

Comparative Effects of Lanthanum Carbonate and Calcium Carbonate on Renal Osteodystrophy in Patients with End-Stage Renal Disease

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Introduction

In patients with chronic renal failure, abnormalities in bone histology known as renal osteodystrophy (ROD) are already observed before dialysis treatment is started (1). Mineral metabolism is of particular importance, since the bone plays a central role in the delicate balance of calcium and phosphorus in the body. Hence, there is a need to control hyperphosphatemia with phosphate binders. Although very effective, aluminum containing compounds accumulate in the body and can lead to the development of low-turnover bone diseases (osteomalacia or adynamic bone), encephalopathy and/or microcytic anemia (2).

Calcium-based binders, particularly when used in combination with vitamin D analogues, may result in over-suppression of PTH and an increased levels of coronary calcification (3). Hence, bone health and vascular calcification may be closely linked in patients with ESRD.

Lanthanum carbonate (LC) is a non-aluminum, non-calcium based phosphate binder. Clinical studies have indicated that the compound is well-tolerated and effectively reduces serum phosphorus levels (4,5). Moreover, the results of a large multi-centre trial by D'Haese *et al.* showed that treatment with LC for 1 year resulted in a tendency towards normalization of bone histomorphometric parameters with no evolution towards low-turnover bone or aluminum-like bone disease (6). Presented here are the results from one centre that participated in a multi-centre trial to assess the effect of LC and calcium carbonate (CC) treatment on the evolution of renal osteodystrophy (ROD) in patients with ESRD.

The aim of this single center analysis bone biopsy based analysis was: (i) to evaluate plasma and bone lanthanum levels after 1-year of LC treatment and during/after a 2-year follow-up period; (ii) to investigate whether bone lanthanum accumulation can be associated with toxicity at the level of bone during and after cessation of lanthanum treatment; (iii) to compare the evolution of renal bone disease during one year of treatment with LC versus CC.

Methods

In an open label, randomized, parallel group study, a cohort of new patients on dialysis was included. The patients were treated with LC for one year (LC-group; n = 10), and received treatment with CC for the next 2 years follow-up

(n = 9). A second group (CC-group; n = 10) received premanently CC treatment. Lanthanum carbonate was titrated up to a maximum dose of 3750 mg elemental lanthanum, and CC to a maximum dose of 9000 mg in order to achieve optimum control of serum phosphorus levels. In all patients tetracycline-labeled transiliac bone biopsies according to the standard practice (7) were obtained at baseline, after 1 year of treatment and the 2 year follow-up period to assess the effects of lanthanum disposition on bone histomorphometry and rate of elimination from bone.

Histological classification of ROD was performed according to the already reported criteria (6). Lanthanum in plasma and bone was regularly measured by means of inductively coupled plasma mass spectrometry (ICP-MS) using methodologies developed and optimized at the Center for Analytical Sciences (CAS) at the University of Sheffield, United Kingdom.

The Ethical Committee of the Medical Faculty, University of Skopje, Macedonia, approved the protocol for the study and written informed consent was obtained from all recruited patients.

Results

At the end of the first year of treatment no significant difference in serum levels of calcium, phosphorous, bone-specific alkaline phosphatase, total alkaline phosphatase, iPTH, 25-(OH)D₃, or 1,25-(OH)₂D₃, compared with baseline levels was reported in either treatment group. However, a comparison of mean serum calcium levels for the first year of treatment showed that the level was higher in the CC group compared with the LC group (2.36 ± 0.28 mmol/L vs. 2.13 ± 0.19 mmol/L; P = 0.02). In addition, the mean serum iPTH level was lower in patients treated with CC (17.6 ± 14.5 pmol/L vs. 41.2 ± 32.6 pmol/L; P = 0.051). At the end of the additional 2-year follow-up period there were no significant differences in biochemical parameters between the two treatment groups.

A mean serum phosphorus level of less than 1.8 mmol/l was achieved during the 1-year trial period. The median dose of elemental lanthanum used was 1250 mg, (range: 750–3000 mg); treatment was well tolerated when taken with meals and no serious adverse events or withdrawals were reported. The median dose of CC used was 2000 mg, (range: 1000–4000 mg). There was significantly higher incidence of hypercalcaemia in CC-treated patients compared with those receiving LC during the study.

