Lanthanum: A Safe Phosphate Binder

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ABSTRACT

Accumulation of inorganic phosphate due to renal functional impairment contributes to the increased cardiovascular mortality observed in dialysis patients. Phosphate plays a causative role in the development of vascular calcification in renal failure; treatment with calcium-based phosphate binders and vitamin D can further increase the $Ca \times PO_4$ product and add to the risk of ectopic mineralization. The new generation of calcium-free phosphate binders, sevelamer and lanthanum, can control hyperphosphatemia without adding to the patients calcium load. In this article, the metabolism of lanthanum carbonate and its effects in bone, liver and brain are discussed. Although lanthanum is a metal cation its effects are not comparable to those of aluminum. Indeed, in clinical studies no toxic effects of lanthanum have been reported after up to four years of follow-up. The bioavailability of lanthanum is extremely low. The effects observed in bone are due to phosphate depletion, with no signs of direct bone toxicity yet observed in rats or humans. The liver is the main route of excretion for lanthanum carbonate, which can be localized in the lysosomes of hepatocytes. No lanthanum could be detected in brain tissue.

Inorganic phosphate plays a role in important cellular functions such as energy storage and signaling, and in bone mineralization. Loss of renal function limits phosphate excretory capacity and causes an increase in serum phosphate level, which together with low ionized calcium levels, contributes to the development of secondary hyperparathyroidism and renal osteodystrophy (ROD). In the long run, these factors cause parathyroid gland hyperplasia and autonomous parathyroid hormone (PTH) production (tertiary hyperparathyroidism) (1,2).

Phosphate accumulation in the body and hyperphosphatemia are associated with an increased mortality risk. In hemodialysis patients, serum phosphate levels greater than 6.5 mg/dl, as well as elevated calcium-phosphate product (greater than 72 mg^2/dl^2) are associated with a significantly increased mortality risk (3). In patients with chronic kidney disease (CKD), there is a linear increase in mortality as serum phosphate rises above 3.5 mg/dl, a level that is still in the normal range (4). Phosphate retention mainly increases cardiovascular mortality, such as death through coronary artery disease and sudden death (5). Physiologic phosphate homeostasis is controlled by a number of phosphaturic factors in addition to PTH, such as FGF-23 and the so-called phosphatonins, while no phosphate retention-inducing factors have been identified so far. Overall, studies indicate that accumulation of phosphate and concomitant hyperphosphatemia form a serious threat to survival in CKD (6).

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The disturbed mineral metabolism that accompanies chronic renal failure contributes to the development of ectopic calcification. Vascular calcification is a prominent feature of cardiovascular disease in uremic patients. In a landmark article, Goodman et al. (7) showed that coronary artery calcification is already present in young hemodialysis patients, shows rapid progression, and is associated with increased serum phosphate and calcium-phosphate product. Vascular calcification in dialysis patients is associated with a higher daily calcium intake from calcium-based phosphate binders (7–9). Hence attempts to control serum PTH levels with calcium-based phosphate binders and vitamin D supplements can further increase the calcium-phosphate product and the risk for ectopic calcification and its associated cardiovascular mortality. In addition to increased calcification of atherosclerotic plaques in the vessel (neo)intima, patients on dialysis also show characteristic calcifications of the vascular media (arteriosclerosis or Mönckeberg sclerosis), which were recently shown to also contribute significantly to the excess cardiovascular mortality observed in uremic patients (8).

In vitro studies have elegantly demonstrated that elevated phosphate and calcium levels are causative players in the cell-mediated process of uremia-related calcification of the vascular tunica media (10). In cultured human aortic smooth muscle cells, a dose-dependent increase in mineral deposition was observed, together with loss of smooth muscle cell differentiation markers and conversion of smooth muscle cells to an osteogenic phenotype, characterized by expression of the osteoblast transcription factor cbfa-1 and the osteoblast protein osteocalcin (11,12). These effects could be inhibited by blocking phosphate entrance into the cell through the sodium/phosphorus cotransporter Pit-1 with phosphonoformic

