Editorial Review

Phosphate binders and management of hyperphosphataemia in end-stage renal disease

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Hyperphosphataemia is a known factor contributing to the increased risk of cardiac death both in patients with end-stage renal disease (ESRD) and in those under renal replacement treatment with dialysis [1,2]. In patients with renal disease, in fact, the well-known relationship between hyperphosphataemia, secondary hyperparathyroidism, bone turnover and extra osseous calcifications has recently been followed by the recognition of a major role played by elevated serum phosphate levels in the induction of vascular calcification [3–5], cardiac interstitial fibrosis and arterial thickening [6] which highly increase the risk of cardiac death [1,2]. In response to these findings, the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) Clinical Practice Guidelines for bone metabolism and disease in chronic kidney disease has recently recommended that more stringent levels for controlling serum phosphorus (serum phosphorus levels be maintained between 3.5 and 5.5 mg/dl) and Ca/P product in order to improve patients' quality of life and longevity [7].

The involvement of the so-called ‘bone–coronary axis’ is the basis for the high clinical interest for serum concentration of calcium and phosphate. In particular, the control or reduction of the phosphate level in dialysis patients has become one of the main therapeutic targets in the management of ESRD.

This review focuses on the treatment of hyperphosphataemia in patients with ESRD and in those under renal replacement treatment with dialysis, and discusses in particular conventional phosphate binders and emerging therapies aimed at reducing the incidence of hyperparathyroidism, bone disease and calcification in these patients.

Management of hyperphosphataemia in ESRD patients

Dietary approach to phosphate retention

In advanced renal failure patients, dietary approach to phosphate reduction is an important step in the treatment of hyperphosphataemia. However, dietary restriction cannot considerably reduce the level of phosphate retention. In fact, the minimum amount of protein of 1.2 g/kg body weight/day, recommended to prevent malnutrition [8] makes planning a diet with <1 g of phosphorous impossible [7].

Dialysis

Regular dialysis treatment on a 240 min, three times a week basis is not able to remove all the phosphorous ingested with a diet containing sufficient amount of protein to avoid malnutrition [9]. Indeed, haemodialysis or peritoneal dialysis on a daily basis, such as short-duration, high-flow dialysis and nocturnal dialysis, can effectively manage phosphorous levels in patients with ESRD, but their use is not widely practiced due to excessive cost. Therefore, most patients on a regular dialysis treatment require additional treatment with phosphate binders to decrease dietary phosphorous.

Phosphate-binding agents

The substantial lack of efficacy of the treatment of hyperphosphataemia with only diet and/or dialysis makes it necessary to focus attention on substances capable of removing the excess of phosphate. 95% of renal failure patients in the advanced stage of their disease must be treated with phosphate binders. The purpose of therapy with phosphate
binders in dialysed patients is either to reduce the phosphoremia or to bring it back to normal range; pre-dialysis phosphoremia must be maintained, theoretically, according to the recommendation of the National Kidney Foundation guideline, between 1.13 and 1.78 mmol/l [7].

In the 1970s the compounds containing aluminium in the form of aluminium hydroxide and the gel of aluminium carbonate were the standard treatment for the control of hyperphosphataemia in ESRD patients because of their highly effective phosphate binding effect. However, the absorption of small amounts of aluminium from these compounds and mainly the aluminium absorbed from the dialysis fluid resulted in accumulation of aluminium in the plasma and tissues of these patients, determining a dialysis-related encephalopathy syndrome when aluminium accumulated in the central nervous system [10]. A high level of reducing aluminium was also involved, in ESRD patients, in the pathogenesis of anaemia [11] and osteomalacia [12] due to aluminium effect on bone matrix mineralization and osteoblast activity. Therefore, owing to the high level of toxicity of aluminium particularly in the central nervous system and at bone levels, aluminium-based phosphate binders for chronic therapy are no longer used, reducing its use to the failure of other treatments and for a short time.