Baseline plasma lanthanum levels (<0.03 ng/ml) in patients receiving LC increased to a mean level of 0.69 ± 0.69 ng/ml at week 12 and reached maximum concentration of 1.26 ± 1.24 ng/ml (range, 0.07–3.29 ng/ml) after 24 weeks of treatment. There was a gradual reduction of the plasma lanthanum concentration to the end of treatment to 0.59 ± 0.52 ng/ml, 6 weeks after lanthanum arrest 0.17 ± 0.12 ng/ml and at the end of the 2-year follow-up (0.10 ± 0.02 ng/ml). There was no significant correlation of the lanthanum dose with any of the plasma or bone lanthanum parameters.

The concentration of lanthanum in bone increased in all patients during the trial (Figure 1a). The median bone concentration in LC patients was $2.7 \mu\text{g/g}$ wet weight (range, 0.5–5.5 $\mu\text{g/g}$) and in the CC group was $0.1 \mu\text{g/g}$ (range, 0.05–0.16 $\mu\text{g/g}$). At the end of the follow-up period the median bone lanthanum concentration in the LC group had decreased to $1.4 \mu\text{g/g}$ (range, 0.5–5.6 $\mu\text{g/g}$). In contrast, the mean bone lanthanum level in the CC group at the end of the follow-up period had increased slightly to $0.15 \mu\text{g/g}$ (range: 0.07–0.27 $\mu\text{g/g}$) (Figure 1b).

