Unsatisfactory control of serum phosphate: Why is it so common and what can be done?

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Introduction

The treatment of disturbed calcium and phosphate metabolism in renal failure continues to be a challenge to the clinical nephrologist. According to the EDTA registry, 40% of uraemic patients on haemodialysis or CAPD are given vitamin D preparations [1]. An even higher proportion receives phosphate binders, but serum phosphate continues to be poorly controlled in many. For good reasons, aluminium-containing phosphate binders have been abandoned, but this has left a certain vacuum which has not been filled by calcium-containing phosphate binders to everyone's satisfaction. Since calcium-containing phosphate binders are not the panacea, it is important to exploit all possibilities to reduce elevated serum phosphate concentrations including (i) reduction of dietary intake of phosphate, (ii) optimization of dialysis efficiency and (iii) correction of metabolic acidosis. These points should be carefully examined before the treatment with phosphate binders is initiated. In the following we try to briefly summarize the accepted therapeutic strategies today.

What may contribute to hyperphosphataemia?

Before prescribing phosphate binders it is wise to consider possibilities other than uraemia which may contribute to hyperphosphataemia. Is the patient ingesting food items with high phosphate intake, e.g. milk or dairy products, or food items with phosphate-containing additives, e.g. sausage, melted cheese, certain pastries containing baking powder, or beverages like Coca Cola and condensed milk? It is also useful to point to the difference between phosphorus (best given as mmol) and phosphate (usually given as mg) in food tables; confusion about this distinction has led to grotesque errors in the past. One should aim at a daily ingestion of phosphate well below 1000 mg, but undoubtedly this is difficult to accomplish. It bears saying that medication containing phosphate, e.g. enemas, should be avoided. Roughly half of the dialysis patients receive active vitamin D metabolites [1]. While their action in reducing PTH concentrations is desirable, they tend to increase intestinal uptake of phosphate and thus contribute to hyperphosphataemia; this is a matter of dosage, however, since recent studies documented no significant change in serum phosphate, when reduced doses, i.e. 0.125 µg/day of calcitriol, were administered [2]. In animal experiments, net intestinal absorption of phosphate is increased by thyroxine or concomitant carbohydrate or sodium, but this is of little practical consequence [3].

Before embarking on therapeutic interventions it is wise to make sure that measured serum phosphate concentrations are not spuriously elevated. This may occur when blood is not quickly spun down, since phosphate leaches from erythrocytes; so-called pseudohyperphosphataemia may also result from analytical error in the presence of dysglobulinaemia, hyperlipidaemia, or conditions like AIDS [4]. Before one embarks on administration of high doses of calcium-containing phosphate binders, it is further advisable to check whether efficacy of dialysis is adequate and whether metabolic acidosis is present. Even optimal haemodialysis three times per week does not eliminate all net phosphate absorbed during 1 week, since one haemodialysis session eliminates approximately 500 mg phosphate only. Nevertheless, increasing efficacy of dialysis by (i) choosing dialysers with large surfaces, (ii) prolonging time on dialysis, (iii) increasing blood flow, or (iv) eliminating recirculation go a long way towards improving phosphate balance. Alternative treatment modalities, e.g. chronic haemofiltration or CAPD, are not superior to haemodialysis at least in principle. CAPD permits elimination of approximately 300 mg phosphate per day.

Metabolic acidosis is known to cause translocation of phosphate from the intracellular space into the extracellular space. Administration of sodium bicarbonate i.v. caused a decrease of serum phosphate from 7.3 mg/dl to 6.5 mg/dl in patients with advanced renal