In the 1990s, calcium carbonate and calcium acetate replaced aluminium-based salts [13] in clinical practice, notwithstanding the high dose of calcium carbonate required to reduce serum phosphorous (average of 6 g/day) to acceptable levels due to the lower phosphate-binding capacity of these compounds [14]. This leads to another major problem that is related to the high levels of ingested calcium besides low compliance due to the large number of pills required. In fact, coronary artery calcification may develop, and it contributes to the increased risk of morbidity and mortality of ESRD patients [1,2]. In addition, the need for vitamin D supplements for the treatment of hyperparathyroidism, along with the treatment with calcium-based phosphate binders may oversuppress parathyroid hormone and increase calcium absorption, leading to low-turnover bone disease [11], hypercalcaemia and associated risks. Finally, the effect of calcium carbonate is linked with the gastric pH, and this should be taken into account when inhibitors of the protonic pump or related analogues are also administered.

Another calcium-based phosphate binder is calcium acetate [15]. It achieves similar phosphate-binding effects as calcium carbonate at a lower dose of calcium (nearly 50%), and its solubility is independent of the level of average pH, and the incidence of hypercalcaemia is smaller compared with calcium carbonate [15]. Calcium acetate, in fact, has been shown to possess better binding ability than calcium carbonate, owing to a better solubility and consequent smaller calcium absorption that leads to fewer hypercalcaemic events, which are the starting point for a dangerous long-term complication such as vascular calcification.

**Newly developed compounds**

All these problems associated with the treatment with both aluminium- and calcium-based phosphate binders have given rise to a significant clinical need for the development and availability of more effective and better tolerated compounds for the management of hyperphosphataemia, which can overcome the limitation of previous therapies.

**Sevelamer hydrochloride**

The first of these agents is Sevelamer hydrochloride [16]. It is a cationic polymer with a phosphate-binding action with no calcium and aluminium that cannot be absorbed through the intestine [17,18].

Sevelamer hydrochloride has been extensively studied both in pre-clinic phase and in clinical application, and it has been observed that the molecule can effectively reduce phosphate plasma level in ESRD patients under dialysis [19–21]. In addition, in comparison with the traditional therapy with calcium- or aluminium-based phosphate binders, treatment with sevelamer was not followed by hypercalcaemia or aluminium ‘poisoning’ [19–22]. The reduced incidence of hypercalcaemia in patients treated with sevelamer would allow treatment with higher doses of calcitriol for a better control of secondary hyperparathyroidism. Moreover, as an additional benefit, sevelamer has been shown to remarkably reduce the serum level of low-density lipoproteins [21], increase high-density lipoproteins by about 20% and decrease parathyroid hormone [23], while very recently, sevelamer was observed in an animal model to reduce the parathyroid gland weight with a reduction in serum parathyroid hormone levels via regression of cell hypertrophy [24]. Finally, a further beneficial effect of sevelamer has been proven on markers of coronary cell hypertrophy [24]. Finally, a further beneficial effect of sevelamer has been proven on markers of coronary artery and aortic calcification compared with calcium-based phosphate binders [23]. The attenuation of vascular and, in particular, coronary calcifications compared with calcium-based phosphate binders in ESRD patients under dialysis has been studied by electron beam computed tomography [25,26]. However, it must be noted that it is not completely established whether the effect of sevelamer on arterial calcification reflects its role as a phosphate-binder or is the main result of its lipid lowering effect [23]. In any case, sevelamer represents a step forward in the management and treatment of hyperphosphataemia. High doses of sevelamer (3.2–8 g/day) are necessary to bring hyperphosphoremia back to target level [23], and the number of pills per day (about 8 x 800 mg tablets) may certainly be a conditioning factor for the patient’s compliance. Given the high cost of sevelamer compared with the traditional phosphate binders, the association of sevelamer with other binders may be
an interesting solution for the patients in order to reduce the amount of calcium and aluminium, improving patient compliance and reducing the cost of the therapy.

