Lanthanum carbonate

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Hyperphosphatemia is associated with increased mortality in patients with end-stage renal disease. Unfortunately, precise, effective control of serum phosphate levels cannot be achieved by dialysis and regulation of dietary phosphate alone. For most patients, effective, safe and convenient phosphate binders are needed. Preclinical studies demonstrate that the new phosphate binder, lanthanum carbonate, has potent phosphate-binding properties at clinically relevant pH levels, and indicate that almost all the lanthanum phosphate formed passes unchanged through the gut. Plasma levels of lanthanum are limited and noncumulative, and the minimal systemic fraction has nonrenal elimination. Clinical trials show that lanthanum carbonate, taken with food, can effectively control hyperphosphatemia in dialysis patients, and has a well-tolerated safety profile. Side effects are largely gastrointestinal and are generally mild to moderate. Lanthanum carbonate treatment may prove instrumental in achieving the increasingly stringent target serum phosphate levels in patients with end-stage renal disease.

Keywords: calcification, chronic renal failure, hemodialysis lanthanum carbonate, osteomalacia, phosphate, renal osteodystrophy

Among the serious consequences of chronic renal failure (CRF) is the progressive decline in the kidney's ability to excrete phosphate and to produce active vitamin D. The resulting hyperphosphatemia and hypocalcemia leads to an increase in parathyroid hormone (PTH) synthesis and release, ultimately leading to the development of secondary hyperparathyroidism [1–3] and a state of disordered mineral metabolism [2].

It is now recognized that hyperphosphatemia exerts deleterious effects on parathyroid function that are independent of changes in calcium and vitamin D homeostasis [4–6]. An elevated serum phosphate concentration, along with a high calcium plus phosphate (Ca × P) product and an increased PTH level, are associated with soft tissue calcification and cardiovascular disease [7,8]. Moreover, a correlation between high levels of serum phosphate or calcium, and an increased risk of mortality in patients with end-stage renal disease (ESRD) has been demonstrated [9,10]. The secondary hyperparathyroidism seen as a consequence of these imbalances in calcium and phosphate metabolism results in bone abnormalities, and there is growing evidence of adynamic bone lesions in predialysis patients, as well as in ESRD patients [11,12].

Net intestinal phosphate absorption is approximately 70 to 80% of dietary intake [11]. There are two components to intestinal phosphate absorption: a passive pathway down an electrochemical potential gradient and an active pathway catalyzed by the Na^+/phosphate cotransporter (NaPi IIb). The latter pathway is responsive to 1,25-dihydroxyvitamin D and is influenced by the phosphate content of the diet. The amount of dietary phosphate absorbed by patients with ESRD is reduced compared with controls. On the basis of studies using the direct recovery of phosphate from stools, it has been determined that the mean absorption may equal only 40 to 60% of the dietary intake [13]. In part, this is due to the decline in renal 1α-hydroxylase activity and progressive 1,25-dihydroxyvitamin D deficiency.

Careful regulation of dietary phosphate intake can help to control serum phosphate levels. However, because most dietary phosphate is derived from protein, it is difficult to achieve phosphate control without a significant reduction in protein intake, which may result in malnutrition [14]. The recommended dietary protein intake according to US government standards is 0.8 g/kg body weight for the adult. This level of protein intake is said to meet 97.5% of the population's needs. However, dietary protein requirements increase with maintenance hemodialysis to a minimum of 1.2 g/kg body weight. For patients with a body weight in the range of 50 to 70 kg and below, the adequate 1.2 g/kg body weight of protein intake would be accompanied by a dietary phosphate intake of between 873 and 1784 mg/day (**Table 1**).

The amount of phosphate removed during hemodialysis varies considerably and is related to a considerable extent to the predialysis serum phosphate level. For example, with a predialysis

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serum phosphate level of between 5 and 6 mg/dl, approximately 700 mg would be removed with each dialysis, equivalent to 2.1 g/week. Measurements from other studies indicate that the average daily phosphate removal by standard 4-h hemodialysis may range from a low of 250 to 300 mg [15,16], up to 500 to 600 mg [16], to a high of 1000 mg [17].

It can be appreciated that the ingestion of 1000 mg phosphate daily, even if only half is absorbed, would result in a net positive balance with hemodialysis three-times weekly. Removal of phosphate by conventional hemodialysis is not usually adequate to prevent hyperphosphatemia. When conventional phosphate binders are used, the phosphate absorbed from the diet may be reduced to 30 to 40% or 406 to 541 mg/day (**Table 1**). To achieve phosphate balance, this would require a protein intake close to or below the recommended daily level.

Treatment with phosphate binders is recommended for the treatment of hyperphosphatemia in patients receiving dialysis, in order to achieve target serum concentrations of 3.5 to 5.5 mg/dl for phosphate levels, as recommended by the Kidney Disease Outcomes Quality Initiative (K/DOQI) Guidelines [18]. Elevated calcium and phosphate levels have been implicated in the increased cardiovascular mortality seen in patients receiving dialysis, and improved phosphate control using a combination of dietary management and appropriate use of phosphate binders is needed to improve outcome for these patients [19].

Aluminum hydroxide is a highly effective phosphate binder; however, treatment is associated with anemia [20], dialysis-related encephalopathy [21,22], and osteomalacia [21,23,24]. Therefore, while aluminium hydroxide is still available for short-term use in patients with very high serum phosphate levels, aluminum is seldom appropriate as treatment for hyperphosphatemia. Aluminum is tightly sequestered in bone for long periods at the sites of bone mineralization, and the resultant toxic effects are cumulative, such that aluminum should be used with caution even as a rescue treatment [25].

