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Lanthanum Carbonate

Treatment of Hyperphosphatemia

Fosrenol™
Foznol™ (former)

Carbonic acid lanthanum (3+) salt (3:2)
Lanthanum sesquicarbonate

$La_2(CO_3)_3$

$C_3La_2O_9$
Mol wt: 457.8440
CAS: 000587-26-8
EN: 274887

Introduction

Abstract

Hyperphosphatemia is a complication of end-stage renal disease associated with significant morbidity and mortality due to alterations in bone metabolism and hypercalcemia, which in turn might impair the cardiovascular system. Current therapeutic options for hyperphosphatemia include dietary restrictions and the administration of phosphate binders, compounds that chelate phosphate in food and prevent its absorption in the gastrointestinal tract. Conventional phosphate binders (*e.g.*, aluminum hydroxide, calcium acetate or calcium carbonate) are effective in reducing serum phosphate levels in patients with chronic renal failure, but they are associated with undesirable long-term toxic effects such as dementia or hypercalcemia. Lanthanum carbonate is a non-calcium, non-aluminum phosphate binder that has been shown to be effective in the treatment of hyperphosphatemia. Compared with conventional phosphate binders, lanthanum carbonate is equally effective and better tolerated, as it is not associated with a significant increase in serum calcium levels or any serious adverse events.

Hyperphosphatemia is a condition rarely seen in the general population but very common among patients with end-stage renal disease (ESRD), a condition affecting approximately 650,000 patients worldwide. It has been estimated that up to 70% of ESRD patients also develop hyperphosphatemia, primarily as a result of a reduction in the excretion rate of phosphorus (1). Hyperphosphatemia is associated with significant morbidity and mortality (2). Excessive serum phosphate levels increase the secretion of parathyroid hormone (PTH) and reduce the synthesis of activated vitamin D and the renal reabsorption of calcium and phosphorus, thereby decreasing bone density, inducing osteodystrophy and ultimately increasing the risk for bone fractures. Another long-term complication is soft tissue deposition of calcium, which in the circulatory system may compromise peripheral blood supply, alter the normal cardiac function and increase the risk for cardiovascular death. It has been reported that subjects with serum phosphate levels higher than 6.5 mg/dl had a relative risk of death 1.27 times higher than subjects with lower serum phosphate levels (3).

The management of hyperphosphatemia involves the use of several strategies aimed at achieving an effective control of the patients' phosphate levels and reducing them to predialysis values of 4.5-5.5 mg/dl. These strategies usually include the introduction of dietary restrictions (*i.e.*, limiting the ingestion of food products rich in phosphates), increasing renal excretion (valid only in patients with normal renal function), the use of dialysis, and the oral administration of phosphate binders. Phosphate binders are compounds that interact directly with the phosphate present in food, thus preventing its absorption in the gastrointestinal tract (4).

The first class of phosphate binders to be developed were aluminum salts, which although effective were associated with long-term toxic effects such as dementia and osteomalacia that severely limited their clinical use. Calcium-containing binders, such as calcium acetate or calcium carbonate, also reduce the serum phosphate levels of patients with hyperphosphatemia but are associated with a higher incidence of hypercalcemia and metastatic calcification, together with other problems that result in

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Table I: Compounds for the treatment of hyperphosphatemia (from Prous Science Integrity®).

Compound	Source	Phase
Phosphatonin	Acologic	Preclinical
Lanthanum Carbonate	Shire Laboratories	Preregistered
Sevelamer Hydrochloride	GelTex/Genzyme General	Launched
Cholestimide*	Mitsubishi Pharma	Phase I

*Launched for another indication

a poor compliance rate (3). Concerns regarding the long-term safety of conventional phosphate binders prompted the search for novel compounds which, while retaining the potential for binding to phosphate in food and thus preventing its absorption, would be better tolerated than aluminum or calcium compounds. Research focused on the rare earth element lanthanum (atomic number 57, atomic weight 159), which was known to have a strong affinity for oxygen donor atoms. The combination of lanthanum salts with chemical compounds containing carboxyl and phosphate groups was shown to form lanthanum phosphate, a molecule relatively insoluble in water that does not cross biological membranes easily (3).

Compounds available and under development for the treatment of hyperphosphatemia are shown in Table I.

