New Phosphate Binding Agents: Ferric Compounds

CHEN H. HSU, SANJEEVKUMAR R. PATEL, and ERIC W. YOUNG
Nephrology Division, Department of Internal Medicine, University of Michigan Medical School, VA Medical Center, Ann Arbor, Michigan.

Abstract. Several prior studies suggest that ferric compounds bind dietary phosphate and possess clinical potential as phosphate binding agents. Therefore, this study was conducted to measure the effect of several ferric compounds on intestinal phosphate binding and absorption. Balance studies lasting 2 to 4 wk were performed in normal and azotemic (achieved by subtotal nephrectomy) rats maintained on a 1.02% phosphorus diet supplemented with ferric salts (formulated to 0.95% Fe) or no ferric salt (control). In rats with normal renal function (average creatinine clearance, 4.0 ml/min per kg), the average net intestinal absorption of phosphate over all balance periods was 103.3 mg/d for the control group versus 84.7 mg/d for the ferric citrate group (P < 0.005). In the azotemic rats (average creatinine clearance, 3.5 ml/min per kg), the average net intestinal absorption of phosphate over all balance periods was significantly lower for the three ferric groups than the control groups (P ≤ 0.02): 95.3 mg/d for the control group versus 75.6 mg/d for the ferric ammonium citrate-treated group (P = 0.058), 77.0 mg/d for the ferric citrate-treated group (P = 0.057), and 62.5 mg/d for the ferric chloride-treated group (P < 0.002). Urinary phosphate excretion fell, sometimes to an even greater extent than did intestinal absorption, yielding no net reduction in phosphate balance in these growing, young animals with relatively preserved renal function. Calcium balance was largely unaffected by the ferric compounds. There were trends toward decreased serum phosphorus and parathyroid hormone concentrations and increased iron and hematocrit in the ferric-treated azotemic groups. All tested ferric compounds were well tolerated, but animal growth was stunted in the ferric chloride animals compared with the control group. Phosphate binding was estimated at 85 to 180 mg per gram of elemental iron, which is comparable to other phosphate binding agents. Ferric salts decrease net intestinal phosphate absorption and hold promise for the treatment of phosphate retention in patients with renal failure.

In healthy individuals, phosphate is primarily eliminated by the kidneys, which effectively regulate phosphate balance and the blood phosphate concentration. Phosphate excretion is compromised in patients with renal failure, resulting in systemic phosphate retention and hyperphosphatemia. Phosphate retention is a major toxic complication of renal failure, potentially contributing to soft tissue mineral deposition, progression of renal disease, and secondary hyperparathyroidism (1–5).

Restriction of phosphate intake can potentially prevent hyperparathyroidism and other toxic manifestations of phosphate retention (2–5). However, dietary phosphate restriction alone is often insufficient to control hyperphosphatemia. Consequently, most patients are treated with orally administered aluminum or calcium salts that bind dietary phosphate and facilitate fecal elimination rather than intestinal absorption. Long-term use of aluminum compounds can cause bone and other toxicities; accordingly, calcium salts have become the phosphate binding agents of choice. However, calcium therapy can be complicated by the development of hypercalcemia and net calcium retention, potentially exacerbating soft-tissue mineralization and organ dysfunction (6–10).

The problems associated with aluminum and calcium salts illustrate the need for new phosphate binding agents. Candidate agents must be effective, safe, well tolerated, and relatively inexpensive. Ferric compounds potentially fulfill these criteria. Several human (11,12) and animal (13–16) studies from many years ago strongly indicate that ferric compounds can bind dietary phosphate and dramatically alter phosphate metabolism.

In view of these early reports, we performed studies in normal and azotemic rats designed to explore the efficacy and tolerability of ferric compounds as phosphate binders. Ferric citrate, ferric ammonium citrate, and ferric chloride were investigated. Our primary goal was to determine whether these compounds could bind dietary phosphate. We also examined other aspects of mineral metabolism and animal viability.