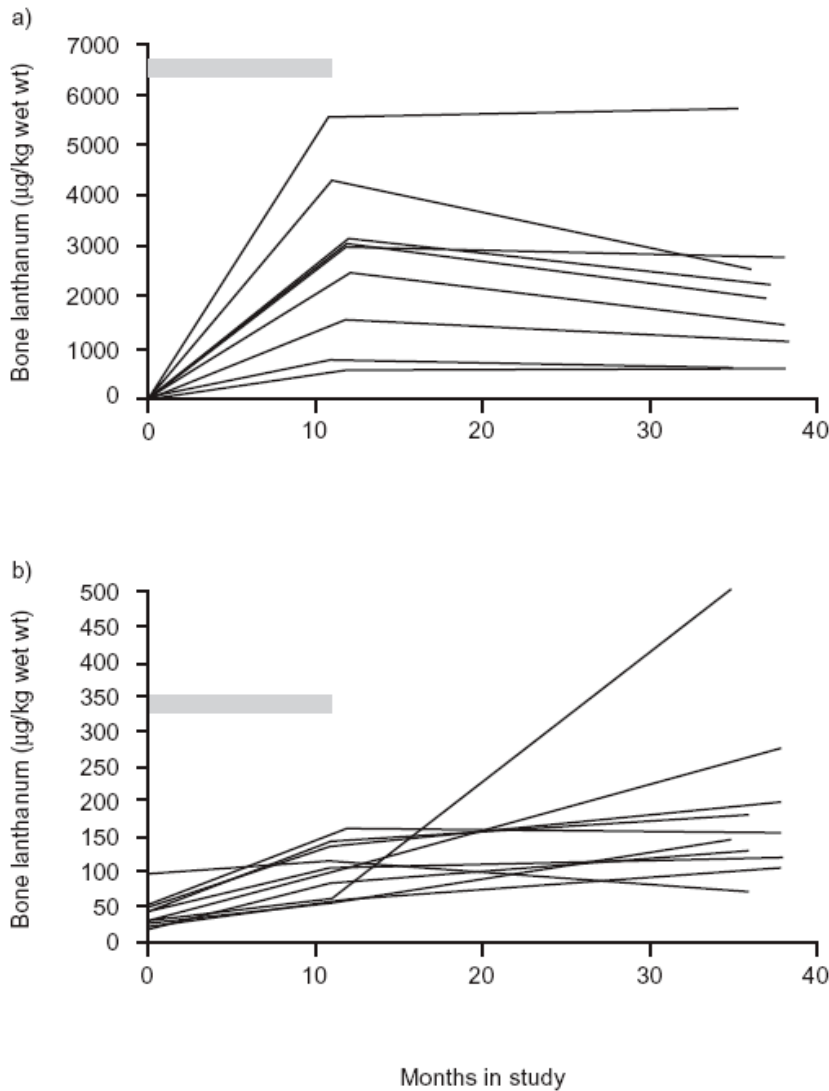


Figure 1. Bone lanthanum concentrations for patients receiving (a) lanthanum carbonate and (b) calcium carbonate treatment for 12 months (the grey bar marks the first year of treatment), followed by 2 years of treatment with calcium carbonate. Each line represents an individual patient. (Please note, graphs (a) and (b) have different scales).

The bone lanthanum content in biopsies from the LC group collected at the end of the 1 year study significantly correlated with plasma lanthanum at 1-year and 2-year

the bone lanthanum content in biopsies taken after the 2 year follow up correlated significantly with plasma lanthanum levels at 1-year ($r = 0.95$; $P < 0.01$).

At baseline, both groups of patients presented a similar distribution pattern of ROD, mixed (Mx) bone disease being the most predominant one. After 1-year of LC-treatment a tendency towards normalisation of bone turnover was seen whilst none of the patients developed low turn-over bone disease expressed as either osteomalacia or adynamic bone (Figure 2). ABD had developed in 30% of the patients in the CC group by the end of the 1-year of treatment and the 2-years follow-up period (Figure 3). The

same evolution was also observed during the 2-year follow-up CC treatment period in the LC-group (22%) (Figure 2). There was no difference between the groups in the number of osteoblasts (osteoblast surface) at baseline biopsy. At 1-year biopsy, an increased number of osteoblast in LC group compared with baseline values and when compared with CC group ($21.23 \pm 15.88\%$ vs. $14.45 \pm 7.92\%$, $P = 0.19$ and $21.23 \pm 15.88\%$ vs. $9.31 \pm 14.82\%$, $P = 0.10$, respectively) was observed.

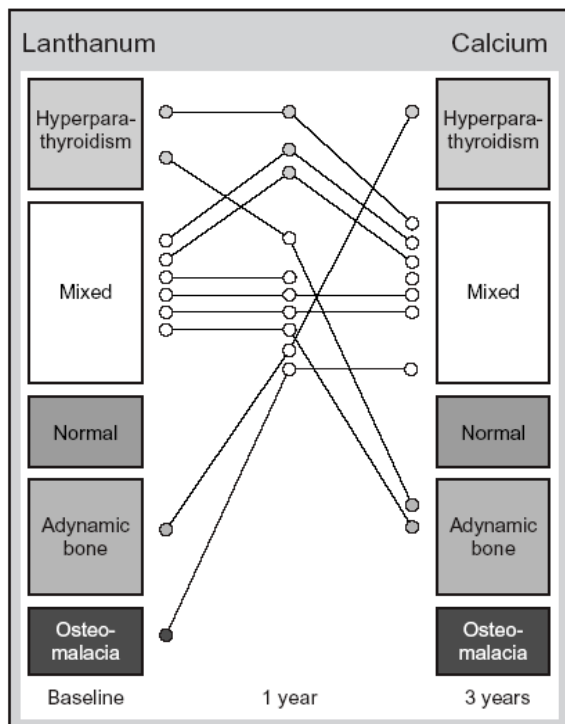


Figure 2. The distribution of various types of ROD diagnosed by histomorphometric assessment of bone biopsies at baseline, after a year of treatment with lanthanum, and after two years of follow up on calcium carbonate.

Discussion

In this study we compared the effects of treatment with LC or CC on the evolution of renal bone disease in dialysis patients. A difference between the two groups was shown at the end of the 1-year study period with no patients in the LC group diagnosed with low-turnover bone disease. However, after the 2 years follow-up on CC, ABD was diagnosed in both groups. Here, the changing pattern of ROD in the LC group should be most probably ascribed to CC treatment, closely resembling the evolution of ROD in the patients being treated with CC during 3 years.

