

Lanthanum carbonate: a new potent non-calcaemic phosphate binder

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ABSTRACT

Hyperphosphataemia is prevalent among end-stage renal failure and dialysis patients. It is associated with renal osteodystrophy, meta-static calcification and increased morbidity and mortality. It is important to control phosphate levels early in the course of chronic kidney disease. However, dietetic restrictions are often difficult to follow and dietary control is of limited effectiveness because phosphate is an integral part of all proteins, and phosphate is not easily removed by dialysis. Phosphate control has not improved over the last twenty years and this is mainly because of the lack of an ideal phosphate binder. Aluminium-based and calcium-based phosphate binders are associated with signifi-

cant side effects despite their efficacy. Sevelamer represents a step forward in the management of hyperphosphataemia, but is not an ideal binder because of its gastrointestinal side effects, tablet burden and cost. Lanthanum carbonate is new potent non-aluminium, non-calcium phosphate binder. Preclinical and clinical studies shown that it is effective and well tolerated with no negative effects on bone histology.

INTRODUCTION

Hyperphosphataemia is prevalent among chronic renal failure and dialysis patients. It is known to stimulate parathyroid hormone and

suppress vitamin D3 production. This leads to renal osteodystrophy (ROD), and is associated with metastatic calcification and increased morbidity^{1,2}. In addition, it may independently contribute to cardiac causes of death through increased myocardial calcification and accelerated vascular calcification^{3,4}.

Hyperphosphataemia correlates significantly with increased hospitalisation, premature death, reduced quality of life and increased cost of care⁵, so that phosphate control is now considered to be of prime importance.

It is important to control phosphate levels early in the course of chronic kidney disease to minimise the likelihood of secondary hyperparathyroidism and cardiovascular and soft tissue calcification. Long-term dietetic restrictions are often difficult to follow and dietary control is of limited effectiveness since phosphate is an integral part of all proteins. Phosphate is not easily removed by dialysis, due to a large sphere of hydration and the complex kinetics of phosphate elimination. Long slow nocturnal dialysis may be effective, but its logistic difficulties and patient acceptance make a therapy appropriate to only a few people⁶. Therefore, oral phosphate binders are needed to control serum levels.

Phosphate control has not significantly improved over the last two decades. Block *et al* found that 50% of haemodialysis patients have a serum phosphate levels > 6.0 mg/dl and 25% of patients have a level higher than 7.4 mg/dl¹. Interestingly, these results were similar to those published by Lowrie and Lew for over 17 000 patients receiving haemodialysis in 1988. Their analysis showed that 25% of patients had a phosphate level higher than 7.2 mg/dl⁷. The UK Renal Registry has serial data on phosphate control and it is evident that most centres have difficulty in achieving the suggested standards. Even in the best performing centres, less than 50% of the haemodialysis patients were within

the target range⁵. This is in part due to the lack of a potent oral non-calcaemic phosphate binder.

Conventionally, hyperphosphataemia has been treated with aluminium- or calcium-based phosphate binders. These agents, despite their effectiveness, are associated with significant side effects, such as aluminium related bone disease and central nervous system toxicity, and increased risks of hypercalcaemia and cardiovascular calcification. Sevelamer hydrochloride has provided an effective alternative and is associated with less coronary and aortic calcification, as well as reduction in serum cholesterol levels. However, gastrointestinal side effects, large bill burden and high cost have limited its use in many European countries. Lanthanum carbonate is the most recent non-calcium, non-aluminium phosphate binder to be developed and this article examines its experimental, clinical and safety profile.

LANTHANUM CARBONATE

1- Chemistry, metabolism, pharmacodynamics and pharmacokinetics

Lanthanum is a rare earth element of transition group IIIb of the periodic table. It was discovered by Carl Gustaf Mosander in 1839. Its name derived from the Greek *lanthanein*, meaning, "to be concealed", indicating that it is difficult to isolate⁸. It is present in tap water but in minute quantities.

