Improving outcomes in hyperphosphataemia

Marc E. De Broe and Patrick C. D’Haese for the Lanthanum Study Group

Department of Nephrology, University of Antwerp, Antwerp, Belgium

Abstract

Preclinical studies have shown that lanthanum has a very high phosphate-binding capacity at gastrointestinal pH, while clinical trials have shown lanthanum carbonate to be an effective, well-tolerated phosphate binder for the treatment of hyperphosphataemia in patients with end-stage renal disease. Optimization of bone health is an important issue in these patients, and, based on theoretical grounds, there have been concerns that lanthanum will have toxic effects on bone similar to those of aluminium. However, compared with aluminium, absorption of lanthanum is extremely low and lanthanum treatment is not associated with systemic toxicity. In addition, unlike aluminium, elimination of lanthanum is not through the kidney, but mainly takes place via the biliary route and is, therefore, independent of renal function. This implies that patients with chronic renal failure are not at an increased risk for accumulation of the element, compared with patients with normal renal function. In animal studies, no adverse effects on bone were seen in healthy animals receiving lanthanum carbonate. In 5/6th nephrectomized rats, very high doses of lanthanum (1000–2000 mg/kg) affected bone mineralization. This was not due to a direct toxic effect on bone, but was secondary to phosphate depletion induced by lanthanum and, as with any gastro-intestinal phosphate-binding agent, can be reversed with a phosphate-supplemented diet. In a phase III clinical trial, bone biopsies were taken from dialysis patients at baseline and after 1 year of treatment with either lanthanum carbonate (median dose, 1250 mg/day) or calcium carbonate (median dose, 2000 mg/day). Patients treated with lanthanum carbonate for 1 year did not experience any of the aluminium-like toxic effects on bone expressed as either osteomalacia or adynamic bone disease.

Keywords: calcium carbonate; end-stage renal disease; hyperparathyroidism; lanthanum carbonate; low-turnover bone disease; renal osteodystrophy

Introduction

Lanthanum is a naturally occurring rare earth element that was discovered in 1839 by Mosander. It is found in the environment, and can be detected in seawater (0.0034 μg/l) and fresh water (0.20 μg/l) [http://www.webelements.com]. As a trivalent hard acid cation, lanthanum has a high affinity for phosphate and, therefore, has been considered a potential candidate for the therapeutic control of hyperphosphataemia in patients with chronic renal failure, particularly those receiving dialysis. In preclinical studies, lanthanum was shown to have a phosphate-binding capacity of >97% in vitro at pH 3–5 [1]. Clinical trials have shown that lanthanum doses of up to 3000 mg/day are effective in controlling serum phosphorus to within target levels in most patients with end-stage renal disease (ESRD) [2]. Lanthanum carbonate thus offers potential as a non-calcium, non-aluminium phosphate-binding agent for the treatment of hyperphosphataemia.

It is becoming increasingly clear that adequate phosphate control may decrease the risk of soft-tissue calcifications and, as such, may have an important impact on outcomes in ESRD. In the light of past experiences with aluminium hydroxide, known to be associated with serious toxic side effects on the central nervous system and bone [3–5], studies assessing the safety profile of lanthanum are necessary, and a profound knowledge of the element’s metabolism and routes of elimination is required. Experimental and clinical data on these issues are summarized in the present paper.