Calcium salts, primarily calcium carbonate and calcium acetate, have become the mainstay of treatment for the management of hyperphosphatemia in patients with ESRD [26,27]. Unfortunately, calcium-based phosphate binders also have a number of limitations, as treatment is associated with hypercalcemia, an increased risk of soft-tissue calcification and adynamic or 'low-turnover' bone disease (as a result of PTH suppression). Patients using calcium-based agents for the treatment of hyperphosphatemia may also require a large number of pills, which can lead to diminished compliance and reduced effectiveness.

Sevelamer hydrochloride, the first calcium- and aluminum-free phosphate binder to be approved for clinical use, was launched in 1999. A number of studies have shown that sevelamer reduced dietary phosphate absorption and serum phosphate levels without the hypercalcemia seen with traditional phosphate binders [28–32]. By current K/DOQI standards [33], however, target levels of phosphate control have not been consistently achieved [29,32], and in some cases patients require large numbers of tablets to attain adequate serum phosphate levels.

Treatment with sevelamer hydrochloride has also been associated with reduced bicarbonate levels during treatment [34,35], probably caused by the anionic exchange with the chloride ions of the molecule, although this issue is controversial. On average, these patients already have low bicarbonate levels so a further reduction with the phosphate binder would not be beneficial. Possible consequences include an increased risk of acidosis and associated mineral release from bone [36].

Approximately 70% of dialysis patients have serum phosphate levels over 5.0 mg/dl (>1.7 mmol/l) despite the availability of phosphate

Table 1. Dietary phosphate content (mean ± standard deviation) at different levels of protein intake in 60 stable hemodialysis patients [14].

Protein intake (g/kg/day)	Patients (n)	Dietary phosphate (mg)	Range	Estimated phosphate absorbed (30–40%) in patients on phosphate binder therapy (mg)
>1.2	15	1353 ± 25	873–1784	406–541
1.0–1.2	10	1052 ± 219	778–1444	315–421
0.8–1.0	15	936 ± 217	480–1352	281–374
0.6–0.8	13	831 ± 142	574–1056	249–332
<0.6	7	599 ± 105	475–760	180–240

binders [9]. Therefore, there is a medical need for additional agents that are well tolerated and effective [7,26].

Lanthanum carbonate (Fosrenol®) received regulatory approval for the control of phosphate levels in patients with ESRD in Sweden in March 2004; further submissions are currently ongoing in a number of European countries, and worldwide. In addition, the US Food and Drug Administration (FDA) approved lanthanum carbonate in October 2004 for the reduction of serum phosphate levels in patients with ESRD.

Chemical profile

The history of the discovery of the so-called 'rare-earth elements' began in 1803 with the identification by Swedish and German chemists of a new mineral called cerite. The rare earth element, ceriumrom, was isolated from cerite. Lanthanum was discovered in 1839 by Carl Gustav Mosander (1797–1858), a Professor of Chemistry and Mineralogy at the Karolinska Medical–Surgical Institute in Stockholm. In 1825 he became convinced that an oxide of another metal was present in cerite and, 10 years later, he isolated a new element, which was given the name lanthana, from the Greek lanthan, meaning 'to lie hidden' or 'to escape notice' [37].

Lanthanum was isolated in relatively pure form in 1923. It is a silvery white metallic element belonging to group 3, period 6 of the periodic table and is often considered to be one of the lanthanides. The lanthanides are divided into the cerium group of lighter elements and the yttrium group of heavier elements. Lanthanum, a member of the cerium group, is never found in nature as the free element. Rather, it is present in 'rare-earth' ores, principally monazite (25% lanthanum) and bastnaesite (38% lanthanum).

The separation of lanthanum and the other lanthanoids is complex and has been one of the most difficult problems within inorganic chemistry. Initially, the metals are extracted as salts from the ores with sulfuric acid, hydrochloric acid and sodium hydroxide. Modern purification techniques involve selective complexation techniques, solvent extraction, and ion-exchange chromatography. Pure lanthanum is usually obtained by reducing the anhydrous fluoride with calcium.

The annual production of rare earths in 2000 was approximately 83,500 tonnes, of which 87% came from China. China possesses more than 50% of the world's rare-earth mineral reserves and produces approximately 88% of the world's consumption. The Baiyunebo mine in Boutou, Inner Mongolia, is a prominent producer of the light rare earths. It should be mentioned that the designation of rare is rather inappropriate, since lanthanum is rare only in comparison to the abundant alkaline earth metals such as calcium and magnesium. The USA is second to China as a major commercial source of the rare-earth metals with smaller amounts from India and Sri Lanka, the former Soviet Union, Brazil and Malaysia.

Lanthanum has an atomic weight of 138.9 and the binding of this trivalent cation is almost exclusively ionic. Lanthanum shows a high affinity for oxygen donor ions such as carboxyl and phosphate groups, and it can form very tight complexes with these ligands. Lanthanum is found in trace amounts in the environment, including food and drinking water, and in the human body [38,39].

As with many naturally occurring elements used in the pharmaceutical industry, lanthanum has a long history of industrial use. It is widely used in the film industry and is also used to coat television tubes, in lighter flints and as a component of fillings for dental caries.

Lanthanide elements form soluble chlorides and nitrates, but their hydroxides, carbonates, and phosphates are highly insoluble. Lanthanum carbonate was chosen for further clinical investigation as an intestinal phosphate binder because of its insolubility and low potential for systemic absorption. When lanthanum carbonate is used clinically as a phosphate binder, it dissociates sufficiently in acidic environments, such as the stomach and upper small intestine, to become available for phosphate binding.