Materials and Methods
Phosphate Binding Effect of Ferric Citrate in Normal Rats

Normal male Sprague Dawley rats (n = 6) were fed a standard rat diet containing 1.02% phosphate (P) and 0.95% calcium (Ca) (ICN Biomedicals, Cleveland, OH) for 2 wk. The dietary phosphate content was verified in our laboratory. An additional six normal male rats were fed the same diet supplemented with 4% ferric citrate for 2 wk. All animals were housed in individual metabolic cages with a food container attached to the outside. Powdered food was used to prevent contamination of urine and stool. The animal was able to reach the
food container but unable to bring food into the cage. Body weight, food consumption, urine output, and stool excretion were monitored daily for 4 d per week for 2 wk. The daily stool and urine measurements for each 4-d observation period were pooled and expressed as the average per day. Blood (1.5 ml) was taken from the tail vein of nonfasted rats in the morning (8 a.m. to 10 a.m.) each week for measurement of plasma phosphorus and creatinine. At the end of the study, blood was obtained from the aorta of anesthetized animals (also from 8 a.m. to 10 a.m.) for measurement of parathyroid hormone (PTH), calcitriol, and iron concentrations.

**Phosphate Binding Effect of Ferric Compounds in Rats with Renal Failure**

The phosphate binding effect of ferric compounds was also studied in Sprague Dawley rats with renal failure, achieved by subtotal nephrectomy. Two-thirds of one kidney was surgically removed by arterial ligation, and the other kidney was removed through a flank incision 3 d later. The control group was fed the standard powdered rat diet containing 1.02% phosphate and 0.95% calcium. The other three groups of animals were fed the standard diet supplemented with one of the following ferric compounds (Sigma Chemical Co., St. Louis, MO): 5% ferric ammonium citrate (molecular weight approximately 325 to 330 kD, 16.5 to 18.5% elemental Fe(3+), 4% ferric citrate (FeC_6H_5O_7, 245 kD), or 4.4% ferric chloride (FeCl_3 · 6H_2O, 270 kD). Each ferric-containing diet was formulated to contain approximately 0.95% elemental iron. Body weight, food consumption, urine output, and stool excretion were monitored daily for 4 d per week over the 4-wk study period using the same techniques described for the rats with normal renal function. Daily measurements from each 4-d balance period were averaged for each week of the study. Blood was taken once weekly for measurement of the plasma phosphorus and creatinine. At the end of the study, blood was obtained from the aorta of anesthetized animals (also from 8 a.m. to 10 a.m.) for measurement of parathyroid hormone (PTH), calcitriol, and iron concentrations.

**Analytical Methods**

All phosphate determinations were measured and expressed as phosphorus. Stools were ashed at 800°C in a muffled furnace for 30 min, and phosphorus was extracted with 10% perchloric acid overnight before phosphorus measurement. Phosphorus and creatinine were measured as described previously (17). Plasma calcitriol was measured in duplicate according to the methods of Reinhardt et al. (18) and Hollis (19). The interassay coefficients of variation were 7.0% for the low control (20 pg/ml, n = 12) and 4.1% for the high control (100 pg/ml, n = 12). The intraassay coefficients of variation were 5.4% for the low control (n = 6) and 4.7% for the high control. Calcitriol recovery averaged 65%. PTH was measured by immunoradiometric assay, using a rat PTH assay kit (Nichols Institute, Capistrano, CA). The plasma iron concentration was measured using a commercial assay kit (Sigma Chemical Co.).

**Statistical Analyses**

Data are shown as mean ± 1 SEM. Statistical analyses were performed using repeated measures ANOVA for the rats with normal renal function. Data from the azotemic animals were analyzed using a mixed model to better accommodate repeated measurements, missing data values (see below), and random effects (20).

**Results**

**Phosphate Binding Effect of Ferric Citrate in Normal Rats**

There were no significant differences in body weight, growth rate, urinary creatinine excretion, and creatinine clearance in the two diet groups (control, ferric citrate) over the 2-wk study (Table 1). Fecal phosphate excretion was higher in the ferric citrate group than in the control group with no difference in phosphate intake (data not shown). Consequently, net intestinal absorption of phosphate was lower in the ferric citrate group than in the control group (Figure 1, left panels; P < 0.005 for treatment effect, time effect not significant). Approximately 85 mg of phosphate (measured as phosphorus)

