Improving phosphate-binder therapy as a way forward

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Abstract
Aluminium- or calcium-based phosphate-binding agents traditionally have been used to treat hyperphosphataemia in patients with end-stage renal disease. Although these agents effectively lower serum phosphorus levels, they are associated with serious side effects. Aluminium-based agents are associated with bone toxicity, renal osteodystrophy and encephalopathy, and calcium-based agents increase the risk of hypercalcaemia and cardiovascular calcification. Consequently, there remains a need for new, safe and effective non-calcium-, non-aluminium-based alternative treatments. Fortunately, several new agents are now available or are in the late stages of development, including sevelamer hydrochloride and lanthanum carbonate. Although sevelamer hydrochloride represents a step forward in the management of hyperphosphataemia, it has several drawbacks and is far from being the ideal phosphate binder. Lanthanum carbonate is the most recent non-calcium, non-aluminium phosphate binder to be developed for the treatment of hyperphosphataemia. Animal studies have shown it to be as effective as aluminium, without the associated toxicity. In clinical studies, lanthanum carbonate significantly reduced serum phosphorus levels, compared with placebo. It shows a similar efficacy to calcium carbonate in controlling serum phosphorus levels, but requires lower doses. In addition, lanthanum carbonate is at least as well tolerated as calcium carbonate, but is not associated with hypercalcaemia. Importantly, it has a positive effect on bone histology, with no evolution towards low bone turnover. Lanthanum carbonate, therefore, moves closer to the ideal phosphate binder.

Keywords: calcium carbonate; end-stage renal failure; hypercalcaemia; hyperphosphataemia; lanthanum carbonate; non-calcium, non-aluminium phosphate binders

Introduction
Approximately 70% of patients with end-stage renal disease (ESRD) have hyperphosphataemia, which, if left untreated, is associated with renal osteodystrophy (ROD), metastatic calcification and increased mortality [1,2]. Despite dialysis and dietary control of phosphate, most of these patients will require a phosphate-binding drug to treat the condition. Traditionally, calcium- and aluminium-based phosphate binders have been used for the treatment of hyperphosphataemia. These conventional phosphate binders, however, are far from ideal; long-term use of these agents is associated with a number of serious side effects.

Aluminium hydroxide is a highly effective phosphate binder, which is as yet unparalleled in terms of efficacy. It became the treatment of choice for hyperphosphataemia in patients with ESRD and remained so for many years, after it was demonstrated to be more effective than calcium-based agents [3], despite some early warning signs [4].

Unfortunately, aluminium accumulates in the tissues of patients with ESRD, largely because of the decline in renal function, the main route of aluminium excretion. Extensive aluminium accumulation is now known to have harmful effects on bone, the brain and the haematopoietic system, leading to serious side effects including ROD (i.e. osteomalacia) and encephalopathy [5–7]. Despite its superior efficacy, its toxicity has severely restricted its use.

In the absence of any alternative treatment, calcium-based agents (calcium carbonate and calcium acetate) became the mainstay for the treatment of hyperphosphataemia in patients with ESRD from the mid 1980s. Although calcium has been shown to be effective at lowering serum phosphorus levels without the negative effects associated with aluminium [8–11], it also has major drawbacks. Calcium-based drugs lack the potency of aluminium and are associated with hypercalcaemia. The increased calcium load resulting from the long-term use of calcium may promote calcification and adynamic bone disease [12–14].

There remains, therefore, a need to develop new, safe and effective non-calcium, non-aluminium drug...
alternatives that provide more normal phosphorus control without severe toxicity. Ideally, a new phosphate binder should be as effective as aluminium without the aluminium-associated toxic effects, possess a favourable safety profile, not cause hypercalcaemia and have a positive effect on bone histology. Such agents would be of enormous benefit in the management of ROD, and may lead to a reduction in cardiovascular risk in patients with ESRD.

Non-calcium-, non-aluminium-based phosphate binders—the way forward

Promising new non-calcium-, non-aluminium-based phosphate binders are available or are in development that may offer effective alternatives to the conventional phosphate binders. These include sevelamer hydrochloride and lanthanum carbonate.

Sevelamer hydrochloride

Sevelamer hydrochloride is the first synthetic non-calcium, non-aluminium phosphate binder to become widely available in the USA and Europe for the treatment of hyperphosphataemia in patients with ESRD. Clinical studies have shown that sevelamer hydrochloride is as effective as calcium-based agents at reducing serum phosphorus levels [15,16]. The potency of sevelamer, however, is low compared with aluminium [17]. Significantly, evidence suggests that sevelamer hydrochloride can protect against calcification, compared with calcium-based agents [18]. These findings suggest that the risk of cardiovascular morbidity in patients with ESRD can be reduced if serum phosphorus can be effectively controlled with a non-calcium-based therapy. Whether this has an effect on reducing mortality is not clear.