Pharmacokinetics & pharmacodynamics

Preclinical pharmacology & toxicology

In vitro studies indicate that lanthanum carbonate binds phosphate as effectively as aluminum hydroxide at clinically relevant pH levels (pH 3, 5 and 7), and is more effective, with a broader pH range, than calcium carbonate and calcium acetate [40,41]. Preclinical studies using a rat model of CRF (5/6th nephrectomized rats), in which reduction in urinary excretion was used as a marker of dietary binding, have shown that when compounds were given daily over 6 weeks, lanthanum carbonate was of greater potency than calcium carbonate or sevelamer hydrochloride [40].

Compared with aluminum, low levels of lanthanum are absorbed. In animals, 0.0007% of oral doses of lanthanum carbonate were absorbed [42], and in humans, under 0.00089% of the oral dose was absorbed [43]. In animal

studies, the main routes of elimination of the absorbed fraction were in the feces via bile (80%) and by direct transport across the gut wall into the lumen (13%). In humans, biliary excretion has not been assessed. However, renal clearance in man is very low in healthy volunteers and ESRD dialysis patients [43], and elimination is proposed to occur by biliary excretion. These studies in animals and humans confirm that elimination of lanthanum carbonate is largely independent of renal function [43], in contrast to the case with aluminum, which is excreted almost entirely in urine [44]. In addition, unlike aluminium, absorption of lanthanum is not increased by citrate compounds.

Studies indicate that there is no significant blood–brain barrier penetration of lanthanum carbonate [45,46]. In oral-dosing studies of up to 80-weeks' duration, very low levels of lanthanum were detected in the median brain and cerebrospinal fluid of animals. Concentrations of lanthanum were consistently below, or around the lower limit, of quantification of the assay (0.05 ng/ml for cerebrospinal fluid and 10 ng/g for brain tissue) [42].

In vivo and *in vitro* animal studies also indicate low potential for adverse effects on the CNS, skeletal, gastrointestinal, cardiovascular, and respiratory systems [40,47]. While very high intravenous doses in dogs (1 mg/kg daily for up to 4 weeks) caused some hepatotoxicity, animal studies using oral treatment at more clinically appropriate doses showed no adverse effects of oral treatment on serum liver markers or histology for treatment periods up to the lifespan of the animals; there was no evidence of genetic or reproductive toxicity; and there was no functional or histopathologic evidence of CNS toxicity [47].

A model of CRF in rats [48] has been used to evaluate the effects of lanthanum carbonate and other phosphate binders on bone structure and mineralization [49]. Changes in bone mineralization in rats with CRF have been seen in preliminary studies using a high dose of sevelamer (1000 mg/kg daily for 12 weeks) [50] and in other CRF rats treated with very high doses of lanthanum carbonate (>1000 mg/kg daily for 12 weeks) [49]. In the latter study, administration of lanthanum carbonate induced a dose-dependent mineralization defect in 43% of CRF rats. However, there was no evidence that lanthanum had any direct toxic effect on osteoblasts, which would, therefore, retain the ability to deposit bone matrix [49]. Notably, mineralization changes as a consequence of severe phosphate depletion are known to occur. Since aggressive phosphate control in itself (with any agent) might promote the development of adynamic bone lesions, testing for markers of bone metabolism or bone biopsy should be perfomed during treatment with phosphate-binding agents. Supporting the conclusion that the lanthanum-induced phosphate depletion in itself either reduced the incorporation of phosphate into bone or increased its mobilization out of bone was the observation that lanthanum concentrations in bone remained low, and no correlation was observed between bone lanthanum levels and development of the mineralization defect. Thus, the effects of lanthanum carbonate administration on bone mineralization were a predictable and indirect effect of phosphate depletion, rather than a direct toxic effect on osteoblast function. The severe depletion of phosphate seen in CRF rats is considered unlikely to occur in ESRD dialysis patients where much smaller doses of lanthanum carbonate (30–50 mg/kg/body weight) are given to treat hyperphosphatemia.

Clinical pharmacokinetics

An early Phase I study demonstrated that lanthanum carbonate is generally well tolerated when taken during or immediately after meals [50]. Therefore, it is recommended that lanthanum carbonate is taken orally in divided doses with meals. The intestinal absorption of lanthanum was increased (an increase of 22% in area under the curve $[AUC]_{0\text{-}t}$) in 36 healthy volunteers when a dose was taken 30 min after eating, compared with a dose taken during eating. In either case, the actual amount absorbed was very low, and the increase in intestinal absorption when the dose was delayed was not considered to be clinically relevant. Peak plasma levels (C_{max}) of lanthanum are usually reached by 4 to 6 h after the first dose and further changes are neither dose proportional nor cumulative.