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**Table 1. Average weight, urinary creatinine excretion, and blood measurements in rats with normal renal function**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Ferric Citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>week 1</td>
<td>274 ± 3</td>
<td>280 ± 3</td>
</tr>
<tr>
<td>week 2</td>
<td>313 ± 5</td>
<td>318 ± 4</td>
</tr>
<tr>
<td>Urine creatinine (mg/d)</td>
<td></td>
<td></td>
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<tr>
<td>week 1</td>
<td>8.7 ± 0.4</td>
<td>9.0 ± 0.8</td>
</tr>
<tr>
<td>week 2</td>
<td>10.0 ± 0.6</td>
<td>9.4 ± 0.6</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min per kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>week 1</td>
<td>4.3 ± 0.3</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>week 2</td>
<td>3.9 ± 0.2</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>Blood values (week 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>16 ± 4</td>
<td>16 ± 3</td>
</tr>
<tr>
<td>calcitriol (pg/ml)</td>
<td>84 ± 2</td>
<td>82 ± 2</td>
</tr>
<tr>
<td>iron (µg/µl)</td>
<td>1.8 ± 0.2</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td>hematocrit (%)</td>
<td>49 ± 1</td>
<td>48 ± 1</td>
</tr>
</tbody>
</table>

*Values are given as mean ± 1 SEM. PTH, parathyroid hormone.

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**Figure 1.** Phosphate (left side) and calcium (right side) metabolism in rats with normal renal function. Average measurements shown for the 1- and 2-wk balance periods. Black bars indicate control animals and stippled bars indicate ferric citrate-treated animals.
was bound per gram of elemental iron (Table 2). Urinary phosphate excretion was also lower in the ferric citrate animals compared with control (Figure 1, \( P \# 0.0001 \) for treatment effect). The decline in urinary phosphate excretion exceeded the reduction in intestinal absorption, yielding a mild increase in net phosphate balance in the ferric citrate group (Figure 1, \( P \# 0.001 \) for treatment effect). Serum phosphorous concentration was not different between the two groups (Figure 1).

Calcium metabolism was not significantly different in the two groups except for a slightly lower (\( P < 0.05 \)) urinary calcium excretion in the ferric citrate group (Figure 1, right panels). There were no significant differences in PTH, calcitriol, iron, and hematocrit (Table 1).

**Phosphate Binding Effect of Ferric Compounds in Azotemic Rats**

The creatinine clearance was approximately 23% lower in the 5/6 nephrectomy group (azotemic) compared to the group with normal renal function: 3.3 \( \text{versus} \) 4.3 mg/min per kg at week 1 and 3.3 \( \text{versus} \) 3.8 ml/min per kg at week 2 (Table 1, Figure 1, \( P < 0.0001 \) for overall effect of partial nephrectomy). Compared to the group with normal renal function, the azotemic animals also had higher serum concentrations of PTH (Tables 1 and 3, \( P = 0.06 \)) and phosphorus (Figure 1 and Figure 3, lower panels, \( P \geq 0.0001 \)) and lower levels of calcitriol (Tables 1 and 3, \( P \geq 0.0001 \)) and hematocrit (Tables 1 and 3, \( P \leq 0.0001 \)). Thus, the overall laboratory profile of the partially nephrectomized animals was consistent with mild azotemia.

Among the azotemic group, the ferric ammonium citrate- and ferric citrate-treated animals grew at the same rate as the control animals (Figure 2, top panel). However, the growth rate was slower for the animals treated with the ferric chloride diet compared to the control animals (Figure 2), with no significant difference in food intake (not shown). The average urinary creatinine excretion was also lower in the ferric chloride group relative to the other three groups over the course of the experiment (Figure 2, middle panel). Creatinine clearance was comparable and stable across all four treatments (Figure 2, bottom panel). Two animals, one in the ferric ammonium citrate group and the other in the ferric citrate group, developed an unknown acute illness on day 22 (fourth week) and were sacrificed.

Figure 3 shows phosphate metabolism for the four experimental groups for each of the four weekly balance periods. Fecal phosphate excretion was higher in the three ferric-treated groups than in controls in the face of comparable phosphate intake (data not shown). Consequently, the net intestinal absorption of phosphate was lower in the ferric-treated animals than in the control group throughout the experiment (Figure 3, top panel, \( P \approx 0.02 \) for overall group differences, \( P = 0.058 \) for ferric ammonium citrate \( \text{versus} \) control, \( P = 0.057 \) for ferric citrate \( \text{versus} \) control, \( P < 0.002 \) for ferric chloride \( \text{versus} \) control, no significant time effect). From the differences in phosphate absorption, the estimated binding capacity of the ferric compounds ranged from 88 to 181 mg of phosphate per gram of elemental iron (Table 2). The ferric compounds were also associated with a reduction in urinary phosphate excretion (Figure 3, second panel, \( P \approx 0.0001 \) for overall group effect.
and for individual paired contrasts with control, no significant time effect that exceeded the fall in intestinal absorption, yielding a nonsignificant (P = 0.27) increase in net balance (Figure 3, third panel). The serum phosphorus concentration tended to be lower in the ferric-treated animals than the control group but the effect was not statistically significant (Figure 3, bottom panel).