Lanthanum carbonate binds phosphate optimally at pH 3-5, while retaining binding activity across the full range of pH 1-7⁹. It is, therefore, able to bind phosphate efficiently at the low pH of the stomach as well as the higher values in the duodenum and jejunum, unlike calcium carbonate. Lanthanum carbonate reduced urinary

phosphate levels to the same extent as aluminium, and more effectively than calcium carbonate or sevelamer¹⁰ in a 5/6 nephrectomized rat model, with urinary phosphate measurement as a surrogate for potency of phosphate binding. It is highly insoluble, and the majority of the oral dose is excreted in the faeces (in rats: 99.36% in faeces; 0.0038% in urine), with less than 2% of administered lanthanum recovered in the urine in an intravenous study with soluble lanthanum chloride in rats (Study SRU/059-Part III). In the same study, in bile duct cannulated rats dosed intravenously, the faecal component was shown to have arisen largely from biliary excretion, with 79% of excreted drug being recovered in bile over a period of 120 hours (Shire Pharmaceutical Group, preclinical Expert Opinion, data on file)¹¹.

In contrast to aluminium, lanthanum does not cross the blood-brain barrier¹², and so the potential for neurological adverse effects is extremely low. Furthermore, there is no evidence that lanthanum carbonate has any effect on the absorption of fat-soluble vitamins¹¹.

Lanthanum carbonate has a low potential to elicit systemic drug-drug interactions. The lack of metabolism, or cytochrome P450 inhibition, indicates that lanthanum carbonate is unlikely to adversely affect the metabolic clearance of other drugs metabolised by these enzymes.

Interaction studies with drugs commonly co-used in end-stage renal failure, such as warfarin, digoxin, frusemide, metoprolol, enalapril and citrate have been completed and provided adequate justification not to recommend further specific precaution for dose adjustment¹¹.

2 - Efficacy

More than 1800 dialysis patients been exposed to lanthanum carbonate for variable times in 3 phase I studies, 10 phase II and III studies, with two long-term safety studies still ongoing.

2-1 Effects on phosphate levels

The results of the preclinical studies have shown that lanthanum carbonate has the characteristics of an effective phosphate binder. A statistically significant decrease in serum phosphate levels was illustrated in patients receiving lanthanum carbonate at doses of 500 to 3000 mg/day, in two double blind, placebo-controlled phase II studies^{12, 13}. The maximal decreases in serum phosphate levels occurred after three weeks of treatment and were maintained over the 4-6 weeks of treatment.

In phase III studies, two trials were performed to evaluate the efficacy and safety of lanthanum carbonate. The first of these trials (Study 302) was a 13-week, randomized, double blind, placebo-controlled, parallel group study. The primary efficacy parameter was reduction of serum phosphate and ability to maintain control to ≤ 1.9 mmol/l (≤ 5.9 mg/dl). 126 haemodialysis patients were titrated on lanthanum up to maximum dose of 3000 mg/day to achieve the target phosphate level. After titration patients were randomised in the double blind maintenance phase to either placebo (N = 44) or continued lanthanum carbonate (N = 49). A significant difference in mean serum phosphate levels was seen (1.91 mg/dL [0.62 mmol/L]; $P < 0.0001$) between the lanthanum carbonate and placebo groups. Serum phosphate levels were controlled at ≤ 1.9 mmol/l in 59% of the patients receiving lanthanum carbonate, compared with 23% of the placebo group. Furthermore, of those patients whose serum phosphate levels were controlled at the time of entering the maintenance phase, 66% of the lanthanum carbonate-treated patients and only 31% of the placebo-treated patients maintained control at study endpoint¹⁴.

Study 301 was a much larger prospective, randomized, European multi-centre, open-label,

comparator study. The primary efficacy parameter was reduction of serum phosphate levels to ≤ 1.8 mmol/l (d" 5.6 mg/dl). The secondary parameter was the maintenance of control at ≤ 1.8 mmol/l for 6 months or longer. In total, 800 haemodialysis patients received treatment in the 6-month comparator phase. After 9 weeks of treatment, both groups had serum phosphate levels of 1.69 mmol/l (Figure 1). In the lanthanum carbonate group, 67.9% of patients showed controlled serum phosphate levels, compared with 65.8% of patients of the calcium carbonate-treated patients. At the end of 6-month maintenance period, there was no significant difference in the proportions of patients with controlled phosphate levels (65.8% vs. 63.9% in the lanthanum carbonate and calcium carbonate groups respectively). Importantly however, lanthanum carbonate resulted in far fewer episodes of hypercalcaemia than calcium carbonate (0.4% vs. 20.2%)¹⁵.