Pharmacokinetic data from Phase I, II and III clinical trials (**Table 2**) have confirmed the findings from preclinical studies that gastrointestinal absorption of an oral dose of lanthanum is minimal. Also – and of some clinical importance in view of the target population consisting of ESRD patients – only a minimal fraction of the absorbed dose of lanthanum is eliminated through the kidneys [43]. For example, a study in healthy volunteers demonstrated that only 0.00003% of a daily dose of 1 g/day

Table 2. Summary of the key Phase I, II and III clinical trials

Effect studied	Study design	Key findings	Ref.
Systemic absorption of lanthanum	Phase I study of healthy volunteers (n = 14) given lanthanum carbonate with meals, at 4718 mg/day or at a maximum tolerable dose on alternate days (Part I)	Plasma lanthanum levels were extremely low, ranging from below the limit of detection to 4.1 ng/g	[50]
Efficacy and tolerability	Double-blind, randomized, placebo-controlled Phase I study in healthy volunteers (n = 12) administered lanthanum carbonate (4718 mg/day) for 3 days (Part II)	Urinary phosphate excretion significantly decreased during lanthanum treatment, indicating effective intestinal phosphate binding. The drug was well tolerated, with limited gastrointestinal side effects. Plasma lanthanum levels ranged from 0.71 to 1.31 ng/ml	[50]
Systemic absorption, safety and efficacy	Phase I study in healthy volunteers (n = 9) randomized to receive either lanthanum carbonate (1 g of lanthanum three-times daily; n = 9) or placebo (n = 3) for 8 days, immediately after food	Plasma lanthanum levels were <1 ng/ml throughout treatment, with minimal evidence of systemic accumulation. Urinary phosphate excretion was significantly reduced by day 6 in the treatment arm compared with placebo	[64]
Tolerability related to timing of food intake	Phase I study in healthy volunteers (n = 36) randomized to receive lanthanum carbonate for 3 days, given with food, and for 3 days given 30 min after food	There was a trend towards more frequent side effects in the with-food group ,but these were mild in severity and did not suggest a clinically meaningful difference. Systemic absorption of lanthanum was low (mean maximum concentration: 0.23 ng/ml in the post food group and 0.21 ng/ml in the with-food group)	[65]
Concomitant administration of lanthanum carbonate and digoxin; effect on pharmacokinetic parameters	Phase I open-label, randomized, crossover study in healthy male volunteers (n = 14) assigned to treatment with digoxin (0.5 mg) alone or 30 min after a fourth dose of lanthanum, 1000 mg, following one day of lanthanum treatment (1000 mg, three-times daily)	Concomitant administration was well tolerated. Pharmacokinetic parameters of digoxin were largely unaffected (elimination half-life was slightly increased with concomitant lanthanum carbonate administration)	[53]
Concomitant administration of lanthanum carbonate and warfarin; effect on pharmacokinetic parameters	Phase I open-label, randomized, crossover study in healthy male volunteers (n = 14) assigned to treatment with warfarin (10 mg) alone or given 30 min after a fourth dose of lanthanum, 1000 mg, following 1 day of lanthanum treatment (1000 mg, three-times daily)	Concomitant administration was well tolerated. Pharmacokinetic parameters of warfarin were not affected	[66]
Concomitant administration of lanthanum carbonate and metoprolol; effect on pharmacokinetic parameters	Phase I open-label, randomized, crossover study in healthy male volunteers (n = 14) assigned to treatment with metoprolol (100 mg) alone or given 30 min after a fourth dose of lanthanum, 1000 mg, following 1 day of lanthanum treatment (1000 mg, three-times daily)	Concomitant administration was well tolerated. Pharmacokinetic parameters of metoprolol were not affected (maximum concentration was marginally decreased with concomitant lanthanum carbonate administration)	[53]
Efficacy and tolerability	Phase II, double-blind, randomized, placebo-controlled study in continuous ambulatory peritoneal dialysis patients (n = 10) administered lanthanum (up to 2250 mg/day) for 4 weeks	Serum phosphate levels significantly fell in the study period, indicating effective phosphate-binding by lanthanum. Three patients had mild nausea, no other side effects were reported	[67]
Efficacy and identification of effective doses	Phase II, double-blind, randomized, placebo-controlled study (n = 144) assessing doses of 225, 675, 1350 and 2250 mg daily	The minimal effective dose was 675 mg/day. Serum phosphate levels fell by 0.95 mg/dl in the 1350-mg lanthanum group and by 1.13 mg/dl in the 2250-mg lanthanum group following 6 weeks of treatment	[56]

All doses stated are of elemental lanthanum.

Table 2. Summary of the key Phase I, II and III clinical trials (Cont.).

Effect studied	Study design	Key findings	Ref.
Dose titration study	Phase II dose-titration study	During the dose titration phase, 70% of patients achieved control of serum phosphate levels	[55]
Effects of lanthanum carbonate on bone metabolism	Open-label, randomized, Phase III study of lanthanum carbonate versus calcium carbonate (n = 98). Bone histomorphology was examined at the beginning of the study and after 1 year	Both treatments were similarly effective in controlling hyperphosphatemia and had similar safety profiles, although hypercalcemia was more frequent in the calcium carbonate-treated group (49 vs. 6%). No negative effects of lanthanum on bone were noted; improvements in the majority of the bone biopsy parameters analyzed were observed	[61,68]
Efficacy and safety of lanthanum carbonate as an oral phosphate binder	Double-blind, dose-titration, randomized, placebo-controlled, Phase III study in hemodialysis patients (n = 126)	At study end point, serum phosphate was controlled in 65% of patients in the lanthanum group and 38% in the placebo group. Lanthanum carbonate was well tolerated. Adverse events (>5% of patients) reported in the lanthanum group were: dialysis graft occlusion (6%), nausea (6%), vomiting (6%) and diarrhea (4%). Incidence of adverse events was similar between both treatment arms	[57]
Efficacy, safety and tolerability	Randomized, 6-month, Phase III study, in which lanthanum carbonate (375–3000 mg/day; n = 533) and calcium carbonate (1500–9000 mg/day; n = 267) were administered in an open-label trial	Following dose titration and throughout the maintenance period, serum phosphate levels were controlled in similar proportions in the two treatment arms. Adverse events were similar, except for hypercalcemia, which was more frequent in the calcium carbonate-treated arm	[58]
Long-term safety and efficacy profile	Phase III, parallel-group, active-comparator, open-label, 2-year study of lanthanum carbonate (n = 682) versus standard therapy (any approved phosphate binder or combination of phosphate binder [n = 676])	Hyperphosphatemia control was similar in the two treatment groups. When corrected for differences in exposure to treatment, adverse events were also similar in the two groups	[59]
Extended long-term safety and efficacy profile	Long-term (1-year) extension study in 77 patients with end-stage renal disease	Long-term control of serum phosphate was maintained by lanthanum phosphate treatment	[69]
Safety and efficacy in Chinese patients	Double-blind study randomizing 61 patients to double-blind phase, with 42 patients completing the study	Lanthanum carbonate is an effective phosphate binder in this patient population. Serum phosphate levels obtained at the last week of double-blind treatment were maintained during the extension period. Levels at the end of the double-blind phase were significantly lower than in placebo patients	[70]