Pharmacological Actions

The first preclinical evidence of lanthanum salts as potential novel phosphate binders was provided by a study that compared the effects of different oral doses of lanthanum chloride hydrate and aluminum chloride hexahydrate in Wistar rats. Lanthanum chloride was as effective as aluminum chloride in decreasing both plasma levels and urinary excretion of phosphorus while increasing its fecal excretion; neither compound significantly modified calcium levels in plasma (5).

The finding that lanthanum carbonate was less soluble in water than lanthanum chloride resulted in the selection of the former for further preclinical development. Lanthanum carbonate was found to have direct effects on the intestinal absorption of phosphate. Using an isolated rat gut preparation infused with radiolabeled phosphate, researchers found that the administration of 15.6 mg/kg and 31.1 mg/kg of lanthanum carbonate for 3 h reduced phosphate absorption by 23% and 37%, respectively. In contrast, incubation with 1.4 and 4.6 mg/kg of aluminum hydroxide reduced absorption by only 5% and 8%. The mean percentage of radiolabeled phosphate absorbed after incubation for 1 h at all doses was 50.2 ± 13.4% for lanthanum carbonate, 59.6 ± 5.3% for aluminum hydroxide and 77 ± 2.5% for control preparations (6).

Lanthanum carbonate doses of 100-2000 mg/kg/day for 12 weeks induced bone histology changes in male Wistar rats with chronic renal failure after 5/6 nephrectomy. Treatment decreased the rate of bone formation rate and increased the osteoid area, but had no effects in rats with normal renal function (7).

These and other effects on serum and urine markers of phosphate homeostasis were similar to those induced by a low phosphate diet and were prevented by supplementation with inorganic phosphates, therefore suggesting that high doses of lanthanum carbonate resulted in a lower gastrointestinal phosphate intake. In animals with a normal renal function, increasing renal tubular absorption would compensate this reduction. Chronic renal failure leads to hyperparathyroidism, which increases vitamin D clearance and thus renders the rat unable to fully compensate the phosphate deficiency; hence the bone mineralization defects (8).

Pharmacokinetics and Metabolism

A randomized, double-blind, placebo-controlled clinical trial conducted in 14 healthy volunteers who received increasing oral doses of lanthanum carbonate up to 9 mg/day for 5 days estimated that less than 0.001% of the dose was absorbed into the systemic blood circulation. The gastrointestinal absorption rate was slow and peaked at 12 h after administration. The mean serum lanthanum levels remained low throughout the treatment and did not exceed 4.1 ng/g (1). These results were confirmed by another study that randomized 9 healthy subjects to receive either placebo or 1 g of lanthanum carbonate three times daily for 3 days. In this case, no evidence of accumulation of lanthanum carbonate in plasma was found, and the drug's elimination half-life was estimated to be approximately 36 h (9).

Dosage timing had little effect on the pharmacokinetics of lanthanum carbonate in healthy subjects. The Cmax values after receiving 1 g of the compound t.i.d. for 3 days were 0.21 and 0.23 ng/ml during and 30 min after eating, respectively (10).

A phase II, dose-finding clinical trial randomized 145 ESRD patients to receive either placebo or lanthanum carbonate administered with meals at doses ranging from 225-2250 mg/day for 6 weeks. At the end of the treatment, the mean blood lanthanum carbonate levels were 0.10 ng/ml with placebo and 0.23-1.16 ng/ml for patients treated with lanthanum carbonate. Compared to placebo, the incidence of gastrointestinal events (*e.g.*, nausea, vomiting and abdominal pain) increased slightly after treatment with lanthanum carbonate; however, no drug-

related serious adverse events were reported and no significant differencess between groups were found for the number of patients who discontinued the trial due to adverse events, serum parathyroid hormone levels >500 pg/ml or serum phosphate levels >10 mg/dl (11).

In another dose-finding, phase III clinical trial, 126 ESRD patients were first treated with lanthanum carbonate until a serum phosphate level of <5.9 mg/dl was reached, and then they were randomized to receive either placebo or a maintenance dose of the drug for 4 weeks. The serum levels of lanthanum carbonate increased from 0.014-0.030 ng/ml at baseline to 0.346-0.778 ng/ml at the end of the study. The incidence of adverse events was dose-dependent and ranged from 33-67%, although less than 2% of these were considered to be drug-related (12).