Similar results were noted in another phase III, open-label study (303), to investigate the effect of lanthanum carbonate compared to calcium carbonate, on bone metabolism in chronic

renal failure patients receiving dialysis. Although the study was not designed to compare the phosphate binding efficacy of the two treatment groups, on average both treatment groups showed well controlled phosphate levels during the study. There was a slight increase at visit 20, but this was following a period when phosphate binder treatment has been interrupted to allow tetracycline labelling prior to bone biopsy (Figure 2, data on file)¹⁶.

In another study, Hutchison et al demonstrated that lanthanum carbonate is effective in reducing serum phosphate to ≤ 1.8 mmol/l regardless of dialysis modality, with patients receiving either CAPD or haemodialysis¹⁷.

Recently, in a Phase II study 144 patients were randomized to 6 weeks treatment with either placebo (n = 32) or with lanthanum carbonate at doses of 225, (n = 27) 675, (n = 29) 1350 (n = 30) or 2250 (n = 26) mg/day. At randomization, serum phosphate levels were similar in all groups, and after six weeks of treatment, levels were controlled to below 5.6 mg/dL in 25 of the 56 patients (44.6%) who received the highest lanthanum doses. After 6 weeks of treatment, phosphate levels were significantly lower in the groups taking 1350 mg lanthanum daily (mean reductions from baseline of -0.95 ± 1.39 mg/dL), and 2250 mg (mean reductions from baseline of -1.13 ± 2.01 mg/dL), compared with the placebo group ($P < 0.001$ vs. placebo)¹⁸.

2-2 Effects on Calcium Phosphate Product (Ca x P product)

Given that lanthanum carbonate has been shown to be an effective phosphate binder, and that it does not contain calcium, it would be expected to have a beneficial effect on Ca x P product. This was well demonstrated in a number of clinical studies.

In phase II studies, the Ca x P product was

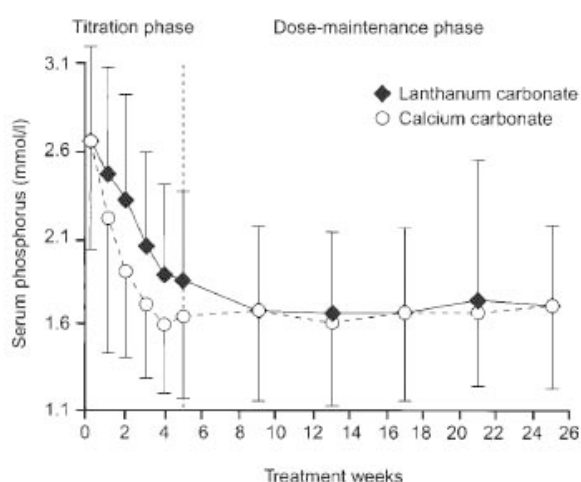


Figure 1 – Mean serum phosphate levels during titration and maintenance treatment (intention-to-treat) in study 301

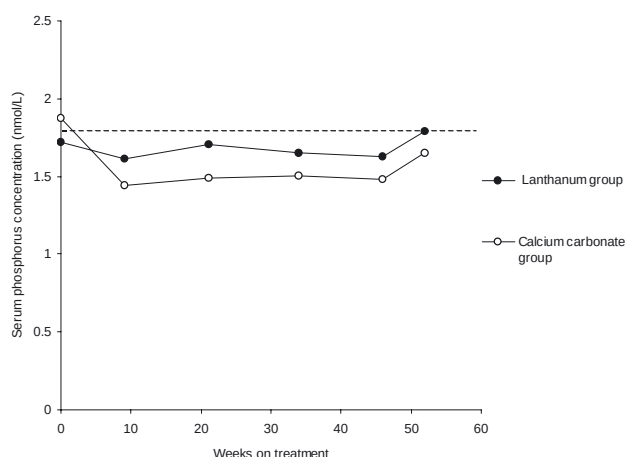


Figure 2 - Phosphate levels over time for Lanthanum carbonate and Calcium carbonate groups (303 study).