Lanthanum metabolism

Compared with aluminium, lanthanum accumulates to a much lesser extent in the body of dialysis patients, mainly because of its ultra-low gastrointestinal absorption and route of elimination. Studies have shown that oral doses of lanthanum carbonate are only minimally absorbed from the gut—in dogs, the rate of absorption is 0.00005% [6]—with the majority of an oral dose being excreted in the faeces. Biliary elimination (80%) and direct transport across the gut wall into the lumen.
(13%) represent the main routes of elimination. This implies that the removal of lanthanum is not dependent on renal function – of a lanthanum dose of 3 g/day in healthy volunteers, 0.6–1.0 μg/day (0.00003%) was excreted in the urine [6] – and that patients with renal insufficiency are not at increased risk for accumulation of the element. This is in contrast to orally administered aluminium, 0.06–0.10% of which is absorbed from the gastrointestinal tract [7,8]. Moreover, in contrast to lanthanum, absorbed aluminium is eliminated mainly via the kidney, and biliary excretion is negligible. After receiving 2.4 g/day oral aluminium hydroxide for 3 days, volunteers had urinary aluminium excretion rates of 70–120 μg/day. When calcium citrate was co-administered with aluminium hydroxide, aluminium excretion increased to 350–603 μg/day [8]. Accelerated mass spectrometry showed that cumulative urinary excretion and skeletal deposition were each 0.05% of the total 26 alumminum dose ingested. More than 90% of the total amount excreted was recovered in the urine within the first 48 h.

In long-term clinical studies in which patients were treated with a range of doses of lanthanum carbonate, serum levels of lanthanum reached a dose-dependent plateau after 2–3 weeks of treatment and then remained stable for >2 years of continuous lanthanum treatment (Shire Pharmaceuticals Ltd, data on file). In addition, median brain and cerebrospinal fluid concentrations of lanthanum in dogs given the maximum tolerated intravenous dose of lanthanum chloride (1 mg/kg/day) for 4 weeks were found to be very low (0.035–0.162 μg/g wet tissue, and 0.22–0.85 μg/ml), suggesting that passage of lanthanum through the blood–brain barrier is minimal [6].

**Lanthanum and bone—preclinical studies**

During animal studies with lanthanum carbonate, no adverse histopathology was identified in the bone of animals with normal renal function in any repeat-dose toxicity study. Moreover, both in vivo and in vitro studies indicate that lanthanum carbonate does not exert any adverse effect on osteoblasts or osteoclasts (Shire Pharmaceuticals Ltd, data on file). This is in contrast to aluminium, which has been shown to have a direct toxic effect on osteoblasts [9]. An early toxicity study in the 5/6th nephrectomized rat model indicated that at very high doses (1000–2000 mg/kg), lanthanum was associated with impaired bone mineralization [10] in the presence of normal osteoblast activity [11]. Subsequent studies using the same rat model have shown, however, that the effects of lanthanum on bone (i) mimicked those induced by feeding a low-phosphate diet; (ii) were normalized with phosphate supplementation [12]; and (iii) were similar to those observed in rats treated with sevelamer, an alternative metal-free organic phosphate-binding agent [13]. These data indicate that the effects on mineralization observed in rats receiving high doses of lanthanum are secondary to phosphate depletion, and do not result from a direct toxic action of the element on bone.

**Lanthanum and bone—a phase III clinical study**

Given the toxic effects of aluminium on bone, assessments of the effects of lanthanum have formed an important part of the evaluation of lanthanum carbonate as a phosphate-binding agent. A randomized, comparator-controlled, parallel-group, open-label study was set up to assess the evolution of renal osteodystrophy (ROD) in dialysis patients receiving treatment with lanthanum carbonate or calcium carbonate for 1 year, with particular emphasis on the possible development of the so-called ‘aluminium-related bone diseases’ (i.e. osteomalacia or adynamic bone disease). Other aims of this study were (i) to investigate the efficacy of lanthanum carbonate compared with calcium carbonate for the management of serum phosphorus levels; and (ii) to evaluate the safety and tolerability of treatment with lanthanum for 1 year.

Patients enrolled into the study were starting dialysis, either those who had started dialysis treatment within the 12 weeks before the start of the study, or those who were scheduled to begin dialysis before randomization. The intention-to-treat population consisted of 98 patients from 12 countries who were randomized to receive lanthanum carbonate (up to 3750 mg/day, n = 49) or calcium carbonate (up to 9000 mg/day, n = 49) for 1 year. Treatment was titrated to a dose sufficient to achieve serum phosphorus levels ≤1.8 mmol/l.

