Phosphate binders on iron basis: A new perspective?

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Phosphate binders on iron basis: A new perspective? Uremic patients on maintenance hemodialysis are in positive phosphate balance. This is mainly the result of the complex elimination kinetics of phosphate during dialysis. Removal of phosphate is less than net dietary intake. Classical phosphate binders such as calcium carbonate, calcium acetate, and aluminum-based compounds are limited by side effects (hypercalcemia) and outright toxicity (aluminum). There have been numerous recent attempts to develop alternative phosphate binders, e.g., polyallylamine-hydrochloride (Renagel), lanthanum carbonate, and trivalent iron-containing compounds. The latter is based on old observations that iron salts may cause hyperphosphatemia and rickets in experimental animals and in patients. This idea has recently been taken up again, and effective inhibition of net intestinal phosphate uptake in non-uremic and uremic rats has been shown using simple iron salts (citrate, chloride, ammonium citrate) and complex compounds (cross-linked dextran and stabilized polynuclear iron hydroxide). In uremic rats, the latter compound reduces urinary phosphate excretion as an indicator of reduced intestinal phosphate uptake and has also been shown to be effective in subjects with preterminal renal failure. So far, no side effects or short-term toxicity has been observed. The compound appears promising and deserves further evaluation.

Hyperphosphatemia continues to be a challenge for the clinical nephrologist. Control of serum phosphate concentration is a central strategy in the treatment of secondary hyperparathyroidism, but it is also important in view of recently recognized cardiovascular hazards of hyperphosphatemia [1].

The mass balance of phosphorus (P) is precarious in the uremic patient on dialysis treatment. A normal Western diet contains approximately 800–1500 mg of P per day [2], of which 50–70% are absorbed in the intestine. It is still uncertain whether the net P intestinal absorption is less in the uremic patient compared to controls [3], but if some intestinal malabsorption of P exists, it does not have a major impact on prevention. According to Hou et al. [4], during a 4-hour hemodialysis session using 1.0 m² cellulose acetate hollow fiber dialyzers, approximately 33 mmol P are removed, so that with thrice weekly dialysis approximately 100 mmol per week are eliminated. This amount is considerably less than the cumulative net weekly adsorption of P in the anuric patient [5], so there is a clear need to prevent intestinal absorption of P so as to achieve neutral P balance.

ELIMINATION KINETICS OF PHOSPHORUS DURING DIALYSIS

Although as a first approximation the elimination of urea follows first-order reaction consistent with uniform distribution in a single compartment, elimination kinetics of P are more complex. Hou et al. [4] as well as previous investigators [6, 7] found a rapid initial decrease of serum P concentration during a dialysis session; as soon as the normal range of serum P concentration was reached, however, the serum P concentration tended to remain constant independent of blood flow [7]. The major proportion of P was eliminated during the first hour. Conversely, upon termination of hemodialysis, a rapid rebound occurred, and within 12 hr approximately 80% of predialysis serum P values were reached [6, 7]. The explanation is that P is sequestered in deep compartments; the transfer rate constants from the intracellular into the extracellular space are small, so that the rate of P exit from intracellular space can no longer keep pace with the rate of removal through dialysis and becomes rate-limiting. That redistribution of P is indeed the bottleneck of P elimination has been nicely illustrated by recent observations [8] showing that more frequent long dialysis sessions, i.e., 6 instead of 3 times per week, permit elimination of substantial amounts of P, so that, paradoxically, even addition of P to the dialysate is necessary in some patients to prevent P depletion [9].

Classical phosphate binders

Very early on, this dilemma forced clinical nephrologists to use phosphate binders in order to sequester P in the intestinal tract and to reduce entry of P into the extracellular fluid space. Historically, calcium carbonate and subsequently calcium acetate had been used most frequently. They are undoubtedly effective, but more recently, with more successful management of hyper-

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parathyroidism and a tendency for PTH (and in parallel bone turnover) to be lower, the risk of hypercalcemia on oral calcium-containing phosphate binders has increased [10]. Although reducing the dialysate calcium concentrations diminishes the risk of hypercalcemia, Argiles et al. [11] showed that, in the long run, dialysate calcium concentrations below 6 mg/dl (1.5 mM) are not safe: they may cause stimulation of the parathyroid gland and loss of bone mineral, particularly if patients are noncompliant with the intake of calcium-containing phosphate binders, so that the calcium balance becomes negative.

Aluminum-containing phosphate binders expose the uremic patient to the hazard of aluminum intoxication [12]. In an ideal world, aluminum-containing phosphate binders should be avoided completely, but, unfortunately, one is often forced to use some when the use of calcium-containing P binders leads to hypercalcemia [10].

**Novel phosphate binders**

The dilemma of side effects (hypercalcemia with calcium-containing P binders) or toxicity (aluminum-containing P binders) led to efforts to develop alternative P binders. One compound, polyaclylamine-hydrochloride (Renagel®) has been intensively investigated in experimental and clinical [13–15] studies. This class of compounds was originally developed to lower plasma lipids, and this effect is still seen with Renagel as well. Polyaclylamine-hydrochloride was shown to lower predialytic plasma P concentrations from 2.93 mM to 2.13 mM in a short-term study, and similar effectiveness was also noted in long-term studies at a maximum daily dose of 5.5 g. It is apparently somewhat difficult to lower P levels, as desired, in the mid-normal range, at least when this P binder is used as monotherapy.