All doses stated are of elemental lanthanum.

of lanthanum was excreted in the urine [51]. It has subsequently been demonstrated that the pharmacokinetics of lanthanum are similar in dialysis patients and healthy volunteers. These data indicate that patients with impaired renal function are not at increased risk of accumulation of lanthanum compared with healthy individuals [51], in that most of an oral dose is excreted unabsorbed in the feces, while the small absorbed fraction is primarily removed by biliary excretion [52].

Data from Phase I studies have also shown that serum levels of lanthanum reach a dose-dependent plateau after 6 weeks of treatment, with a mean maximum serum concentration of just 1 ng/ml [51]. Lanthanum is not metabolized, and, *in vitro*, is not a substrate for or an inhibitor of the major drug-metabolizing enzyme, cytochrome P450. This creates a low potential for drug–drug interactions. Phase I studies using healthy volunteers have shown that the pharmacokinetics of digoxin, warfarin and metoprolol are relatively

unaffected by concomitant dosing with lanthanum carbonate [53]. The lack of drug–drug interactions allows lanthanum carbonate to be coadministered with these agents without the need for dose adjustments or additional precautions.

Clinical efficacy

The efficacy and safety of lanthanum carbonate were first demonstrated in Phase I trials in healthy volunteers. Reduced urinary phosphate excretion – used as an index of gastrointestinal phosphate binding – was observed in individuals who received doses of lanthanum carbonate of up to 4718 mg elemental lanthanum/day [50,54].

An open-label, Phase II, dose-titration trial, involving 59 patients with CRF who were receiving either continuous ambulatory peritoneal dialysis (n = 39), or hemodialysis (n = 20), demonstrated the ability of lanthanum carbonate to effectively reduce serum phosphate levels [55]. In this study, patients were titrated on a weekly basis with an initial total daily dose of 375 mg elemental lanthanum increased up to a maximum of 2250 mg. If the target phosphate levels of 4.0 to 5.6 mg/dl (1.3–1.8 mmol/l) was achieved after the first 375-mg daily dose, dosage was reduced to 250 mg daily after the next visit. Other patients were maintained on the dose that achieved target serum phosphate levels until completion of the 4-week titration period. After treatment with lanthanum carbonate, mean phosphate levels decreased progressively throughout the study to a mean value of 5.5 mg/dl (1.7 mmol/l), a mean reduction from baseline of 1.7 mg/dl (0.54 mmol/l) ($p < 0.05$).

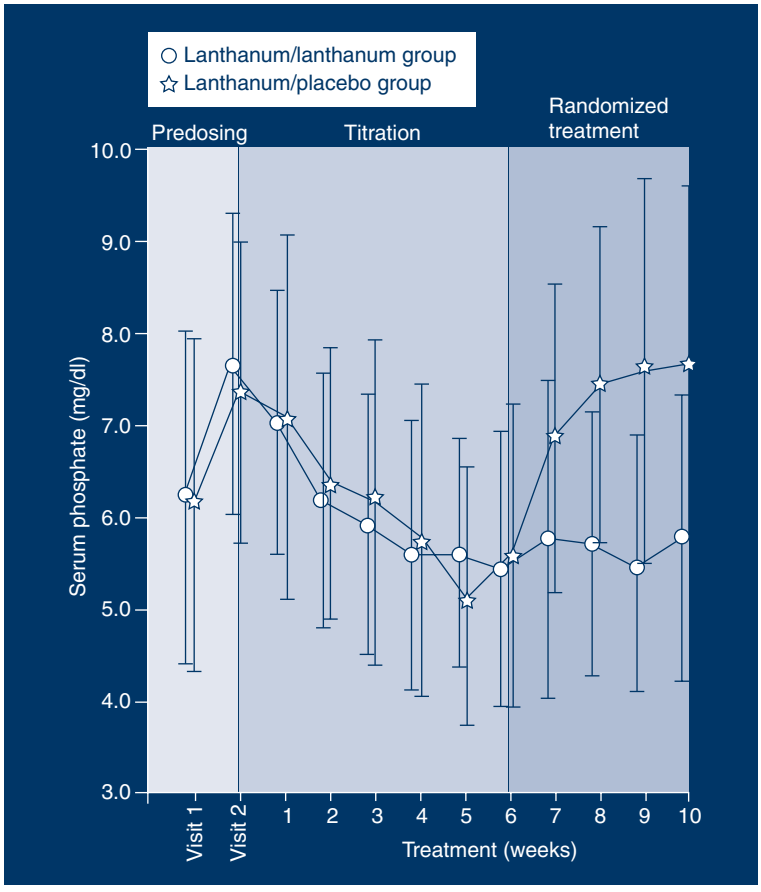
The mean dose of lanthanum at the end of titration was 1278 mg; and at the completion of titration (week 4 of treatment), a serum phosphate concentration of 5.6 mg/dl (1.8 mmol/l) or less was achieved in 35 out of 50 patients (70%). The treatment was effective regardless of which form of dialysis was given.

