Alternative phosphate binders: an update

K. Schaefer

St Joseph-Krankenhaus I, Medical Department II, Baümerplan, Berlin, Germany

Introduction

Treatment of uraemic hyperphosphataemia remains a major challenge to the nephrologist caring for patients with chronic renal insufficiency. Treatment for elevated serum phosphate levels is not only required in dialysis patients, but also in patients with preterminal renal failure. Phosphate retention undoubtedly plays an important role in the genesis of secondary hyperparathyroidism together with the known deficiency of the active vitamin D metabolite 1,25-dihydroxyvitamin D$_3$ (calcitriol). The role of restriction of dietary intake of phosphate is limited, since a low-phosphate diet entails the risk of malnutrition. What is the phosphate balance in renal failure? Intestinal absorption of phosphate is not diminished in renal failure, in contrast to intestinal absorption of calcium. Intestinal uptake of phosphate is approximately 50% of dietary phosphate intake, i.e. about 450–500 mg of phosphate per day are absorbed from the 900–1000 mg of phosphate in the diet. This is true both in healthy individuals and in patients with renal failure [1]. Consequently, in patients with renal failure, intestinal phosphate binders are necessary to prevent intestinal absorption of phosphate, so that phosphate balance is maintained despite reduced renal excretion of the compound. In patients with preterminal renal failure, renal elimination of phosphate is largely a function of residual GFR. In oliguric dialysis patients, the net amount of phosphate eliminated primarily depends on the efficacy of dialysis (i.e. dialysance of phosphate).

An added difficulty in the treatment of hyperphosphataemia of uraemic patients relates to the fact that many patients receive calcitriol to treat or prevent secondary hyperparathyroidism. According to several animal experiments, calcitriol considerably increases active intestinal absorption of phosphate. As a consequence, when uraemic patients are treated with calcitriol, it is plausible to assume that even more than 50% of ingested phosphate is absorbed in the intestine.

Because of the risk of aluminium intoxication, the use of aluminium-containing intestinal phosphate binders should be restricted as much as possible. The main alternative intestinal phosphate binders are calcium salts. Current interest has mainly focused on calcium carbonate and calcium acetate. Table 1 gives a complete list of the phosphate binders for which controlled information is available.

Calcium carbonate

Currently the most widely used intestinal phosphate binder is calcium carbonate, the first phosphate binder that was proposed for the management of hyperphosphataemia in uraemic patients. Twenty-five years ago, Clarkson et al performed balance studies which documented that calcium carbonate reduces the elevated serum phosphate levels of patients with renal failure [2]. This has been confirmed by more recent studies [3]. Unfortunately, however, Clarkson et al and more recently Sheikh et al and Ramirez et al noted that the use of calcium carbonate was complicated by the high intestinal uptake of calcium from this compound [4,5]. In an analysis of 237 uraemic patients, mostly on dialysis, an average of 8.1 ± 4.9 g of calcium carbonate per day was required to lower serum phosphate levels [6]. The proportion of elementary calcium in calcium carbonate is 40%. If one assumes that about 25% of elementary calcium in calcium carbonate will be absorbed in the intestine, the net daily uptake of calcium from food and, if any, from the dialysis fluid. This exposes the patient to the risk of a positive calcium balance and the side-effect of soft-tissue calcification. Such risk is even greater in patients treated with

Table 1. List of alternative phosphate binders

| Calcium acetate         |
| Calcium alginate       |
| Calcium carbonate      |
| Calcium citrate        |
| Calcium gluconate       |
| Calcium ketoglutarate   |
| Calcium ketovaline      |
| Magnesium carbonate    |
| Magnesium hydroxide    |

(Phosphonoformic acid)
calcitriol and the associated tendency to develop hypercalcaemia. In the above study [6] the incidence of hypercalcaemia was 61.6% (146/237) as shown in Figure 1.

In agreement with the study of Sheikh et al [4] our own observations document that calcium carbonate binds phosphate mainly in an acid milieu (pH around 5), while the phosphate binding capacity is clearly reduced in the neutral pH range [4,7]. It is therefore plausible to assume that uraemic patients with deficient gastric acid secretion cannot be successfully treated with calcium carbonate. These patients require compounds that bind phosphate independent of the pH. Calcium carbonate should be taken with meals. This exposes the patient to a further potential hazard; the lowered bioavailability of iron: Prather and Miller [8] showed that calcium carbonate lowered intestinal absorption of iron in rats (Table 2).

Despite these limitations, calcium carbonate still has an important role to play in the management of uraemic patients. It follows from the above, however, that a dose of 2 g of elementary calcium per day should not be exceeded. This is particularly important in patients who are also treated with calcitriol.