More recently, an open-label study compared the tolerability and pharmacokinetics of lanthanum carbonate in 10 chronic renal failure patients requiring hemodialysis and 8 healthy individuals. All subjects participating in the study received two single doses of 1 g of lanthanum carbonate separated by a period of 2 weeks, and then 1 g three times daily for 11 days. In chronic renal failure patients, both the C_{max} and the area under the curve values for the drug were lower before dialysis than after dialysis (0.559 *vs.* 0.296 ng·h/ml, and 6.361 *vs.* 3.099 ng·h/ml, respectively). These results suggested that hemodialysis might affect the pharmacokinetic parameters of lanthanum carbonate. The incidence of adverse events was also higher among patients with chronic renal failure compared to healthy volunteers, but the authors suggested that this difference might be derived from the poorer health status of these patients (13).

The potential interaction of lanthanum carbonate with other drugs was the subject of two open-label, crossover studies in healthy volunteers. In one of these studies, 14 subjects received either digoxin 0.5 mg alone or 30 min after 4 oral doses of 1 g of lanthanum carbonate three times daily. The addition of lanthanum carbonate had no significant effects on the C_{max} or the area under the curve for digoxin and only slightly increased the latter's serum half-life; however, the differences were not considered to be clinically relevant. A similar study in 14 healthy volunteers randomized to receive a single dose of 10 mg of warfarin alone or combined with 4 doses of 1 g three times daily of lanthanum carbonate reported no significant pharmacokinetic interactions between these two drugs. Neither study found significant changes in the safety profile of lanthanum carbonate when combined with digoxin or warfarin (14, 15).

Clinical Studies

The phosphate binding capacity of lanthanum carbonate was first assessed in healthy subjects using phosphate urine excretion as a surrogate marker of phosphate absorption in the gastrointestinal tract, based on the assumption that the kidneys would maintain controlled serum phosphate levels. These preliminary studies reported that lanthanum carbonate dose-dependently decreased urine phosphate excretion to one-third of the value found with placebo after treatment with 9.0 g/day for 3 days or 3.0 g for 5 days (1, 9).

A double-blind, randomized, placebo-controlled clinical trial assessed the efficacy and safety of lanthanum carbonate in 34 hemodialysis patients. When administered at daily doses of 125-750 mg t.i.d., the drug reduced the mean serum phosphate levels of the patients from 2.24 to 1.70 mmol/l (16). Additional information on the pattern of reduction of serum phosphate levels induced by oral lanthanum carbonate was provided by another dose-finding clinical trial. A total of 145 hemodialysis patients aged >18 years and with serum phosphate levels of 5.6 mg/dl or more received either placebo or lanthanum carbonate at daily doses of 225, 675, 1350 or 2250 mg, divided with meals. After 6 weeks of treatment, the drug had induced dose-dependent reductions in the serum phosphate levels of the patients, which reached statistical significance in those patients receiving the two highest doses (17). The results of these studies and some that follow are summarized in Table II.

Two multicenter, open-label, comparative, randomized clinical trials compared the long-term efficacy of lanthanum carbonate with that of conventional phosphate binders in hemodialysis patients with hyperphosphatemia. The percentage of patients who showed controlled serum phosphate levels was similar after receiving daily lanthanum carbonate doses of 375-3000 mg than after being treated with conventional phosphate binders for 6 months (65.8% *vs.* 63.9%, respectively) or 2 years (43-48% in each group). The drug was associated with a lower incidence of hypercalcemia (defined as serum calcium levels >2.6 mmol/l) compared to calcium carbonate. Gastrointestinal adverse events were also the effects most commonly reported after treatment for up to 2 years with lanthanum carbonate. The overall incidence of adverse events was approximately 6% higher with conventional phosphate binders, but this difference might be explained at least in part by the fact that patients treated with conventional therapies also tended to remain in the study for longer periods of time, therefore increasing the period of time during which an adverse event might appear. Conventional therapies were also associated with a higher incidence of serious adverse events (65.4% *vs.* 51.0%) and a significantly higher mortality rate (6.0% *vs.* 2.6%) (18, 19).

The effects of lanthanum carbonate were also determined in patients with ESRD and renal osteodystrophy. An open-label study randomized 98 patients to receive either lanthanum carbonate (maximum dose of 3750 mg/day) or calcium carbonate (maximum calcium dose of 9 g/day) for 50 weeks. Both treatments were well tolerated and effective in controlling serum phosphate levels and improving bone histology parameters. Additional studies established that lanthanum carbonate was associated with a lower incidence of hypercalcemia in patients with ESRD compared to conventional phosphate binders (20-22).