The efficacy of lanthanum carbonate versus placebo in hemodialysis patients was evaluated in a Phase II, double-blind, dose-ranging study [56], and later in a Phase III double-blind trial. It is important to note that these studies were initiated before the revision of the K/DOQI guidelines, which recommended that serum phosphate concentration should be maintained below 5.5 mg/dl (1.76 mmol/l) [33]. In the Phase II study, after a washout period, 144 patients were randomized to 6 weeks treatment during which they received placebo (n = 32) or treatment with lanthanum carbonate at lanthanum doses of 225 (n = 27), 675 (n = 29), 1350 (n = 30) or 2250 (n = 26) mg/day. A total of 56% of patients were male, the mean age was 56 years, and all had received dialysis for at least 6 months. At randomization, serum phosphate levels were similar in all groups, and after 6 weeks of treatment, serum phosphate levels were controlled to below 5.6 mg/dl (1.79 mmol/l) in 25 of the 56 patients (44.6%) who received the two highest lanthanum doses. After 6 weeks of treatment, phosphate levels were significantly lower in the lanthanum groups receiving 1350 mg/day (mean reductions from baseline of -0.95 ± 1.39 mg/dl), and 2250-mg/day (mean reductions from baseline of -1.13 ± 2,01 mg/dl), compared with the placebo group ($p < 0.001$ vs. placebo) [56]. Significant reductions in phosphate levels versus placebo were seen by the second week of treatment in the lanthanum group receiving 1350 mg/day, and by the first week of treatment in the 2250 mg/day group.

In the Phase III study, after a washout period of 1 to 3 weeks, 126 hemodialysis patients were given increasing doses of lanthanum carbonate, up to a maximum of 3000 mg elemental lanthanum daily, in order to achieve the target serum phosphate level of 5.9 mg/dl (1.89 mmol/l) or lower. After titration, 93 patients were randomized to receive either placebo (n = 44) or lanthanum carbonate (n = 49) for a 4-week, double-blind, maintenance phase. By the end of dose titration, daily dosing was 750 mg/day or less in 11 out of 126 patients (9%), 1500 mg/day in 25 patients (20%), 2250 mg/day in 37 patients (29%) and 3000 mg/day in 53 patients (42%). During dose titration, reduction of serum phosphate was seen within 1 week during dose titration, and was sustained for up to 6 weeks of treatment. At the study end point, the mean difference in serum phosphate between the lanthanum carbonate and placebo treatment arms was 1.91 mg/dl (0.62 mmol/l; $p < 0.0001$; $p < 0.0001$) (**Figure 1**). Mean Ca × P product ($p < 0.0001$) and serum PTH levels ($p < 0.01$) were also significantly lower with lanthanum carbonate versus placebo [57].

Lanthanum carbonate and calcium carbonate have been directly compared in a Phase III study, of 6 months' duration in patients who had received at least 3 months dialysis [58]. This open-label study consisted of a screening and washout phase, a dose-titration phase during which lanthanum carbonate (375–3000 mg/day; n = 510) and calcium carbonate (1500–9000 mg/day; n = 257) were administered, and a maintenance phase. Efficacy data showed that differences in the control of serum phosphate were observed during titration (57.8% in the lanthanum carbonate group versus 70.3% in

Figure 1. Variation in serum phosphate concentrations over the course of a 6-week titration period and a 4-week randomized treatment period.



Lanthanum/placebo patients received lanthanum carbonate during titration and then equivalent placebo tables during randomized treatment (Reproduced with kind permission from *Am. J. Kidney Dis.*).

the calcium carbonate group); however, this was due to patients receiving a low dose of lanthanum carbonate at the start of the titration period (375 mg), compared with the calcium carbonate-treated patients (1500 mg). Control of serum phosphate levels was similar between the two treatment arms during the maintenance phase (65.8 vs. 63.9%, lanthanum carbonate versus calcium carbonate, respectively). Reductions in Ca × P product were generally greater with lanthanum carbonate maintenance treatment than with calcium carbonate. While there were similar reductions in Ca × P product in the titration phase, by the end of the maintenance phase, Ca × P product was reduced to a greater extent in lanthanum carbonate-treated patients. In addition, serum calcium levels were consistently higher in the calcium carbonate group, leading to an observed decrease in PTH levels [58].

Preliminary data from long-term, open-label studies have shown that the control of serum phosphate levels is maintained for up to 2 years, similar to standard therapy (any approved phosphate binder or combination of phosphate binders) [59] with data available from some patients with up to 3 years of lanthanum carbonate exposure [60].

Clinical safety & tolerability

No toxic effects of lanthanum carbonate have been reported in clinical trials to date, confirming the safety profile shown in animal studies [42,55–57,61].

In Phase I trials, healthy volunteers received doses of lanthanum carbonate without serious adverse effects [50]. In short-term trials, lanthanum carbonate has a similar side-effect profile to placebo, with a slightly increased incidence of nausea and vomiting [57].