Although sevelamer hydrochloride represents a major advance in the management of hyperphosphataemia, it is not ideal and has a number of drawbacks. The inconvenient pill burden, large pill size and formulation may impact on compliance. In addition, the phosphate-binding capacity of sevelamer hydrochloride is reduced at lower pH, and this may explain the low potency, compared with aluminium [19]. Optimal phosphate binding for sevelamer hydrochloride occurs at pH 7, whereas the pH is much lower than this in the stomach and first part of the duodenum.

Another potential disadvantage is that preclinical studies suggest that sevelamer hydrochloride at high doses may reduce the absorption of fat-soluble vitamins, such as vitamin D, from the gastrointestinal tract [20]. Thus, there is concern that high doses of sevelamer hydrochloride may affect vitamin D treatments. However, it has yet to be shown whether sevelamer hydrochloride has any effects on vitamin absorption in clinical practice.

Sevelamer hydrochloride has been shown to reduce bicarbonate levels, most probably because of its hydrochloride content [21]. Although the clinical relevance of this remains debatable, recommendations have been made to monitor bicarbonate levels closely during treatment with sevelamer hydrochloride [21].

Lanthanum carbonate

Lanthanum carbonate is the most recent non-calcium, non-aluminium phosphate binder to be developed for the treatment of hyperphosphataemia. In preclinical studies, lanthanum carbonate has been shown to be as effective as aluminium in binding phosphate (Figure 1) [21], but without the associated toxic effects. It binds phosphate optimally at pH 3–5, while retaining binding activity at pH 1–7 [22]. Lanthanum carbonate is, therefore, able to bind phosphate efficiently at the low

![Fig. 1. Phosphate-binding capacity of lanthanum carbonate vs other phosphate binders in 5/6th nephrectomized rats.](image-url)
pH of the stomach as well as at the higher values in the duodenum and jejunum. Lanthanum carbonate also has no effect on the absorption of fat-soluble vitamins.

Lanthanum carbonate has a low potential for accumulation compared with aluminium, with only 0.00005% of an oral dose being absorbed in the canine gastrointestinal tract (Shire Pharmaceuticals Group, data on file) vs 0.05–0.1% for aluminium [23]. Most importantly, there is minimal tissue accumulation. For example, in multi-dose studies in uraemic rats, accumulation of lanthanum carbonate (3 μg/kg at a dose of 2 g/kg) in bone was low, compared with aluminium (30 μg/kg at a dose of 0.6 g/kg) (Shire Pharmaceutical Development, data on file). This is hypothesized to be largely due to the different routes of elimination for aluminium and lanthanum. Unlike aluminium, lanthanum is eliminated primarily by the liver and not the kidneys, with ~80% of absorbed lanthanum being eliminated in the bile and 13% directly across the gut wall [24]. In rats, the majority of an oral dose is excreted in the faeces (99.3%), while urinary excretion accounts for only 0.004% [25]. In man, urinary excretion in healthy individuals represents only 0.000031% of the administered dose [26].

The results of preclinical studies have shown lanthanum carbonate to possess the properties of an effective phosphate binder. As a result, the efficacy and safety of lanthanum carbonate have been investigated extensively in phase II and phase III clinical trials. Currently, 19 clinical studies have been completed involving >2500 patients and healthy volunteers. More than 500 patients with ESRD have received lanthanum carbonate treatment for at least 12 months.

**Phase II studies.** Two double-blind, placebo-controlled phase II studies have been conducted to establish the effective dose and to assess the efficacy of lanthanum carbonate vs placebo, in patients with ESRD (Table 1) [27,28]. Statistically significant decreases in serum phosphorus levels were observed in patients receiving lanthanum carbonate at doses of 1350 mg/day or higher, compared with placebo (Figure 2). Doses of between 1350 and 2250 mg/day were effective in reducing and maintaining phosphorus levels in the majority of patients. Serum phosphorus levels decreased more quickly with lanthanum, 2250 mg/day, and maximal decreases occurred after 3 weeks of treatment and were maintained over the 4–6 week treatment periods. Overall, mean serum calcium levels remained unchanged in both groups, but the calcium × phosphorus (Ca × P) product was significantly higher in the placebo group owing to uncontrolled serum phosphorus levels.

**Phase III studies.** Two pivotal phase III studies have been 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 consisting of three parts [29]. Part 1 was a 3-week, washout period (n = 163). Part 2 was a 6-week, open-label, dose titration period (n = 126). During this period, patients received lanthanum carbonate, 750 mg/day, titrated up or down

![Fig. 2. Mean serum phosphorus levels in patients receiving lanthanum carbonate, >1350 mg/day, compared with placebo. Reproduced from Joy and Finn [29], with permission from the National Kidney Foundation © 2003.](image-url)
to 375, 750, 1500, 2250 or 3000 mg/day in order to reduce serum phosphorus to ≤1.9 mmol/l (≤5.9 mg/dl). Part 3 was a 4-week, double-blind, maintenance period (n = 94) when patients were randomized to receive lanthanum carbonate (n = 50) or placebo (n = 44). The primary efficacy parameter was the ability to maintain control of the serum phosphorus level [≤1.9 mmol/l (≤5.9 mg/dl)].