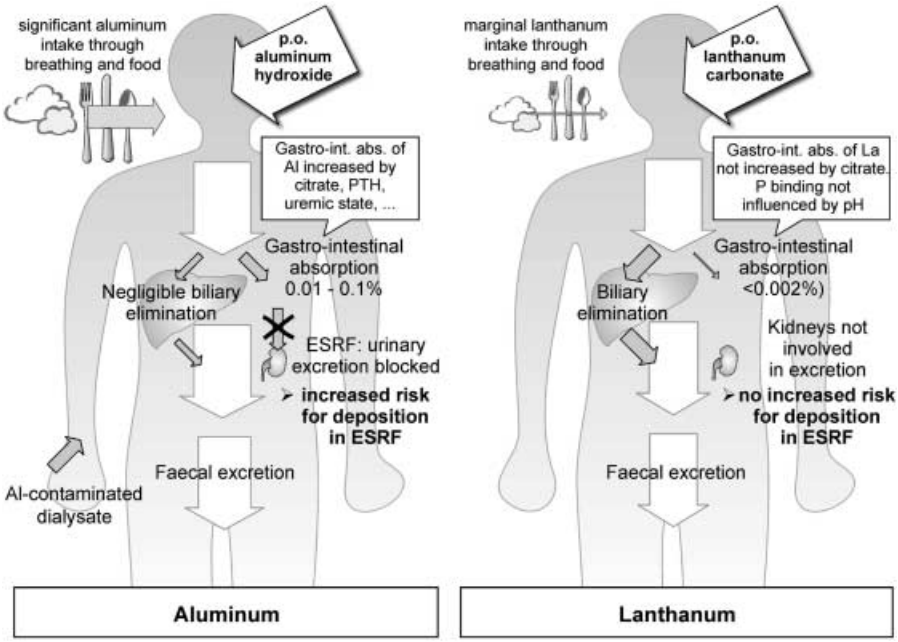

FIG. 1. Metabolism of two trivalent cations: aluminum and lanthanum. In contrast to aluminum, there is no increased deposition of lanthanum in end-stage renal disease compared to patients with normal renal function. Adapted from Behets et al. (23).

acid (11). In epigastric arteries of uremic patients undergoing transplantation, the presence of calcification was associated with expression of cbfa-1 (13), alkaline phosphatase, and the bone matrix proteins osteopontin, bone sialoprotein, and collagen type I (14), confirming the cell biological parallels between vascular calcification and bone formation. Several proteins possessing a high calcium affinity, such as matrix Gla protein, osteoprotegrin, osteopontin, and fetuin, may modulate the ectopic calcification process in the vasculature by their ability to act as natural inhibitors of these calcifications.

The available calcium-free phosphate binders include sevelamer hydrochloride (a nonaluminum, noncalcium-containing hydrogel of cross-linked poly(allylamine hydrochloride) that binds phosphate anions through ionic exchange with chloride) and more recently, lanthanum carbonate. These products can control phosphate levels without inducing calcium overload. In comparison with calcium-based phosphate binder therapy, treatment with sevelamer slowed down the progression of coronary artery and aortic calcification in dialysis patients (15,16). However, apart from its phosphate binding activity, sevelamer also acts as a bile acid sequestrant (17), resulting in lowering of total and low-density lipoprotein (LDL) cholesterol, and can induce acidosis by exchange of bicarbonate with chloride ions (18). These additional effects can also influence the calcification process. However, no studies on the effect of lanthanum carbonate, which is a pure phosphate binder, on vascular calcification in dialysis patients are available yet.

Lanthanum belongs to the group of elements known as the "lanthanides." It is the most electropositive (cationic) element of the rare earth group, is uniformly trivalent, and its binding is almost exclusively ionic. It is a hard "acceptor" with an overwhelming preference for oxygen-containing anions. Therefore the most common biological ligands are the carboxyl and phosphate groups (PO_4^{3-}) with which it can form very tight complexes.

In comparison with aluminum, lanthanum accumulates to a lesser extent in the body of dialysis patients, mainly because of its ultralow gastrointestinal absorption and biliary elimination of the small absorbed fraction (Fig. 1). Studies have shown that the absolute bioavailability of lanthanum in man is less than 0.002%, with the majority of an oral dose being excreted in the feces. Biliary elimination (80%) and direct transport across the gut wall into the lumen (13%) represent the main routes of elimination. Therefore the elimination of lanthanum is not dependent on renal function; of a lanthanum dose of 1 g/day in healthy volunteers, only 0.00003% was excreted in the urine (19), indicating that, compared with individuals with normal renal function, chronic renal insufficiency patients are not at an increased risk for accumulation of the element. This has been confirmed in several phase 1 clinical studies, which have indicated similar plasma exposure and pharmacokinetics of lanthanum in dialysis patients and healthy individuals (19).