Treatment is generally well tolerated, with gastrointestinal effects among the most common adverse events. In a double-blind, randomized, placebo-controlled trial in hemodialysis patients, vomiting was reported in 6% of patients receiving lanthanum carbonate versus 2.3% of patients receiving placebo [57]. Nausea, diarrhea and dialysis graft occlusion were also among the most frequently reported events; the incidence of nausea was 6.0 vs. 4.5%, diarrhea was 4.0 vs. 6.8% and dialysis graft occlusion was 6 vs. 2.3% (lanthanum carbonate versus placebo, respectively).

Detectable serum levels of lanthanum have been observed in a small proportion of patients prior to treatment, presumed to be due to exposure to lanthanum in the environment. In clinical trials, mean serum levels were seen to increase slightly by the third week of treatment, or during the titration phase, but remained extremely low (maximum: 0.776 ng/ml), and stabilized or reduced during further treatment [57]. The results suggest that lanthanum levels are not proportional to lanthanum dose [56].

The side-effect profile of lanthanum carbonate has also been shown to be similar to that of calcium carbonate [58]. In the 6-month study of lanthanum carbonate (375–3000 mg/day; n = 510) versus calcium carbonate (1500–9000 mg/day; n = 257), adverse events were generally similar in the two treatment arms, except for hypercalcemia, which occurred more frequently in the group treated with calcium carbonate (20.2 vs. 0.4% in the lanthanum carbonate group) [58].

Safety data from a 2-year comparative study of lanthanum carbonate versus standard therapy (primarily calcium-based phosphate binding agents or sevelamer) have also been presented. This open-label study randomized 1358 hemodialysis patients to treatment with lanthanum carbonate (n = 682) or to treatment with their previous conventional phosphate binders. In the standard therapy group at baseline, approximately 80% of patients were receiving calcium-based therapy, approximately 16% were receiving sevelamer, and approximately 4% were receiving 'other' therapy not otherwise specified. Nausea and vomiting were the most common adverse events in both treatment arms, and the side-effect profiles (corrected for treatment exposure) were similar for lanthanum carbonate and conventional agents, with the exception of greater hypercalcemia in the conventional treatment group (4.3 vs. 8.4%, lanthanum carbonate versus conventional treatment, respectively) [59].

A randomized, open-label, parallel-group study has compared the evolution of renal osteodystrophy in dialysis patients receiving lanthanum carbonate or calcium carbonate [61]. A total of 98 patients were randomized to receive lanthanum carbonate (n = 49) or calcium carbonate (n = 49); bone biopsies were taken at baseline and after 1 year of treatment. Blood samples were also taken at regular intervals and adverse events were monitored. Primary response parameters were mineralization lag time, percentage osteoid surface and volume, percentage osteoblast surface, bone formation rate, percentage osteoclast surface and mean erosion depth. The results indicated that, unlike patients treated with calcium carbonate, dialysis patients treated with lanthanum carbonate showed almost no evolution towards adynamic or low-turnover bone disease during 1 year's treatment, and there was no evidence of any aluminum-like adverse bone effects. Approximately three-quarters of patients in each treatment arm had normal or increased bone turnover at baseline. The latter suggested the presence of hyperparathyroid bone disease (osteitis fibrosa cystica). Development of adynamic bone lesions was seen in only one of 26 patients (4%) receiving lanthanum carbonate but in six of 23 patients (26%) receiving calcium carbonate. Overall, at 1 year, the total number of patients with adynamic bone lesions, osteomalacia, or hyperparathyroid bone disease had decreased from 12 (36%) to six (18%) in the lanthanum carbonate group, but had increased from 13 (43%) to 16 (53%) in the calcium carbonate group [61]. Bone lanthanum levels were also measured in this study; the patients treated with lanthanum carbonate had a median bone concentration of 1.8 μg/ml; the highest value in any patient was 5.5 μg/ml [61]. Assessment of bone lanthanum levels has also been carried out in 11 patients treated with lanthanum carbonate for up to 4.5 years (± 3 months) [62]. The maximum levels observed in any patient was 9.8 μg/g wet weight, and lanthanum treatment was not associated with any mineralization defect [62]. Bone kinetics have also been assessed in detail in a small cohort of patients (n = 10) receiving lanthanum carbonate for up to 4.5 years, and no evidence was found for an imbalance between bone growth and bone resorption over this time period [63]. These results demonstrate that lanthanum carbonate treatment induces a mild hyperparathyroid state and may reduce the risk of adynamic bone lesions in ESRD patients. ESRD patients with bone disease are also at increased risk of calcification, due to an inability to buffer an excess of serum calcium; lanthanum carbonate may therefore provide a treatment option with substantial advantages over calcium-based treatment for these patients.

Preliminary clinical data from dialysis patients treated for up to 3 years indicate that lanthanum carbonate demonstrates good long-term tolerability with a consistent adverse event profile regardless of the length of treatment exposure [60].

The total number of patients who have been exposed to lanthanum carbonate as of November 2004 is 2765. The findings from this extensive clinical trials program indicate that treatment with lanthanum carbonate is well tolerated by healthy subjects and dialysis patients.