Another approach is the development of lanthanum-based compounds. Lanthanum-chloride-hydrate was studied in animal experiments [16], and little tissue uptake and toxicity was noted. A clinical study using lanthanum carbonate is currently underway, but the results are not available.

A third line of products concerns trivalent iron salts. The available information on this interesting group of compounds will be discussed below.

**Fe-III based phosphate binders**

Several anecdotal clinical observations [17, 18] document that ferric compounds bind dietary phosphate and lower serum phosphate when given orally and even intravenously [19]. Iron salts have been shown to reduce bone ash in Guinea pigs [20], to retard growth and induce phosphate depletion in rats [21, 22], and to cause phosphate-deficiency rickets in chicken [23] as well as in swine [24].

This line of observation lay dormant for a long time, but recently has been independently taken up by several groups of investigators. Spengler et al. [25] studied cross-linked iron dextran, i.e., iron (III)oxide-hydroxide-modified dextran [26], as an oral phosphate binder in the rat. This was based on phosphate-binding studies in aqueous solutions and whole blood [27], which had shown remarkable P binding efficacy. Binding was pH-dependent and maximal at pH 2–3, but when passage of the phosphate binders through the intestine was simulated in vitro by varying the pH over 6 hours, net binding capacity was still substantial and reduced only modestly compared to pH 2. Iron (III)oxide-hydroxide dextran beads were exposed to chick duodenum to assess whether Fe was mobilized from the compound. Enzymatic iron liberation was very limited at best. In vivo studies with rats showed that, while plasma phosphate concentrations remained virtually unchanged when rats were fed with phosphate binder-containing food, the amount of P excreted in the urine was lowered by a factor of 15. It was concluded that 1 g of this P binder will bind approximately 0.65 mM of P. If one extrapolates to a 70 kg human being, approximately 15 g/day of the binder would be necessary. No animal died in the study by Spengler et al. [25], animals grew and toxicity studies, including necropsy after 8 weeks of exposure, failed to reveal any evidence of subacute toxicity. Using an organic ferric compound, Hsu et al. [28], possibly unaware of this preceding study, fed ferric ammonium citrate and ferric chloride to normal and azotemic rats. They were on a 1.02% P diet to which the ferric salts had been added. Urinary P excretion was consistently lowered. Since intake was unchanged, obviously net intestinal absorption had been lowered. The authors calculated that the binding capacity was 88–181 mg of P per g of elemental iron.

Two recent observations point to the potential usefulness of these compounds in humans. We [29] examined 13 patients with stable preterminal renal failure (median serum creatinine 5.4 mg/dl). The patients were hyperphosphatemic (median fasting plasma P 2.2 mM) on stable dietary P intake. After two weeks on no oral P binders, 3 × 2.5 g stabilized polymeric Fe hydroxide was given with meals for 4 weeks—a deliberately suboptimal dose. This dose caused a median decrease of fasting plasma P of 20%. Urinary P excretion was lowered even more, i.e., by 37%. Apart from a certain laxative action and black discoloration of feces, no side effects were noted in this short-term study. Figure 1 shows the individual changes in plasma phosphate and urinary P excretion rate. Of note, no significant changes in serum iron and serum ferritin were noted. In a preliminary study, Chang et al. [30] investigated 32 dialyzed uremic patients who were treated either with conventional phosphate binders (calcium carbonate and/or aluminum-containing compounds) or a non-ionic ferric polymaltose complex (Ferrum® chewable tablet, Hausmann Laboratories, Switzerland) containing 1.78 mmol elemental iron per tablet. After wash-out of the P binders, plasma P was 2.64 and
2.53 mm in the two groups, which subsequently received conventional P binders again or Ferrum tablets, respectively. Ferrum was less effective than conventional P binders. A mean decrease of 0.38 mm P was seen after 8 weeks compared with 0.85 mm in controls, but at least proof of principle is provided by this preliminary observation. There was no significant change in ionized calcium, ferritin, serum iron, or iron saturation.

**SUMMARY**

Various Fe(III) compounds are effective and presumably safe P binders. Further information is required with respect to absorption of iron (which may be a benefit in disguise in the age of erythropoietin treatment) and potential long-term side effects, e.g., binding of drugs, micronutrient binding. Nevertheless toxicity studies in animals are very reassuring. The palatability of these compounds is remarkable (as we noted in self experiments) and there were no complaints when patients received the substance [29]. Further details are currently being assessed in a randomized prospective controlled study in dialyzed patients. A potential advantage of these compounds is the favorable relation between cost and effectiveness.

Whether the combination of P binders and inhibitors of the intestinal Na,P-transporter [31] is a useful strategy will require further studies. Available substances, e.g. Niceritorol [31], are not free of side effects, but it is not excluded that in the future, non-absorbable specific inhibitors with no systemic side effects can be developed.

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No text content available.