**Calcium acetate**

The above shortcomings of calcium carbonate have recently focused attention on calcium acetate. The study of Sheikh et al [4] documented that in-vitro calcium acetate (unlike calcium carbonate) binds phosphate independently of pH. In healthy volunteers, equimolar amounts of calcium acetate bound phosphate more effectively than did calcium carbonate. When they compared doses of calcium acetate and calcium carbonate which were equally effective in reducing intestinal absorption of phosphate, a lower net intestinal uptake of calcium was found with the use of calcium acetate. This finding was confirmed in dialysis patients. For any given amount of elementary calcium, calcium acetate binds twice as much phosphate as does calcium carbonate [9]. In dialysis patients as well, somewhat lower net intestinal uptake of calcium was found with calcium acetate, but the difference was modest in magnitude, i.e. 41 mg calcium [9]. The efficacy of calcium acetate as a phosphate binder has been confirmed by others [10]. The incidence of hypercalcaemia is definitely lower with calcium acetate than with calcium carbonate (Figure 1). Hypercalcaemia was seen in 61.6% of patients treated with calcium carbonate, but only in 15.1% of patients treated with calcium acetate. As one would anticipate from these observations, the average daily dose of elementary calcium required to control sodium phosphate was 1.6 g with calcium acetate compared to 3.2 g with calcium carbonate (Figure 2). While calcium carbonate was shown to diminish intestinal uptake of iron [8], calcium acetate (but not calcium carbonate) was reported to lower intestinal uptake of zinc in dialysis patients [11]. If these observations are confirmed, it will be necessary to investigate whether supplementation with zinc is necessary in patients treated with calcium acetate.

**Comparison of calcium carbonate and calcium acetate**

Analysis of clinical trials in dialysis patients shows that both calcium carbonate and calcium acetate are effective in treating the hyperphosphataemia of renal failure. Figure 3 illustrates the changes of serum calcium in 237 patients on calcium carbonate studied in 11 therapeutic trials. Similar information is available for 252 patients on calcium acetate studied in 10 therapeutic trials [10].

Figure 4 shows the changes in serum phosphate. Both compounds cause a significant decrease in serum phosphate levels, i.e. from a mean of 2.10 mmol/l to 1.78 mmol/l with calcium carbonate and from 2.2 mmol/l to 1.8 mmol/l with calcium acetate (P < 0.01).

Significant differences were found between calcium

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**Table 2. Effect of calcium carbonate on iron availability in rats**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hb (day 0)</th>
<th>Hb (day 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>81 ± 10 g/l</td>
<td>142 ± 16 g/l</td>
</tr>
<tr>
<td>CaCO(_3)-low</td>
<td>79 ± 13 g/l</td>
<td>132 ± 16 g/l</td>
</tr>
<tr>
<td>CaCO(_3)-high</td>
<td>81 ± 9 g/l</td>
<td>109 ± 12 g/l</td>
</tr>
</tbody>
</table>

Modified from [8].

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**Fig. 1.** Incidence of hypercalcaemic episodes in patients taking either calcium carbonate (CaCO\(_3\)) or calcium acetate (CaAc).

**Fig. 2.** Dosage of calcium carbonate and calcium acetate in same patients as in Figure 1.
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• M.

Calcium carbonate
Calcium acetate

Fig. 3. Changes of serum calcium in patients taking either calcium carbonate (n = 237) or calcium acetate (n = 252). (B, begin; E, end.)

Table 3. Necessary dosages of calcium carbonate or calcium acetate to bind a hypothetical amount of phosphorus

<table>
<thead>
<tr>
<th>Daily intake of phosphorus, for example 975 mg.</th>
<th>Absorption = 50% = 487.5 mg Phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g Ca²⁺ as CaCO₃ binds = 43 mg P</td>
<td>1 g Ca²⁺ as CaAc binds = 106 mg P</td>
</tr>
<tr>
<td>To bind 487.5 mg one needs 11.32 Ca²⁺ as CaCO₃</td>
<td>or</td>
</tr>
<tr>
<td>Therefore, in order to bind 487.5 mg P</td>
<td>≈ 28 g CaCO₃ are needed = 56 tablets with 200 mg Ca²⁺</td>
</tr>
<tr>
<td>≈ 18 g CaAc are needed = 16 tablets with 250 mg Ca²⁺</td>
<td></td>
</tr>
</tbody>
</table>

Carbonate and calcium acetate with respect to the incidence of hypercalcaemia and the amount of elementary calcium required to control hyperphosphataemia. In both respects, calcium acetate was more advantageous (Figures 1, 2).

We have commented upon the amount of dietary phosphate that has to be bound in the intestine in order to maintain a neutral phosphate balance in the face of diminished renal excretion of phosphate. This requires daily administration of considerable amounts of calcium acetate and particularly calcium carbonate (Table 3). This illustrates that current treatment modalities leave much to be desired.