Figure 4 shows calcium metabolism for the four groups. The week 3 results, showing negative calcium absorption and balance, suggest anomalous measurements. Calcium metabolism was not significantly different among groups except for a slightly higher (P ≤ 0.0001) urinary calcium excretion in the ferric-treated groups.

Among the azotemic animals, there was a nonsignificant trend toward lower PTH concentrations in the ferric-treated groups compared to the control animals (Table 3). There were no significant group differences in the serum calcitriol concentration. The plasma concentration of iron was higher in the ferric-treated animals than in controls, significantly so for the ferric citrate group. All three ferric-treated groups had a higher average hematocrit level than the control group, suggesting some degree of intestinal iron absorption (Table 3).

Discussion

Phosphate retention is a common problem in patients with renal failure. In the early stages of renal disease, the plasma phosphorous concentration is usually maintained in the normal range, presumably due to hyperparathyroidism, which stimulates urinary phosphate excretion. However, the plasma phosphate concentration may not accurately reflect total body phosphate content (21), and these patients are still prone to net phosphate retention. Overt hyperphosphatemia often develops when the GFR falls below approximately 20 ml/min. For end-stage renal disease patients, the estimated phosphate absorption is 4200 mg/wk (assuming dietary intake of 1000 mg/d and a fractional absorption of 60%) (22), and the average phosphate removal by hemodialysis is 3171 mg/wk (23). Thus, in the absence of treatment with binders, phosphate accumulates in the body at a rate of approximately 150 mg/d. Phosphate retention may be exacerbated in patients who are treated with calcitriol (22). In many patients with renal failure, phosphate retention cannot be controlled with dietary phosphate restriction or dialysis (23), necessitating the use of phosphate binding agents.

Calcium compounds have been preferentially used to limit phosphate absorption. However, most patients with end-stage renal disease are in positive calcium balance because they lack a reliable route of calcium excretion (10). The use of calcium salts as phosphate binders further disposes patients to hypercalcemia and, in association with phosphate retention, potentially contributes to soft tissue mineralization and organ dysfunction. The problems associated with calcium and aluminum compounds highlight the pressing need for alternative phosphate binding agents for treatment of patients with renal failure.

Ferric compounds possess heretofore under-appreciated promise as phosphate binding agents. In 1941, Liu et al. reported that ferric ammonium citrate caused hypophosphatemia in the one patient who received the drug (11). Subsequently, Liu and Chu used ferric ammonium citrate (6 to 12 g/d) to successfully control hyperphosphatemia in two patients with chronic renal failure (12). The iron compound was well tolerated except for occasional diarrhea. Animal experiments also suggested that ferric salts, such as aluminum, can profoundly affect phosphate metabolism. Ferric salts were found to dramatically reduce bone ash, plasma phosphate, urinary phosphate excretion, and bone phosphorus in guinea pigs and rabbits (13). Ferric compounds also induced phosphate depletion in growing rats as manifest by growth retardation, hypophosphatemia, decreased bone ash, decreased total body calcium, and decreased total body phosphorus (14,15). Ferric salts also produced severe rickets and hypophosphatemia in chicks after 3 wk of treatment (16). In the current study, we sought to extend these prior observations by directly measuring the effect of ferric compounds on intestinal phosphate absorption in normal and azotemic animals.

We found that ferric compounds effectively bound dietary phosphate, as evidenced by a decrease in urinary calcium excretion and an increase in net balance (Figure 3, third panel). The serum phosphorus concentration tended to be lower in the ferric-treated animals than the control group but the effect was not statistically significant (Figure 3, bottom panel).