This is in contrast to orally administered aluminum, of which 0.01–0.10% is absorbed from the gastrointestinal tract (Fig. 1) (20,21), and which is mainly eliminated via the kidney, biliary excretion being negligible. When calcium citrate was coadministered with aluminum hydroxide (2.4 g/day), aluminum excretion increased from 70–120 mg/day up to 350–603 mg/day (21). Citrate does not influence gastrointestinal absorption of lanthanum.

Lanthanum and Bone

In experimental studies, no effects of lanthanum on bone have been observed in animals with normal renal

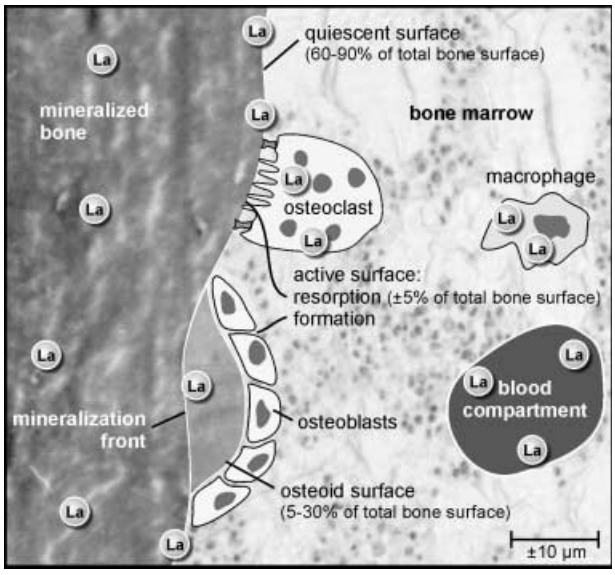

FIG. 2. Using the highly sensitive methodology of X-ray fluorescence, lanthanum was found at several sites in human bone.

function loaded with lanthanum at doses up to 2000 mg/kg/day for 2 years (22). On the other hand, rats with chronic renal failure loaded with doses of 1000–2000 mg/kg/day for 12 weeks showed an impairment of bone mineralization (23). However, several further studies produced evidence that the observed lesions were pharmacologically mediated and resulted from phosphate depletion induced by the administration of high doses of lanthanum carbonate rather than being the consequence of a direct toxic effect of the compound.

Further evidence of the absence of any direct toxicity of lanthanum on bone includes the fact that bone lanthanum concentration does not correlate with the various histomorphometric bone parameters, and the effects of lanthanum on bone mimic those induced by feeding a low-phosphate diet, are normalized with phosphate repletion (24), and are similar to those observed in rats treated with sevelamer (25). Moreover, whereas in dialysis patients with aluminum-related bone disease (expressed either as osteomalacia or adynamic bone) aluminum accumulation was accompanied by a decreased number/activity of osteoblasts (26), such an effect was not seen after lanthanum loading in either rats or humans (27).

Clinical Studies

Studies in animals and humans have shown that lanthanum is deposited in bone and liver. Localization of lanthanum in bone, obtained by means of X-ray fluorescence at the European Synchrotron Radiation Facility, Grenoble, France, showed the element to be present at both active and quiescent sites of bone mineralization, independent of the type of ROD, as well as diffusely distributed throughout the mineralized bone matrix, especially in rats and humans with increased bone turnover (Fig. 2). Lanthanum was also found in cells in close proximity to the resorption lacunae (osteoclasts, macrophages) (28).

