: the Framingham Heart Study. *JACC Cardiovasc Imaging* 2014; 7: 59–69
10. Ishimura E, Okuno S, Kitatani K et al. Significant association between the presence of peripheral vascular calcification and lower serum magnesium in hemodialysis patients. *Clin Nephrol* 2007; 68: 222–227
11. Chakraborti S, Chakraborti T, Mandal M et al. Protective role of magnesium in cardiovascular diseases: a review. *Mol Cell Biochem* 2002; 238: 163–179
12. Marangon N, Lindholm B, Stenvinkel P. Nonphosphate-binding effects of sevelamer—are they of clinical relevance? *Semin Dial* 2008; 21: 385–389
13. Chiu Y-W, 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. Kendrick J, Cheung AK, Kaufman JS et al. HOST Investigators. FGF-23 Associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol* 2011; 22: 1913–1922
15. Gutierrez OM, Mannstadt M, Isakova T et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008; 359: 584–592
16. Jean G, Terrat JC, Vanel T et al. High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients. *Nephrol Dial Transplant* 2009; 24: 2792–2796
17. Wolf M, Molnar MZ, Amaral AP et al. Elevated fibroblast growth factor 23 is a risk factor for kidney transplant loss and mortality. *J Am Soc Nephrol* 2011; 22: 956–966
18. Gutierrez OM, Januzzi JL, Isakova T et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation* 2009; 119: 2545–2552
19. Faul C, Amaral AP, Oskoui B et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; 121: 4393–4408
20. Deger SM, Erten Y, Pasaoglu OT et al. The effects of iron on FGF23-mediated Ca-P metabolism in CKD patients. *Clin Exp Nephrol* 2013; 17: 416–423
21. Yokoyama K, Hirakata H, Akiba T et al. Effect of oral JTT-751 (ferric citrate) on hyperphosphatemia in hemodialysis patients: results of a randomized, double-blind, placebo-controlled trial. *Am J Nephrol* 2012; 36: 478–487
22. Dwyer JP, Sika M, Schulman G et al. Collaborative Study Group. Dose-response and efficacy of ferric citrate to treat hyperphosphatemia in hemodialysis patients: a short-term randomized trial. *Am J Kidney Dis* 2013; 61: 759–766
23. Yokoyama K, Akiba T, Fukagawa M et al. A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis. *Nephrol Dial Transplant* 2014; 29: 1053–1060
24. Lee CT, Wu IW, Chiang SS et al. Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study. *J Nephrol* 2014 May 20. [Epub ahead of print]
25. Lewis JB, Sika M, Koury MJ et al. For the Collaborative Study Group. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. *J Am Soc Nephrol* 2014 Jul 24. pii: ASN.2014020212. [Epub ahead of print]
26. Iida A, Kemmochi Y, Kakimoto K et al. Ferric citrate hydrate, a new phosphate binder, prevents the complications of secondary hyperparathyroidism and vascular calcification. *Am J Nephrol* 2013; 37: 346–358
27. Sinsakul M, Sika M, Koury M et al. Collaborative Study Group. The safety and tolerability of ferric citrate as a phosphate binder in dialysis patients. *Nephron Clin Pract* 2012; 121: c25–c29
28. Mutell R, Rubin J, Bond T et al. Reduced use of erythropoiesis-stimulating agents and intravenous iron with ferric citrate: a managed care cost-offset model. *Int J Nephrol Renovasc Dis* 2013; 6: 79–87

29. Thomas A, Peterson LE. Reduction of costs for anemia-management drugs associated with the use of ferric citrate. *Int J Nephrol Renovasc Dis* 2014; 7: 191–201
30. Gupta A. Ferric citrate hydrate as a phosphate binder and risk of aluminum toxicity. *Pharmaceuticals (Basel)* 2014; 7: 990–998
31. Wüthrich RP, Chonchol M, Covic A et al. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. *Clin J Am Soc Nephrol* 2013; 8: 280–289
32. 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
33. Phan O, Maillard M, Peregau C et al. PA21, a new iron-based non-calcium phosphate binder, prevents vascular calcification in chronic renal failure rats. *J Pharmacol Exp Ther* 2013; 346: 281–289
34. Wilhelm M, Gaillard S, Rakov V et al. The iron-based phosphate binder PA21 has potent phosphate binding capacity and minimal iron release across a physiological pH range in vitro. *Clin Nephrol* 2014; 81: 251–258
35. Geisser P, Philipp E. PA21: a novel phosphate binder for the treatment of hyperphosphatemia in chronic kidney disease. *Clin Nephrol* 2010; 74: 4–11
36. Chong E, Kalia V, Willsie S et al. Drug-drug interactions between sucroferric oxyhydroxide and losartan, furosemide, omeprazole, digoxin and warfarin in healthy subjects. *J Nephrol* 2014 Apr 4. [Epub ahead of print]

Received for publication: 4.11.14; Accepted in revised form: 10.12.14