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phosphate and decreased intestinal phosphate absorption in both normal and azotemic rats (Figures 1 and 3). There was also a commensurate decrease in urinary phosphate excretion, presumably as an adaptive response to the diversion of dietary phosphate to the stool in these young growing rats. The ferric compounds did not decrease phosphate balance because the decline in urinary excretion exceeded the decline in net intestinal absorption. The failure to reduce net phosphate balance probably reflects the fact that the rats were in a rapid growth phase and the degree of renal dysfunction in the azotemic animals was mild. Animals with more advanced renal failure would probably be less able to maintain phosphate balance by altering renal excretion. The study achieved its central objective of demonstrating that ferric compounds can bind dietary phosphate and reduce intestinal absorption, consistent with earlier reports. PTH levels, which were elevated in the azotemic animals, also tended to decrease in the ferric-treated groups. In addition, there was evidence for increased iron absorption and a corresponding increment in hematocrit among the animals treated with ferric compounds. Thus, ferric compounds could potentially ameliorate several problems of renal failure including phosphate retention, iron deficiency, and anemia. The ferric compounds had little direct effect on calcium balance (Figures 1 and 4).

In general, the ferric compounds used in this study appeared to be well tolerated. Food intake was comparable in all groups of animals. Body weight, growth, and urinary creatinine excretion (partly a marker of muscle mass) were similar among the control, ferric citrate, and ferric ammonium citrate groups (Figure 2). However, growth and creatinine excretion were lower in the animals treated with ferric chloride. Two azotemic animals treated with different ferric compounds became ill during the fourth week of the study, but a connection with the treatment seems doubtful.

Although our study has demonstrated that ferric compounds can effectively bind dietary phosphate, long-term safety has not been fully addressed. Toxicity in humans has been observed in association with ingestion of large quantities of iron, particularly in children (24,25). Acute iron poisoning is usually associated with blood iron concentrations above 5 μg/ml (26), much higher than the levels seen in this study (Table 3). The manifestations of iron toxicity, as reported in patients and experimental models, can include gastrointestinal hemorrhage, hepatic injury, coagulation defects, metabolic acidosis, shock, bone deposition, hemosiderosis, hypoparathyroidism, nephrotoxicity, and depressed myocardial contractility (27–31). For ferric ammonium citrate, the LD_{50} was 1.75 g/kg for guinea

Figure 3. Phosphate metabolism in azotemic animals for balance studies at each of 4 wk. Treatment groups: control, black; ferric ammonium citrate, wavy; ferric citrate, stippled; ferric chloride, cross-hatched.

Figure 4. Calcium metabolism in azotemic animals for balance studies at each of 4 wk. Treatment groups: control, black; ferric ammonium citrate, wavy; ferric citrate, stippled; ferric chloride, cross-hatched.
patients with renal failure. However, the iron was administered in the fasting state by gastric lavage, which would increase iron absorption and the risk of intestinal hemorrhage (33,34). In addition to possible direct iron toxicities noted above, ferric citrate could theoretically enhance the absorption of dietary aluminum. Although the possibility of iron toxicity must be further considered, it is reassuring to note that the widespread use of oral iron compounds for the treatment of iron deficiency in renal patients has not been associated with serious problems to date.

Of the compounds used in this study, ferric chloride was the most potent phosphate binder (Table 2), but it depressed the growth rate of these young animals (Figure 2). Ferric ammonium citrate was also effective in this study and in an earlier report involving two patients with renal failure (12), but the ammonium could exacerbate metabolic acidosis and present problems in patients with abnormal liver function. Ferric citrate demonstrated none of these real or theoretical problems and also demonstrated efficacy as a phosphate binder.

The dose of ferric compounds used in the present animal experiments was equivalent to approximately 240 g/d for a 70-kg adult person. Many factors determine the efficacy of phosphate binding agents, including the compound solubility, gastrointestinal motility, food mixing characteristics, and pH of the gastrointestinal tract (35). Nonetheless, ferric compounds appear to compare favorably with current phosphate binding agents. The ferric compounds bound 80 to 180 mg of phosphate per gram of elemental iron (Table 2) compared to 180 mg of phosphate per gram of aluminum, 40 mg of phosphate per gram of elemental calcium as CaCO₃, and 100 mg of phosphate per gram of elemental calcium as calcium acetate (35,36). Ferric citrate is odorless and nearly tasteless and offers other potential benefits. The absorbed citrate is converted to bicarbonate, which could ameliorate the metabolic acidosis of renal failure. Furthermore, it appears that the absorbed iron could treat the iron deficiency that frequently occurs in erythropoietin-treated renal patients (Table 2). Ferric compounds merit further investigation as phosphate binding agents for patients with renal failure.

References

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