(The horizontal dotted line represents the level below which serum phosphate was considered controlled - 1.8 mmol/L)

unsurprisingly significantly higher in the placebo group due to uncontrolled serum phosphate levels^{12,13}. In study 302, Ca x P product was significantly lower in the lanthanum carbonate treated patients than placebo treated (mean $\pm$ SD: 52.37 ± 14.89 vs. 66.59 ± 18.30 mg²/dl²; $P < 0.0001$, data on file)¹⁹. Similarly, in study 301, the reductions in Ca x P product were generally greater with lanthanum carbonate maintenance treatment than with calcium carbonate (-1.59 vs. -1.26 mmol²/l²)¹⁷.

In study 303 (bone histomorphometry study), the mean calcium x phosphate values were generally similar for both the lanthanum and calcium treated groups and showed no particular trend as a result of treatment. The ranges of calcium phosphate levels were also similar between treatment groups. This was partly due to effective control of serum and dialysate calcium in the calcium carbonate-treated patients and partly due to the absence of a strict target for serum phosphate control in this study (Figure 3)¹⁶.

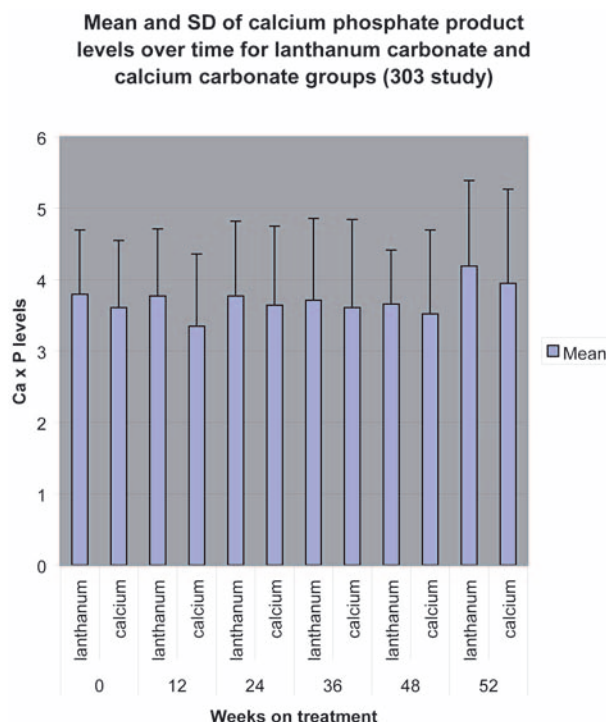


Figure 3 – Mean Calcium Phosphate Product levels over time for lanthanum carbonate and calcium carbonate groups (303 study).

2-3 Effects on Parathyroid Hormone (PTH)

None of lanthanum carbonate studies have been designed with the effect on serum PTH as a primary end-point. Indeed it is very difficult to do this in a clinical setting since PTH is influenced by many factors including serum calcium, phosphate, vitamin D status and modality of dialysis. Understanding of PTH metabolism is still evolving, but it is now appreciated that whilst severe hyperparathyroidism should be controlled quickly, over-suppression of PTH is associated with the adynamic bone lesion, an increased Ca x P product, and vascular calcification.

In study 302, the mean serum PTH levels were significantly lower after lanthanum carbo-

nate treatment compared with placebo, presumably reflecting better phosphate control (mean $\pm$ SD: 209.41 $\pm$ 152.65 vs. 291.80 $\pm$ 194.82 pg/ml; $P < 0.01$, data on file)¹⁴. Likewise, in study 301 the median serum PTH levels decreased by around 5% during 5 months of maintenance treatment with lanthanum carbonate and increased by around 15% with calcium carbonate²⁰. However, in study 303 (bone histology) the mean and median PTH levels for the lanthanum group showed stability throughout treatment and the extent of the data ranges did not show substantial change. In the calcium carbonate group however there was general reduction in both mean and median PTH levels during the middle period of the study and larger variations in the data range (Figure 4, data on file)¹⁶.