As the accumulation of cations in bone goes along with an interaction between the cation of interest and bone calcium, knowledge of the molar bone cation:calcium ratio is of particular interest for a better understanding of its potential to disrupt bone mineral structure. Regarding lanthanum (molecular weight 139), the highest concentration observed in the bone of dialysis patients was 9.5 µg/g (67 nmol/g) wet weight after 4.5 years of treatment with lanthanum carbonate (2.5–3.0 g/day). Considering a bone calcium concentration of 120 mg/g (3 mmol/g) and assuming a homogeneous distribution of lanthanum throughout the bone, the molar bone lanthanum:calcium ratio would be as low as 2×10^{-5}, that is, only 1 out of 50,000 calcium atoms would be replaced by lanthanum. If one assumes lanthanum to accumulate in only 1% of the total bone volume, still only 1 out of 500 calcium ions would be replaced by lanthanum, and any effect on either bone mineral crystal nucleation, crystal growth, or structure would not readily be expected. Applying the same reasoning to aluminum and assuming the total amount of the element (up to 50 µg/g, 1.8 µmol/g) is localized in only 1% of the total bone volume (a reasonable assumption in patients with aluminum-related osteomalacia in which the element is localized at the osteoid-calcification front of the bone), the molar bone aluminum:calcium ratio would be 6×10^{-2}. In other words, 1 out of 16 calcium atoms would be replaced by aluminum, increasing the probability of toxic effects at the level of apatite nucleation, crystal growth, or structure.

A randomized, comparator-controlled, parallel-group, open-label study was set up to assess the evolution of ROD in dialysis patients receiving treatment with lanthanum carbonate versus calcium carbonate for 1 year, with particular emphasis on the possible development of aluminum-like bone diseases, that is, osteomalacia or adynamic bone (29).

Paired bone biopsy specimens were taken in 63 patients at the start and after 12 months of treatment with either lanthanum carbonate ($n = 33$) or calcium carbonate ($n = 30$). The bone biopsies were assessed for lanthanum content, and were examined for histologic and histodynamic changes.

After 1 year of lanthanum carbonate treatment, serum lanthanum levels were slightly increased, although not dose-dependently (mean serum levels ranging from 0.51 to 1.08 ng/ml), and reached a plateau within 12 weeks of treatment. After 1 year of treatment with lanthanum carbonate, bone lanthanum levels did not exceed 5.5 µg/g wet weight (median 1.8 µg/g).

The distribution of the different types of ROD at baseline was comparable between the two groups, with mixed ROD being the most common type. 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. Overall, five out of seven (71%) lanthanum carbonate-treated patients with low-turnover bone disease (adynamic bone or osteomalacia) at baseline, and 80% (four out of five) of those with baseline hyperparathyroidism evolved toward a normalization in bone turnover, compared with three

Parameter	Lanthanum carbonate (n = 682)	Standard therapy (n = 677)	P-value*
1 year			
ALT (U/L)	17.8 ± 12.2	17.3 ± 12.5	
Change from baseline	*−1.3 ± 15.9*	*0.03 ± 13.0*	*0.197*
GGT (U/L)	43.9 ± 81.7	48.6 ± 76.2	
Change from baseline	*−0.5 ± 47.1*	*4.9 ± 44.4*	*0.107*
2 years			
ALT (U/L)	17.0 ± 10.4	15.5 ± 17.6	
Change from baseline	*−2.17 ± 15.1*	*−1.16 ± 11.0*	*0.421*
GGT (U/L)	42.8 ± 84.2	44.6 ± 68.1	
Change from baseline	*−0.6 ± 49.7*	*2.8 ± 43.5*	*0.425*

*from mixed effects model to compare the change from baseline

Normal values: ALT (men): < 30 U/L, women: < 19 U/L; GGT: 0-51 U/L

FIG. 3. Liver enzymes after treatment with lanthanum carbonate or standard therapy (32).

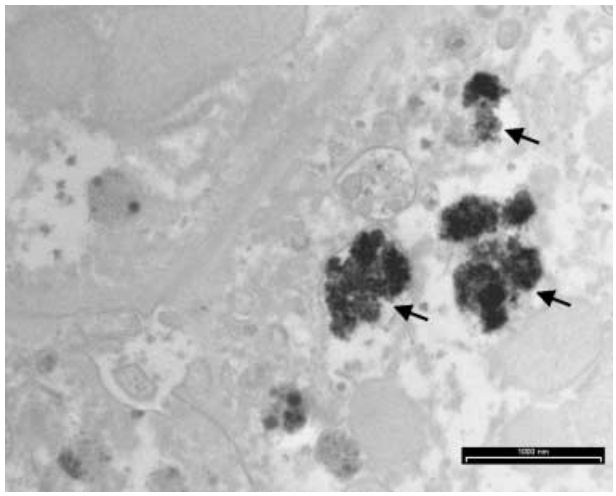

FIG. 4. Lanthanum in a crystalline, granular-like form was found in the lysosomes (black arrows) of the hepatocytes. No lanthanum was detected in other organelles such as mitochondria, nucleus, cytoplasm, or Golgi apparatus. Transmission electron microscopy of the liver tissue of lanthanum loaded rats. Rats were loaded with a very high dose of 0.3 mg/kg/day intravenously over 4 weeks (31).

out of seven (42%) and three out of six (50%) calcium carbonate-treated patients, respectively.