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<th>Table 1. Ten reasons for failure of phosphate control</th>
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<td>1. Pseudohyperphosphataemia (incorrect sample handling; analytical error)</td>
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<td>2. High dietary phosphate (consider phosphate-containing additives in food items)</td>
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<td>3. (High doses of) active vitamin D metabolites</td>
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<td>4. Phosphate-containing drugs (enema, infusion)</td>
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<td>5. Inadequate efficacy of haemodialysis (treatment time; dialysate surface; fistula flow; recirculation)</td>
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<td>6. Advanced osteitis fibrosa (efflux of P from bone independent of intestinal P uptake)</td>
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<td>7. Metabolic acidosis</td>
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<td>8. Patient non-compliance with phosphate binders</td>
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<td>9. Incorrect intake of phosphate-binders (ingestion out of step with meals; in doses not tailored according to phosphate content of meals)</td>
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<td>10. Inefficiency of calcium carbonate because of anacidity (spontaneous or after medication)</td>
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failure and an initial arterial pH of 7.29. The same was found with oral correction of the acidosis [5]. Conversely, induction of metabolic acidosis by provoking renal loss of bicarbonate via administration of acetazolamide caused an increase in serum phosphate from 5.7 mg/dl to 6.6 mg/dl with a concomitant increase in serum-PTH concentration [6]. It is interesting to point to the opposing effects of calcitriol which mitigates metabolic acidosis during administration of acetazolamide, but aggravates hyperphosphataemia [7]. It is also relevant to consider that acidosis may adversely affect PTH secretion, since in animal experiments and cross-sectional studies of uraemic patients a correlation was found between plasma bicarbonate and pH on the one hand and intact PTH levels on the other [8,9].

**Which phosphate binders to choose?**

If all the above has been considered, and if necessary corrected, one has to resort to phosphate binders. Since aluminium-containing phosphate binders should be used only in exceptional circumstances, the question arises whether calcium acetate or calcium carbonate should be chosen. What do we recommend? We see a slight advantage in favour of calcium acetate. The effect of calcium carbonate is pH dependent. Calcium carbonate is less effective or ineffective in the presence of gastric anacidity. In some but not all studies calcium carbonate caused more hypercalcaemia [10]. It is less effective on a molar basis, so that greater amounts (g of substance) of calcium carbonate are required. Against these shortcomings of calcium carbonate stands the fact that acceptance by patients, an important determinant of compliance, is somewhat less with calcium acetate. Calcium-containing phosphate binders are bedevilled by the ever-present risk of soft-tissue calcification secondary to hypercalcaemia and/or positive calcium balance [11]. Another potential side-effect has recently emerged with the demonstration that calcium carbonate reduces intestinal iron absorption and causes negative protein balance [12,13]. Thus it was recently shown that in healthy subjects treated with an increasing amount of calcium carbonate the urinary and fecal excretion of nitrogen increased, thereby causing a negative nitrogen balance. Irrespective of whether one prescribes calcium carbonate or calcium acetate, the patient does require particular monitoring when he or she is simultaneously on vitamin D metabolites. Such metabolites have the dual side-effects of increasing intestinal calcium and phosphate absorption. One strategy to mitigate the risk of hypercalcaemia is to lower dialysate calcium concentration, as discussed elsewhere [14]. This manoeuvre may permit higher doses of oral calcium salts without incurring hypercalcaemia; but there is the threat of negative calcium balance when the patient is non-compliant and does not ingest calcium salts.

Which are the most frequent errors in managing serum phosphate of dialysis patients? It is a sad truth that in 1994 predialytic serum phosphate levels are not in the recommended range in many dialysed patients. In the table we summarize 10 points that should be considered when elevated levels of serum phosphate are encountered. Before blindly increasing the dosage of phosphate binders as a knee-jerk reaction, one should check analytical accuracy, dietary intake, co-medication and efficiency of dialysis (which may be lower than anticipated unless the ‘dose of dialysis’ delivered is monitored); correction of metabolic acidosis acidosis and adjustment, i.e. reduction, of the dose of active vitamin D metabolites may help.

As long as only four interventions are available to lower serum phosphate, i.e. (i) reduction of dietary intake, (ii) correction of metabolic acidosis, (iii) increasing the efficacy of dialysis, and (iv) prescription of calcium-containing phosphate binders, control of serum phosphate will remain difficult and require supervision by careful and critical nephrologists. If control is still suboptimal in 1994, at least today a clearer insight into the mechanisms involved is present, and thus hopefully a better grasp of the problem.

**References**