After screening, any existing phosphate binder treatment was stopped and double tetracycline labelling was carried out. At 2–6 days after labelling, the first bone biopsy was taken. Patients were then randomized to receive lanthanum carbonate or calcium carbonate. After 12 months of treatment (or at the time of the last visit if treatment had lasted longer than 6 months), double tetracycline labelling was again carried out and a second bone biopsy taken. The bone biopsies were assessed for lanthanum content, and were examined for histological and histodynamic changes. Patients were categorized into the different types of ROD and normal bone as follows:

**Adynamic bone:** bone formation rate (BFR) < 5% of age- and sex-corrected mean, and osteoclast surface (OcS) < 20% of age- and sex-corrected mean.

**Hyperparathyroidism:** BFR more than twice age- and sex-corrected mean, and OcS > 100 times age- and sex-corrected mean.

**Osteomalacia:** mineralization lag time > 100 days, and osteoid volume more than five times age- and sex-corrected mean.

**Normal:** BFR and OcS within 2 SDs of the age- and sex-corrected mean.

**Mixed bone lesion:** all bone biopsies that do not fulfil the criteria listed above.
Serum blood samples were taken at each study visit for routine biochemistry and haematology tests. Blood samples were also assessed for serum lanthanum levels.

Results

Of the 98 patients randomized to treatment, 68 completed the study, with 63 pairs of bone biopsies suitable for histomorphometric analysis. The median doses of lanthanum carbonate and calcium carbonate used in the study were 1250 mg/day (maximum, 3750 mg/day) and 2000 mg/day (maximum, 9000 mg/day), respectively. Both treatments were well tolerated during the 1-year treatment period. Gastrointestinal symptoms were the most common adverse events (lanthanum: 53% vs. calcium: 49%) and were generally mild in severity.

In both groups of patients, serum phosphorus levels decreased during treatment and were well controlled throughout the trial. Serum calcium levels increased in the calcium carbonate group and decreased in the lanthanum carbonate group, with a higher incidence of hypercalcaemia (defined as a serum calcium level >2.65 mmol/l) in the calcium group (49%) than in the lanthanum group (6%). The number of hypercalcaemic episodes reported as adverse events was also greater in the calcium carbonate group (35%) than in the lanthanum carbonate group (6%). These results confirm efficacy and safety data for lanthanum that have been published previously [2].

Parathyroid hormone (PTH) levels remained unchanged in the lanthanum group and decreased in the calcium group. 1,25-Dihydroxyvitamin D₃ levels remained unchanged in both groups, and no differences were seen between the two groups with regard to vitamin D usage.

Serum lanthanum levels were slightly increased from baseline after 1 year of lanthanum carbonate treatment: mean serum levels at 1 year in the highest dose groups ranged from 0.51 to 1.08 mg/l. Serum lanthanum levels were not dose dependent and reached a plateau after 12 weeks of treatment. After 1 year of treatment with lanthanum carbonate, bone lanthanum levels did not exceed 6 mg/g wet weight (median: 1.8 mg/g). In the calcium-treated group, bone lanthanum levels showed a slight increase over the course of the study, with a maximum value of 1.0 mg/g.

At baseline, almost all patients had some form of ROD; two patients in the lanthanum group and no patients in the calcium group had normal bone at baseline. The distribution of the different types of ROD was similar between the two groups, with mixed ROD being the most common type (Figure 1). After 1 year of treatment, lanthanum carbonate was associated with a reduction in each of the more extreme forms of ROD (i.e. hyperparathyroidism, adynamic bone disease and osteomalacia). Calcium carbonate was associated with an increase in the proportion of patients with hyperparathyroidism or adynamic bone disease (Figure 1). Overall, 71% (5/7) of lanthanum carbonate-treated patients with low-turnover bone disease (adynamic bone or osteomalacia) at baseline, and 80% (4/5) of those with baseline hyperparathyroidism evolved towards a normalization in bone turnover, compared with 42% (3/7) and 50% (3/6) of calcium carbonate-treated patients, respectively (Figure 2). Moreover, in the calcium carbonate group, six patients developed adynamic bone disease compared with only one patient from the lanthanum carbonate group. The latter patient had been treated with calcitriol throughout the study period, despite PTH levels below the optimum level for patients with ESRD. Overall, the proportion of patients with adynamic bone disease, osteomalacia or hyperparathyroidism in the lanthanum carbonate group decreased from 36 to 18% after 1 year of treatment, whereas the proportion of patients with these types of ROD increased from 43 to 53% in the calcium carbonate group (Figure 2). No correlations between bone lanthanum content, PTH levels or bone histology were found.