**Lanthanum carbonate**

Recently another substance has raised interest as a phosphate binder: lanthanum carbonate [27]. Lanthanum carbonate is a calcium- and aluminium-free compound that has been shown to possess phosphate-binding activity similar to aluminium, with the advantage of minimal absorption [27,28]. The activity as a phosphate binder of lanthanum carbonate is very specific with an optimal binding that ranges from pH 3 to 5. Its absorption is extremely low with consequentially extremely low retention in tissues [28], and a high amount of ingested lanthanum is eliminated in the faeces (its main route of elimination is biliary) [28]; therefore, it should not be accumulated in tissues of patients with reduced renal function. Patients with ESRD treated with lanthanum carbonate up to 2.5–3.8 g/day for up to 2 years have been reported to obtain effective reduction of serum phosphorous level [29–31]. Long-term clinical studies, however, documented increased serum levels of lanthanum in treated patients [32], and this gave rise to great concern in the issue of long-term safety of lanthanum carbonate. In animal models of chronic kidney disease, oral lanthanum administration led to its increased content in liver, lung and kidney [33,34] and decrease in bone formation rate and osteomalacia [35].

Lanthanum-carbonate-treated patients have, however, also been shown to reach a significantly reduced calcium/phosphate product and parathyroid hormone level compared with the placebo [29]. Hypercalcaemia was not associated with treatment, and adverse effects were comparable with those recorded in the placebo group. In addition, the evolution towards normal of bone histomorphometric parameters was documented in a 12 month bone biopsy study [36,37]. These studies showed improved histomorphometric parameters, no progression towards low-turnover bone disease and no evidence of bone complications associated with aluminium-based phosphate binders [36,37]. Moreover, it has been reported that 11 patients treated with lanthanum carbonate for more than 4 years did not reveal any evidence of aluminium-like toxic effects at bone biopsies [38]. Finally, improvements of bone health and prevention of metastatic calcification in ESRD patients is another advantage obtained with the use of this compound because of its reduced incidence of hypercalcaemia.

Lanthanum carbonate, therefore, is an effective, at least as effective as calcium carbonate, well-tolerated phosphate binder [39,40]. However, despite the very encouraging results, further studies involving larger numbers of patients are needed to definitively establish the long-term safety of lanthanum regarding tissue deposition, as well as its efficacy on vascular calcifications or outcomes in treated patients, which also need to be confirmed in the long term.

**Trivalent iron preparations**

Stabilized polynuclear iron hydroxide is a new compound, which has shown in vitro remarkable phosphate-binding capacity. It is an insoluble polynuclear iron hydroxide, which acts through a formation of an iron–phosphate complex. Although the study of this compound is still in the pre-clinical stage [41], this compound has demonstrated a phosphate binding efficacy comparable with other non-calcium, non-aluminium phosphate binders. However, the long-term safety with respect to iron release and to potential interaction with absorption of micronutrients requires further investigation.

**Conclusions**

Hyperphosphataemia develops in most patients with ESRD. It has been addressed as a factor playing an important role in the increased cardiovascular morbidity of these patients, which remains the major cause of death in ESRD and dialysis patients. Hyperphosphataemia, in fact, in addition to inducing its known hyperparathyroid and osteodystrophic consequences, has been recently associated with soft tissue and vascular calcification, which in ESRD and dialysis patients are strongly associated with increased cardiovascular disease.

Dietary restriction, capable of acceptably reducing the level of phosphate retention, induces malnutrition; therefore the only dietary approach is largely insufficient. Dietary intake of phosphorous recommended to avoid malnutrition in ESRD and dialysis patients, however, exceeds the phosphorous-clearing capacity of intermittent thrice weekly dialysis, making the control or reduction of phosphate level in dialysis patients one of the main therapeutic targets in the management of ESRD. Additional treatment with phosphate binders to decrease phosphorous level is therefore required.

Treatment with phosphate binders has achieved this need. The traditional aluminium- and calcium-based phosphate binders have been used, and calcium-based phosphate binders in particular are still currently used, but treatment with these compounds is not free from complications such as aluminium retention and/or hypercalcaemia. The efforts to search for a non-aluminium and non-calcium phosphate binder has led to the introduction of two compounds, sevelamer hydrochloride and lanthanum carbonate, which, together with other recently developed compounds, the trivalent iron preparations, (still under study), represent without doubt a step forward in the management and treatment of hyperphosphataemia.

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References


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