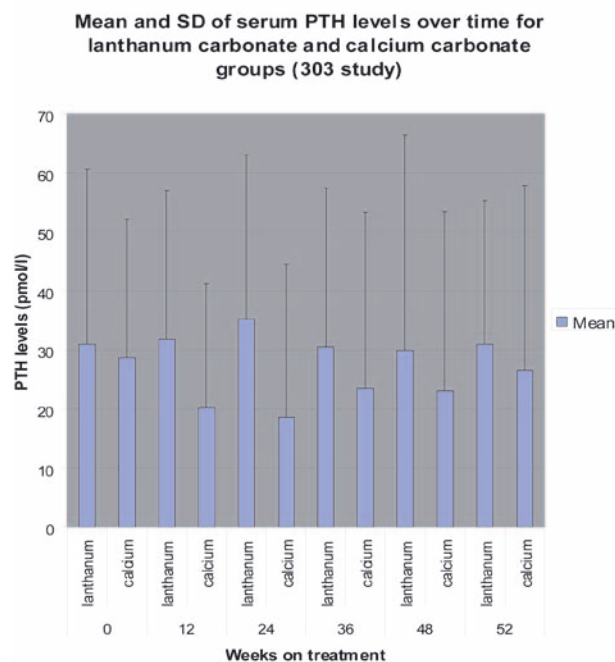


Figure 4 - Mean serum PTH levels over time for lanthanum carbonate and calcium carbonate groups (303 study)

2-4 Effects on calcium levels

Many patients with ESRD experience hypercalcaemia rather than hypocalcaemia despite the reduced intestinal absorption of calcium. Certainly, several factors contribute to this, including vitamin D therapy, additional calcium supplied from the dialysate, low bone turnover states and use of calcium containing phosphate binders^{21,22}. Lanthanum carbonate treatment has a potential significant advantage in reduction of hypercalcaemic episodes.

In study 303, 6% of patients in the lanthanum group and 48% of patients in the calcium carbonate group had at least one episode of hypercalcaemia (serum calcium > 2.65 mmol/l) (Figure 5, data on file)¹⁶. The number of hypercalcaemic episodes for the lanthanum group was low and similar to that observed during lanthanum treatment in a previous study (LAM-IV-301 Clinical Study Report).

2-5 Effects on bone histomorphometry

Preliminary data on the localization of lanthanum in bone in rats have shown that it is present at both active and quiescent sites of mineralization, independent of the type of renal osteodystrophy²³.

In study 303 (bone histomorphometry - 98 patients), the effects of lanthanum carbonate and calcium carbonate on the development and progression of renal osteodystrophy over one year were evaluated in end-stage renal failure patients undergoing dialysis. At baseline, 98% (48/49) of patients in each group had renal osteodystrophy. Renal osteodystrophy subtypes were similarly distributed in both groups with 'mixed' renal osteodystrophy by far the most prevalent type of bone lesion at baseline. After one year of treatment, there was a trend towards improved bone histology in both treatment

Mean and SD of calcium levels in lanthanum and calcium groups (303 study)

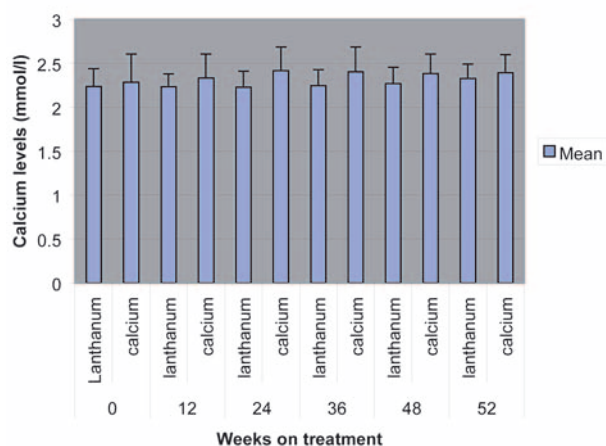


Figure 5- Mean serum calcium levels over time for lanthanum carbonate and calcium carbonate groups (303 study)

groups. However the patients with low bone turnover lesions (adynamic bone disease or osteomalacia) at baseline, tended to show improved bone histology in the lanthanum carbonate group, compared with those in the calcium carbonate group where low bone turnover lesions persisted (71% vs. 42% respectively). Only 1 (4%) of the lanthanum carbonate treated patients evolved towards adynamic bone compared with 6 (26%) patients in the calcium carbonate treated group²⁴. Therefore, it appears that the evolution towards low bone turnover that is often seen in calcium treated dialysis patients is not observed in dialysis patients treated with lanthanum. Furthermore, no correlations between bone lanthanum content, PTH levels or bone histology were found¹⁹. No evidence of an aluminium-like effect on osteoblast function was evident.