In summary, 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 number of patients with these types of ROD increased from 43% to 53% in the calcium carbonate group. In the lanthanum group, no aluminum-like effects on bone were observed.

Lanthanum and Liver

Since the liver is the main excretory organ of lanthanum, it is not surprising to find some deposition of the element at this site. However, clinical studies with up to 4 years of follow-up have not disclosed any hepatotoxic effect of the drug in patients treated with this phosphate binder (Fig. 3). Twelve weeks of lanthanum loading by oral gavage of 2000 mg/kg/day to rats with moderate renal failure resulted in concentrations of 1.5 μg/g and 3.5 μg/g of lanthanum in bone and liver, respectively. Brain levels remained below the detection limit. Other tissues such as heart, skin, and lung showed no tissue deposition of lanthanum.

In order to identify the localization of lanthanum in the liver, lanthanum chloride was administered by daily intravenous injection to rats with normal renal function at a 0.3 mg/kg dose over 4 weeks. The total liver lanthanum concentrations varied between 30 and 50 μg/g.

Liver fragments of treated as well as untreated animals were fixed in 4% formaldehyde in phosphate buffer and postfixed in reduced osmium tetroxide (OsO_4). After dehydration and embedding in Epon, 100 nm, 500 nm, and 1000 nm sections were prepared. These were examined by conventional imaging in a Zeiss transmission electron microscope (TEM) at 50 kV or a Philips TEM (at 80 kV) either without or after counterstaining with lead citrate, at magnifications varying between 1800× and 85,000×.

For the energy dispersive X-ray (EDX) analytical work, an atmospheric thin window Oxford instrument was connected to a CM20 TEM instrument equipped with a lanthanum hexaboride (LaB_6) single crystal filament operating at 200 kV, 120 kV, or 80 kV. For the electron energy loss spectroscopy (EELS), a postcolumn GIF2000 instrument was used in connection with an Ultratwin CM30 TEM instrument equipped with a field emission gun (FEG) and operating at 300 kV. The combined use of these techniques indicated lanthanum to be present in the lysosomes of the hepatocytes (Fig. 4). No lanthanum was detected in mitochondria, the nucleus, or cytoplasm. Furthermore, most of the lanthanum was found in lysosomes at the biliary pole of the hepatocyte and within the bile canaliculus (30).

Lanthanum and Brain

In a number of experimental studies, lanthanum was determined to be in several regions of the brain after administration of intravenous doses of 30–300 mg/kg/day over 4 weeks and oral gavage of 1500 mg/kg/day. No lanthanum could be detected (less than 6 ng/g).

Conclusion

Lanthanum carbonate is an effective aluminum- and calcium-free phosphate binder. The drug is well tolerated and the reported incidence of gastrointestinal side effects is comparable with reports on calcium-containing phosphate binders.

Available bone biopsy data in dialysis patients treated for up to 4 years with lanthanum carbonate indicate low-level bone deposition, the highest concentration ever measured in any patient being 9.4 μg/g. Ultrastructural

localization indicates a heterogeneous distribution of lanthanum in the bone of rats and man. The low molar lanthanum:calcium ratio is unlikely to cause physicochemical interactions of the metal with hydroxyapatite development and structure. Furthermore, no adverse cell biological effects of lanthanum on osteoblasts have been observed in animals or humans.

The presence of lanthanum in the bile and in the lysosomes of the liver is consistent with excretion of lanthanum by the liver via the transferrin receptor-endosomal-lysosomal-bile canaliculus pathway. Clinical studies of up to 4 years have not disclosed any hepatotoxic effect of the drug in patients treated with this phosphate binder. In summary, these data indicate that the heavily protein bound lanthanum follows a transcellular pathway during its passage through the liver.

No lanthanum could be detected in the brain of rats fed orally or after intravenous administration of high doses of lanthanum over 4 weeks. Further studies unraveling the speciation of lanthanum in biological fluids will contribute to a further understanding of its metabolism and kinetics.

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