The bone lanthanum concentrations maximally increased to approximately 6 µg/g during lanthanum treatment, but there was no any direct delayed toxicity on bone histomorphometry, as shown by osteoblasts number in LC

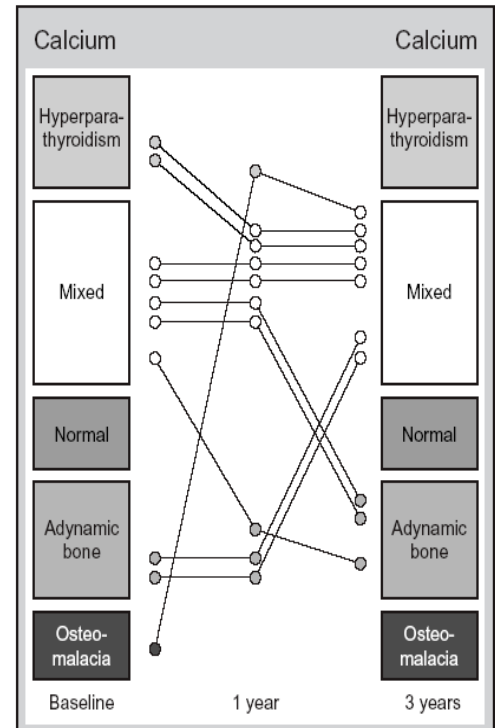


Figure 3. The distribution of various types of ROD diagnosed by histomorphometric assessment of bone biopsies at baseline, after a year and after further two years on calcium carbonate treatment.

group when 1-year and 2-years biopsy data were compared ($21.23 \pm 15.88\%$ vs. $20.27 \pm 15.70\%$; $P = 0.98$). This goes in line with the increased PTH level at the 2-year follow-up compared to the end of the 1-year study in LC group (112.2 ± 157.5 pmol/L vs. 41.2 ± 32.6 pmol/L; $P = 0.15$). The groups didn't differ in PTH at the end of the 2-year follow up (112.2 ± 157.5 pmol/L vs. 67.4 ± 64.5 pmol/L; $P = 0.42$). The suppression of PTH production in the CC group observed at 1-year may be due to persistently higher serum calcium concentration or higher incidence of hypercalcemia compared with the LC group. Lanthanum concentrations declined over the 2-year follow-up period, indicating that there was slow removal of lanthanum from bone following the cessation of treatment. Plasma lanthanum levels at the end of the 2-year

follow up period were comparable between the treatment groups (LC, 0.10 ± 0.02 ng/ml; CC, 0.07 ± 0.02 ng/ml). The finding of significant correlations between bone and plasma lanthanum levels in LC treated patients should be interpreted with caution. Indeed, in view of the differences in kinetics between bone and serum lanthanum measurement of plasma lanthanum levels may not be considered a reliable index for the assessment of the total body burden or the bone lanthanum content.

The present study indicated that treatment with LC or CC for 1 year could effectively control serum phosphorus levels in patients with ESRD, confirming the previous reports (4,5). On the other side, the treatment with CC lead to a greater incidence of hypercalcaemia and has also been linked to coronary artery calcification (3), suggesting that effective maintenance of calcium homeostasis may be an important factor in preventing patient morbidity and mortality. In addition, patients with low bone turnover have a reduced capacity to produce and mineralize bone (8), as well as a reduced ability to manage exogenous calcium loads (9). Therefore, it is possible that the observed trend towards a low bone turnover state during treatment with calcium-based binders may contribute to an increased risk of cardiovascular and soft tissue calcification reported in this patient group. The bone in patients receiving LC moved away from low turnover bone disease, and no cases of hypercalcaemia were reported in these patients, suggesting that treatment had no adverse effects on cardiovascular function. However, further studies are required to investigate potential effects on patient morbidity and mortality.

Conclusions

Treatment with LC was not associated with deterioration of bone status in patients with ESRD. The moderate accumulation of lanthanum in bone during LC treatment and the persistence of the element in bone during wash-out showed no evolution towards low-bone turnover, unlike CC treated patients and no aluminium-like effects on bone.

Acknowledgements

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