Other intestinal phosphate binders

Table 1 lists several other phosphate binders currently in use. Much less controlled information is available on these compounds. Calcium alginate and calcium gluconate have relatively poor phosphate binding capacity so that concomitant treatment with aluminium hydroxide is required. The dose of calcium citrate required to control serum phosphate levels is so high that it entails a considerable risk of hypercalcaemia [3]. Furthermore, citrate significantly augments intestinal absorption of aluminium so that concomitant use of aluminium-containing phosphate binders is strictly contraindicated.

Phosphate binders containing magnesium should not be used in uraemic patients who are not on dialysis because of the risk of uncontrolled hypermagnesaemia. When magnesium-containing phosphate binders are administered to patients on dialysis, magnesium-free dialysis fluid should be chosen. There are data to indicate that magnesium carbonate favourably affects serum phosphate levels. The necessity of changing the composition of the dialysis fluid, however, is a considerable drawback in our view [3].

Calcium ketovaline has an efficacy comparable to that of calcium carbonate or calcium acetate. In contrast to calcium carbonate, calcium ketovaline will bind phosphate in vitro mainly at neutral pH. Our own studies showed that the amount of elementary calcium required to lower phosphate levels effectively with calcium ketovaline is comparable to that required with calcium acetate [7]. The high price of calcium ketovaline is a disincentive to its use despite its efficacy.

Preliminary reports point to the efficacy of calcium ketoglutarate as a phosphate binder [12]. Although the mechanism of phosphate binding has not been fully elucidated, its main effect is presumably that of an intestinal phosphate binder. There have been suggestions that alpha-keto-glutaric acid directly influences PTH secretion, but this has not been confirmed.

A novel approach to lower phosphate concentrations is the use of phosphonoformic acid (PFA). PFA inhibits sodium-dependent phosphate transport in the renal tubules and in intestinal mucosa. Animal experiments also indicate that PFA reduces intestinal phosphate absorption in vivo [13]. The therapeutic potential of PFA in renal patients has not been explored.

Use of calcium-containing phosphate binders in patients on calcitriol therapy

All calcium-containing phosphate binders entail the risk of hypercalcaemia. The risk is even augmented when patients are treated with calcitriol, since calcitriol...
increases the active intestinal transport of calcium. The risk of severe hypercalcaemia exists even in calcitriol-treated dialysis patients not on calcium-containing phosphate binders [14]. We have recently shown that it is possible to reduce the risk of hypercalcaemia in dialysis patients on calcium carbonate or calcium acetate; this can be done by administering calcitriol at night rather than in the morning [15]. In this controlled prospective study we also demonstrated that serum phosphate is less effectively controlled by calcium-containing phosphate binders when calcitriol treatment has led to hypercalcaemia (Table 4). Presumably stimulation of intestinal phosphate uptake by calcitriol is so marked that intestinal phosphate binders become insufficient. In view of these adverse effects of calcitriol, the minimum dose required to suppress the parathyroids should be re-evaluated.

**Adjustment of dialysate calcium**

An attempt has been made to reduce the risk of hypercalcaemia during calcium carbonate therapy by choosing a lower calcium concentration in the dialysate. This approach is not without hazards. Balance studies indicate that the calcium balance becomes negative when the calcium concentration in the dialysate is lower than 1.6 mmol/l [16]. Lowering the calcium concentration in the dialysate is only safe if the patient actually takes the prescribed dose of calcium-containing phosphate binders, because only then can the negative calcium balance incurred during the dialysis session be compensated by the net calcium uptake across the intestine in the interdialytic interval. Low dialysate calcium concentrations also affect cardiovascular functions. Further investigation is required to determine how far dialysate calcium concentrations can be lowered without incurring cardiovascular risks [17,18].

The risk of negative calcium balance is even greater in patients subjected to regular ultrafiltration or chronic haemofiltration with negative fluid balance, i.e. in patients with considerable convective loss of calcium.

Convective loss of calcium is not such a problem in patients on CAPD. Calcium-containing phosphate binders are also necessary in these patients and lowering the calcium concentration in the CAPD fluid may be less problematical in that population [19,20].

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**References**


**Table 4. Serum phosphate levels in patients receiving a concomitant therapy with calcitriol**

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
<th>Night</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b</td>
<td>e</td>
</tr>
<tr>
<td>S-phosphate mmol/l</td>
<td>1.74±0.66</td>
<td>1.41±0.48</td>
</tr>
<tr>
<td>(normoacalcaemic patients)</td>
<td></td>
<td></td>
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<tr>
<td>S-Phosphate mmol/l</td>
<td>1.76±0.36</td>
<td>1.76±0.35</td>
</tr>
<tr>
<td>(hyperacalcaemic patients)</td>
<td></td>
<td></td>
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</tbody>
</table>

(b = begin; e = end).