In April 2002, Shire Pharmaceuticals submitted an NDA for lanthanum carbonate under the brand name

Table II: Clinical studies of lanthanum carbonate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Open, crossover	Lanthanum carbonate, 1 g p.o. t.i.d. x 3 d [with food] Lanthanum carbonate, 1 g p.o. t.i.d. x 3 d [30 min after meal]	36	Lanthanum carbonate was well tolerated and showed a good safety profile when administered both while eating and 30 min afterwards	9
Chronic renal failure	Randomized, double-blind	Lanthanum carbonate, 225 mg/d x 6 wk Lanthanum carbonate, 675 mg/d x 6 wk Lanthanum carbonate, 1350 mg/d x 6 wk Lanthanum carbonate, 2250 mg/d x 6 wk Placebo	145	Lanthanum carbonate was as well tolerated as placebo and caused no serious adverse events in patients with end-stage renal disease	11
Hemodialysis, chronic renal failure	Open	Lanthanum carbonate, 1 g po od on d 1 and 14 → 1 g po tid x 11 d [on d 17-26] → 1 g po sd [on d 28]	18	Lanthanum carbonate was well tolerated in healthy volunteers and in hemodialysis patients with chronic renal failure	13
Hemodialysis, chronic renal failure	Randomized, double-blind	Lanthanum carbonate, 125 mg [up to a max/d 2250 mg over 4 wk] po tid x 8 wk Lanthanum carbonate, 125 mg [up to a max/d 2250 mg over 4 wk] po tid x 8 wk	34	Lanthanum carbonate was well tolerated and effectively reduced the serum levels of phosphate in dialysis patients	16
Hemodialysis, chronic renal failure	Randomized, double-blind	Lanthanum carbonate, 225 mg/d po x 6 wk Lanthanum carbonate, 675 mg/d po x 6 wk Lanthanum carbonate, 1350 mg/d po x 6 wk Lanthanum carbonate, 2250 mg/d po x 6 wk Placebo	196	Lanthanum carbonate was safe and effective in the treatment of hyperphosphatemia secondary to end-stage renal disease	17
Chonic renal failure	Randomized, open, multicenter	Lanthanum carbonate, 375-3000 mg/d po x 5 wk → Maintenance dose x 20 wk (n=533) Calcium carbonate, 1500-9000 mg/d po x 5 wk → Maintenance dose x 20 wk (n=267)	800	Lanthanum carbonate was better tolerated and as effective as calcium carbonate in controlling serum phosphate levels in patients with hyperphosphatemia secondary to end-stage renal disease	18
Hemodialysis, chronic renal failure	Open	Lanthanum carbonate, 375-3000 g/day po x 6 wk → Maintenance dose x 2 y (n=632) Standard therapy (n=633)	1228	Lanthanum carbonate was well tolerated and as effective as standard therapy in reducing serum phosphate levels in patients with hyperphosphatemia secondary to chronic renal failure	19
Chronic renal failure	Open	Lanthanum carbonate, 3.75 g/d x 50 wk Calcium carbonate, 9 g/d x 50 wk	98	Lanthanum carbonate was as effective as calcium carbonate in improving the osteodystrophy symptoms found in patients with end-stage renal disease, but was associated with a lower incidence of hypercalcemia	20
Hemodialysis, renal failure		Lanthanum carbonate, 3750 [max] mg/d po x 1 y (n=10) Calcium carbonate, 9000 [max] mg/d po x 1 y (n=10)	20	Lanthanum carbonate was well tolerated and as effective as calcium carbonate in reducing serum phosphate levels in dialysis patients	21
Hemodialysis	Randomized	Lanthanum carbonate, titrated over 6 wk until PO4 <5.9 mg/dl → maintenance dose x 4 wk Lanthanum carbonate, titrated over 6 wk until PO4 <5.9 mg/dl → Placebo	126	Lanthanum carbonate was well tolerated and effective in patients on chronic hemodialysis, reducing the PO4xCa product and PTH without causing hypercalcemia	22

Foznol™ (later changed to Fosrenol™) in the treatment of secondary hyperphosphatemia in hemodialysis patients with chronic renal failure. The product is also being evaluated for approval by the regulatory authorities of Canada and the European Union. In March 2003, Shire Pharmaceuticals received an approvable letter issued by the FDA requesting additional information on Fosrenol™, and the company expects to be able to launch the product in the U.S. before the end of 2003 (23-27).

Source

Shire Pharmaceutical Group plc (GB); licensed from AnorMED Inc. (CA).

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