Discussion

Lanthanum carbonate is an effective, well-tolerated, phosphate-binding agent [1] that is minimally absorbed from the gastrointestinal tract. Evidence has been presented showing that doses of lanthanum sufficient to provide control of hyperphosphataemia have no adverse effects on bone after 1 year of treatment. Unlike calcium carbonate, patients receiving dialysis who are treated with lanthanum carbonate show almost no evolution towards low-turnover bone disease over 1 year.

After 1 year of treatment with lanthanum carbonate, serum lanthanum levels rarely exceed 1 mg/l. Compared with the blood compartment, absolute bone lanthanum concentrations may be up to four orders of magnitude higher than this. Indeed, after 1 year of treatment, the

![Fig. 1. Distribution of renal osteodystrophy types at baseline and after 1 year of treatment with lanthanum carbonate or calcium carbonate.](image-url)
The highest bone lanthanum level was 6 μg/g [14], while the highest level ever seen in a dialysis patient was 9 μg/g after 4 years of lanthanum treatment [Shire Pharmaceuticals Ltd; data on file]. Considering a bone calcium level of 120 mg/g, however, one should reasonably not expect a direct physicochemical effect of lanthanum on bone mineralization given the fact that, with the highest bone lanthanum levels encountered in dialysis patients, the molar lanthanum to calcium ratio in bone is as low as $2 \times 10^{-5}$. In other words, lanthanum would be able to replace only 1 calcium atom out of 50,000 in the apatite crystal structure. Even if the total amount of lanthanum were contained in only 1% of the total calcified bone volume, only 1 out of 500 calcium atoms would be replaced by lanthanum. Furthermore, experimental data indicate that lanthanum does not directly affect osteoblast number or activity [11, Shire Pharmaceuticals Ltd; data on file]. Although further studies are needed to exclude a direct effect of lanthanum on bone mineralization and osteoblast function, it is worth noting that aluminium-related bone disease can develop within the first year of treatment with aluminium hydroxide [15], while no such effects were seen with lanthanum carbonate.

An important advantage of lanthanum carbonate, compared with calcium-based phosphate-binding agents, is a lower incidence of hypercalcaemic episodes. Amongst many other factors, disorders of mineral metabolism, principally hyperphosphataemia and hyperparathyroidism, have been associated with coronary artery and other soft-tissue calcification [16]. A direct correlation between either the calcium × phosphorus product [17] or the presence and extent of arterial calcifications [18] and mortality in hemodialysis patients has been shown. Although a direct association of the serum calcium concentration with cardiovascular disease is less evident than that of the phosphorus concentration [19], a direct relationship between the degree of coronary artery calcification and the dose of oral calcium ingested was shown by Goodman et al. (2000) in young adults with ESRD [20]. Recently, an attenuated progression of coronary and aortic calcification has been demonstrated in patients treated with sevelamer, compared with those receiving calcium carbonate [21]. To what extent this may also result in a reduced cardiovascular mortality is much less clear.

Currently, there are no data that allow a simultaneous assessment of metastatic calcification and bone status in patients treated with lanthanum carbonate. In view of the finding that patients consistently showed a marked reduction in the frequency of hypercalcaemia during clinical trials, further studies examining the extent to which lanthanum carbonate offers any benefit on cardiovascular calcification are required.

In conclusion, lanthanum carbonate is an efficient, well-tolerated phosphate binder. Compared with calcium carbonate, treatment with lanthanum carbonate led to a greater evolution away from severe types of ROD. Moreover, there was no evidence for aluminium-like toxic effects on bone after 1 year of lanthanum treatment.
References


