Managing mineral balance in end-stage renal disease

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Introduction

Calcium and phosphorus exist in a delicate balance in the body, with bone playing a central role in maintaining whole-body calcium–phosphorus homeostasis. The balance of phosphorus and calcium in healthy individuals is maintained through the complex interplay between parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D3 (calcitriol). If serum calcium levels fall, PTH acts to increase renal reabsorption of calcium and bone dissolution, as well as increasing the conversion of vitamin D to calcitriol. Calcitriol increases calcium absorption in the small intestine, and also acts as a negative feedback on the production of PTH.

As renal function declines and ultimately fails, the resulting hyperphosphataemia disrupts the balance between calcium, PTH and calcitriol. Disruptions in this balance lead to important pathology of bone and the cardiovascular system, as discussed by Malluche et al., and Goodman in this Supplement.

Treatment of hyperphosphataemia

Since the 1960s, a variety of agents have been used to actively regulate mineral absorption and secondary hyperparathyroidism associated with hyperphosphataemia in end-stage renal disease (ESRD; Figure 1). The earliest agents were calcium carbonate and aluminium-based phosphate binders, which had been used previously by gastroenterologists for their antacid properties. Aluminium salts are the most effective phosphate-binding agents known, but these compounds are absorbed in the gastrointestinal tract and are eliminated from the body via the kidneys. Thus, in patients with impaired renal function, there is substantial accumulation of aluminium [1,2]. This leads to severe toxic effects on bone [3] and the central nervous system (CNS), including dialysis encephalopathy [4] and an unconfirmed link with Alzheimer’s disease [5].

Due to the toxic effects of aluminium, calcium-based phosphate binders (calcium carbonate and calcium acetate) became the mainstay of treatment for hyperphosphataemia in the 1980s. More recently, it has become clear that the use of calcium salts in patients with ESRD can lead to an increased risk of hypercalcaemia and metastatic calcifications [6], which are, in turn, associated with an increased risk of cardiovascular mortality [7]. Thus, there is a need for non-calcium, non-aluminium phosphate binders.

In recent years, the lipid-binding agent sevelamer hydrochloride has been shown to have moderate phosphate-binding properties. Importantly, the risk of cardiovascular calcification is reduced with sevelamer. However, the potency of sevelamer as a phosphate binder is greatest at pH 7 [8,9], rather than at the acidic pH levels found in the stomach. Moreover, sevelamer is not selective for phosphate ions and will bind other negatively charged ions such as chloride and bicarbonate [8]. Thus, the phosphate-binding capacity of sevelamer is likely to be lower than that of aluminium. In addition, sevelamer has been associated with metabolic acidosis [10] and concerns have been raised that it may also affect the absorption of lipid-soluble vitamins, including vitamin D [11], although this has not been proven.

Optimizing treatment

As research progresses into the pathogenesis of renal osteodystrophy and calcification in ESRD, and clinical management methods continue to evolve, guidelines for renal care require regular updating. For example, the National Kidney Foundation recently published revised guidelines as part of the Kidney Disease Outcomes Quality Initiative (K/DOQI), stating that

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serum phosphorus should be maintained in the range 1.1–1.8 mmol/l (3.5–5.5 mg/dl) and the calcium × phosphorus product maintained below 4.44 mmol²/l² (55 mg²/dl²) [12]. To reach these targets, novel phosphate-binding agents that possess certain essential properties are required:

- Effective phosphate binding
- Low systemic absorption
- Good long-term safety/tolerability
- Non-hypercalcaemic action
- High patient acceptability.

Agents that possess these features should provide distinct therapeutic advantages over currently available treatments. One agent in development that may possess some or all of these properties is lanthanum carbonate.

The lanthanides

The lanthanides are a group of elements that occur widely in nature and are also found in trace amounts biologically. Lanthanide compounds have been used extensively in research as probes to examine the activity of calcium ions in biological systems [13], and ointments based on the lanthanide cerium are used to treat burns [14].

Lanthanum

Lanthanum, which was first characterized by Mosander in 1839, shows the typical properties of a rare earth element and exists in solution as a trivalent cation. Lanthanum is readily found in the environment and is present in drinking water in many areas in ng/ml quantities. As a result, lanthanum is present naturally in healthy individuals and in patients with renal impairment (Shire Pharmaceuticals Ltd, data on file).

Lanthanum carbonate

Lanthanum carbonate has undergone extensive preclinical and clinical evaluation for use as a phosphate-binding agent in dialysis patients. To date, >1700 patients have been treated with lanthanum carbonate, with some patients being treated for up to 3 years. De Broe and D’Haese, and Hutchison present important efficacy and safety data for lanthanum carbonate in this Supplement.

Summary

Patients with renal failure experience disturbances in calcium and phosphorus metabolism, which lead, in turn, to important abnormalities in bone and the cardiovascular system. Over the years, a variety of agents have been used to control phosphorus levels in these patients. Aluminium is the most effective phosphate binder, but is associated with toxic effects in bone and the CNS. Calcium salts are also effective, but recent evidence shows that increased calcium load can lead to metastatic calcification and increased mortality. The non-calcium, non-aluminium phosphate binder sevelamer leads to a reduced incidence of hypercalcaemia, but has some problems of its own [15].

Lanthanides have been used in biological research and medicine for many years, while lanthanum itself is found in the environment and in the bodies of healthy individuals and patients with ESRD. Lanthanum carbonate has undergone extensive preclinical and clinical trials and is a candidate for an agent that meets many of the requirements for an optimal phosphate binder.

References