Emerging treatment guidelines from official & professional bodies

The Renal Association's Standards Document (2002) states that, 'serum phosphate (measured before a dialysis session in hemodialysis patients) should be below 1.8 mmol/l' [71]. The rationale behind this recommendation is that the rapid rebound of serum phosphate that occurs after dialysis limits the effects of standard hemodialysis on serum phosphate, and therefore it is very difficult to achieve normalization of serum phosphate in patients receiving standard hemodialysis three-times weekly. The standards document also states that the use of phosphate binders (taken with meals) can control hyperphosphatemia in most patients. Further recommendations include that,

'the choice of agents should be individualized as all currently available agents carry different cost–benefit and risk–benefit ratios'. The phosphate-binding agents mentioned are aluminum hydroxide, calcium carbonate, calcium acetate and sevelamer hydrochloride, and the risks associated with the use of calcium and aluminum salts are highlighted by the report.

The recent publication by the National Kidney Foundation (NKF) of the K/DOQI Practice Guidelines has stimulated discussion and controversy among health professionals involved in the care of patients with ESRD [72]. These guidelines state that in a patient with stage 5 chronic kidney disease (CKD), serum phosphate concentration should be between 3.5 and 5.5 mg/dl. This has raised some concern that, although these guidelines are welcome, it may not be possible to achieve and maintain the target values without using newer agents (such as calcimimetic agents and noncalcium-containing phosphate binders), which may have significant cost implications [73,74]. However, a positive view has been voiced from the perspective of nurses and dieticians, presenting the guidelines as an incentive to the whole patient-care team to strive towards these targets as a means of improving patient outcomes [75].

Expert commentary & outlook

The prevalence of ESRD is rising rapidly, particularly in developed countries. The aging profile of the populations in these countries and the increasing prevalence of diseases such as diabetes mellitus mean that the situation is likely to worsen over the next decade and beyond. The burden to the individual, to healthcare systems, and to society as a whole, will increase – in terms of morbidity, mortality and utilization of resources. In the past few years, there has been a growing awareness of the need for high quality outcomes research, to monitor the impact of care of patients with ESRD on clinical events, quality of life, and healthcare costs [76].

Two major initiatives were launched in the late 1990s: K/DOQI, which convened panels of experts to develop evidence-based guidelines for clinical practice; and the Dialysis Outcomes and Practice Patterns Study (DOPPS), which gathers data on practice patterns in dialysis units in 12 countries.

More recently, the Kidney Disease: Improving Global Outcomes (KDIGO) program was established to develop and implement guidelines for clinical practice, making use of the international scope of DOPPS. Together, these important programs will facilitate the development and implementation of evidence-based guidelines, worldwide. It is likely that lanthanum carbonate will play an important role in helping to achieve the goals of these guidelines in patients with ESRD.

The K/DOQI guidelines have defined CKD in five stages using glomerular filtration rates (GFR):

- Stage 1 (GFR: 90 ml/min/1.73 m^2 with kidney damage)
- Stage 2 (GFR: 60–90 ml/min/1.73 m^2)
- Stage 3 (GFR: 30–60 ml/min/1.73 m^2)
- Stage 4 (GFR: 15–30 ml/min/1.73 m^2)
- Stage 5 (GFR > 15 ml/min/1.73 m^2 or on dialysis)

Highlights

- Hyperphosphatemia in end-stage renal disease patients is an important contributor to mortality, and precise, effective control of serum phosphate levels is needed.
- Aluminum-based phosphate binders have been largely replaced by calcium-based binders to avoid aluminum toxicity.
- Calcium-based binders are effective but increase the risk of vascular calcification.
- The polymeric phosphate binder sevelamer can reduce vascular calcification, but poses issues of patient compliance.
- In preclinical studies, lanthanum carbonate showed potent phosphate binding at clinically relevant pH, with almost all the lanthanum phosphate product passed unchanged through the gastrointestinal tract.
- Systemic exposure to lanthanum is limited and noncumulative, and the tiny systemic fraction shows nonrenal elimination.
- In clinical trials, lanthanum carbonate taken with food, was effective in controlling hyperphosphatemia in dialysis patients, with a well-tolerated safety profile. Side effects are largely gastrointestinal in nature and are generally mild to moderate.
- Lanthanum carbonate shows no evidence of osteoblast toxicity.
- Lanthanum carbonate treatment may prove instrumental in achieving the increasingly stringent target serum phosphate levels in patients with end-stage renal disease.

There are nearly 8 million Americans with stage 3 or 4 CKD, and defining optimal treatment for these patients will be an important goal during the next 5 years.

In patients with stage 3 or 4 CKD, abnormalities in calcium and phosphate can be demonstrated, along with deficiency in active vitamin D (1,25-dihydroxyvitamin D; calcitriol) metabolism and early hyperparathyroidism. The presence of risk factors for cardiovascular and progressive kidney disease have been increasingly observed in patients with early disease [77]. When one considers the public health consequences of ESRD, early intervention is important. Defining and optimizing guidelines and treatments for hyperphosphatemic patients with stage 3 or 4 disease (GFR of ~30 ml/min/1.73 m^2) [77] will be a primary goal during the next 5 years. Improved disease management will require meticulous definition of the upper limit of an acceptable phosphate level. Ideally, this should be set no higher that 4.0 mg/dl (rather than the 4.5 mg/dl currently recommended). In fact, in a survey of subjects with varying degrees of CKD, the mean value of the serum phosphate was close to 3.0 mg/dl until the creatinine clearance fell below 50 ml/min [77]. It is known that early dietary phosphate restriction may modify or prevent the rise in PTH levels. Work over the next 5 years should aim to determine if early use of a phosphate binder along with the judicious replacement of vitamin D compounds has a favorable impact on the development of hyperparathyroidism, the presence of metabolic bone disease and the complications associated with cardiovascular disease.

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