3 - Safety and tolerability

3-1 Serum and bone lanthanum levels

In human studies serum lanthanum levels are very low, but increased slightly from baseline levels after one year's treatment. Mean serum lanthanum levels in the highest dose groups ranged between 0.51 and 1.08 µg/l. The levels did not appear to be dose dependent and reached a plateau after 12 weeks of treatment. Bone lanthanum levels did not exceed 6 µg/g-wet weight (median 1.8 µg/g) after twelve months of treatment. Furthermore, even in the calcium carbonate-treated group, bone lanthanum levels showed a slight increase over the course of the study reaching a maximum value of 1.0 µg/g²⁵. This probably reflects the fact that some areas of Europe have relatively high lanthanum levels in tap water and local vegetables.

3-2 Adverse effects

The overall rate of 'adverse events' of all types in reported studies of patients receiving lanthanum carbonate was 88%, compared to 90% for standard therapy (any other phosphate binder or combination treatment) and 43% in placebo groups. Indeed, the high rate of adverse events is a reflection of the general morbidity in these chronically ill patients. The most common category of adverse events for all patients was gastrointestinal system disorders at 58%, 57% and 14% for lanthanum carbonate, standard therapy and placebo respectively¹¹.

In general, the incidence of adverse effects was similar in the lanthanum carbonate and calcium carbonate groups except for hypercalcaemia (6% vs. 35% of patients respectively (data on file)²⁰. There were no clinically meaningful changes in vital signs with either treatment¹⁷. The overall rate of deaths for patients

receiving lanthanum carbonate was 6.2%, compared to 11.5% in standard therapy, although this difference is probably accounted for by differences in duration of exposure to treatment. The most common category of death was 'heart rate and rhythm disorders', regardless of the treatment received. This would be expected in a population where cardiovascular disease is known to be the major cause of death on dialysis. Likewise, there was a high incidence of vascular access complications (dialysis graft and catheter complications including infection/occlusion) in patients treated with lanthanum carbonate (23%) and standard therapy (33%). However, less than 1% of these events were considered related to either active treatment¹⁷.

Long-term experience with lanthanum carbonate in patients continues to increase, such that over 1800 patients have been exposed in total - 996 for more than 6 months, 604 for more than 12 months, 299 for more than 18 months, 205 for more than 24 months and around 40 for more than 36 months, with some subjects now reaching 5 years on continuous treatment.

The proportion of long-term exposure patients with controlled serum phosphate was high throughout; 71.7% at week 58 (start of 24-month extension), 76.1% at mid-point (week 75), and 68.9% at endpoint (week 154). These long-term results suggest that safety, tolerability and efficacy of lanthanum carbonate in dialysis patients are maintained over 3 years of treatment²⁶.

4 - Where are we now?

Lanthanum carbonate (FOSRENOL®, Shire Pharmaceutical Group Ltd.) received regulatory approval for the control of phosphorus levels in patients with ESRD in Sweden in March 2004. However, this was the first step in securing marketing approval through Europe. Submission has also been made by Shire to gain marketing

approval in Canada, whilst development continues in Japan. On 27th October 2004, the FDA approved Fosrenol® (lanthanum carbonate), a new non-calcium, non-aluminium phosphate binder that reduces serum phosphate levels in patients with end-stage renal disease (ESRD)¹⁶. It is now available to US patients having appeared on the market during early 2005.

5 - Conclusions

Lanthanum carbonate is promising new non-calcium, non-aluminium, potent phosphate-binding agent, which achieves desirable phosphate levels in the majority of patients and may enable better management of bone turnover without over-suppression of serum PTH. It is effective across the full range of pH encountered in the upper GI tract, and appears well tolerated in doses up to 3000mg daily. Doses of 1350-2250 mg of lanthanum carbonate are effective in reducing and maintaining serum phosphate levels, but higher doses may be required in some patients. However, serum phosphate levels decreased most quickly with doses of 2250 mg, and maximum decreases occur after three weeks of treatment at these doses. Although concerns were expressed initially that it might have aluminium-like side effects, no evidence of this has been found despite careful long-term studies of biochemical and histological indices. These studies now extend beyond 4 years and will be continued.

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