At study end-point, there was a highly significant difference in mean serum phosphorus levels between the lanthanum carbonate and placebo groups (intention-to-treat, 5.94 mg/dl vs 7.85 mg/dl, respectively; drug-placebo treatment difference, 1.91 mg/dl; P < 0.0001). Serum phosphorus levels were controlled at ≤5.9 mg/dl in 59% of patients receiving lanthanum carbonate, compared with 23% in the placebo group (Figure 3). Of those patients whose serum phosphorus levels were controlled at the time of entering the maintenance phase, 66% of lanthanum carbonate-treated patients and 31% of placebo-treated patients maintained control at study end-point. Ca × P product (52.37 ± 14.89 vs 66.59 ± 18.30 mg²/dl²; P < 0.0001) and serum parathyroid hormone (PTH) levels (209.41 ± 152.65 vs 291.80 ± 194.82 pg/ml; P < 0.01) were also significantly lower with lanthanum carbonate vs placebo. The incidence of drug-related adverse events was similar between placebo- and lanthanum carbonate-treated patients.

The second study (Study 301) was a prospective, randomized, multicentre, open-label, comparator study divided into five parts (Figure 4) [27,30]. After 1–3 weeks of washout, patients with hyperphosphataemia [serum phosphorus > 1.80 mmol/l (5.58 mg/dl)] were randomized to 5 weeks of dose titration with lanthanum carbonate (lanthanum dose, 375–3000 mg/day) or calcium carbonate (calcium dose, 1500–9000 mg/day), followed by a 20-week maintenance period. The primary efficacy parameter was reduction of serum phosphorus levels to ≤1.8 mmol/l (≤5.6 mg/dl). The secondary efficacy parameter was the maintenance of control at ≤1.8 mmol/l for 6 months or longer. PTH, calcium and Ca × P product levels were also monitored throughout the study.

In total, 800 haemodialysis patients received treatment in the 6-month comparator phase. After 9 weeks of treatment, both groups had serum phosphorus levels of 1.69 mmol/l (Figure 5). In lanthanum

Fig. 3. Proportion of patients with phosphorus control in Study 302. Reproduced from Joy and Finn [29], with permission from the National Kidney Foundation © 2003.

Fig. 4. Design of Study 301.
carbonate-treated patients, 67.9% of patients showed controlled serum phosphorus levels, compared with 65.8% of patients in the calcium carbonate group. At the end of the 6-month maintenance period, there was no significant difference in the proportions of patients with controlled phosphorus levels (65.8% vs 63.9% in the lanthanum carbonate and calcium carbonate groups, respectively). At the end of the maintenance phase, reductions in Ca × P product were generally greater with lanthanum carbonate maintenance treatment than with calcium carbonate (−1.59 vs −1.26 mmol²/l²). The median serum PTH level decreased by ~5% during 5 months of maintenance treatment with lanthanum carbonate, and increased by ~15% with calcium carbonate (Table 2). Lanthanum carbonate was well tolerated and resulted in fewer episodes of hypercalcaemia than calcium carbonate. A greater incidence of hypercalcaemia was reported as an adverse event in patients treated with calcium carbonate (20.2%) than in those treated with lanthanum carbonate (0.4%).

During part 4 of the study, when all of the patients were switched to lanthanum treatment, serum phosphorus continued to be controlled in ~60% of patients (≤1.8 mmol/l). However, the mean serum calcium levels in patients treated with calcium carbonate in part 3 declined to those observed at screening. In addition, recent data on part 5 of the study have demonstrated that lanthanum carbonate maintains efficacy and has a good safety profile over a period of 3 years of treatment (Shire Pharmaceutical Group, data on file).

**Lanthanum carbonate—effects on bone**

In a large-scale, open-label study, the comparative long-term effects of lanthanum carbonate and calcium carbonate on the development of ROD were evaluated in ESRD patients undergoing dialysis. At baseline, 98% (48/49) of patients in each group had ROD. ROD subtypes were distributed similarly in both groups, with mixed ROD being the most common. After 1 year of treatment, of the patients with low bone turnover (adynamic bone disease or osteomalacia) at baseline, a greater proportion in the lanthanum carbonate group approached normalization, compared with those in the calcium carbonate group (71% vs 42%, respectively). Only one (4%) lanthanum carbonate-treated patient evolved towards adynamic bone, compared with six (26%) patients in the calcium carbonate group. Lanthanum carbonate was well tolerated, and serum phosphorus levels were well controlled (≤1.8 mmol/l) with both lanthanum carbonate and calcium carbonate. The incidence of hypercalcaemia was lower with lanthanum carbonate, compared with calcium carbonate (6% vs 48%, respectively).

**Conclusions**

Conventionally, hyperphosphataemia has usually been treated using aluminium- or calcium-based phosphate-binding agents. Although these agents are effective, they are associated with serious side effects. Aluminium-based agents are associated with bone and central nervous system toxicity, and calcium-based agents increase the risk of hypercalcaemia and cardiovascular calcification. As a consequence, there is a need for new, safe and effective non-calcium, non-aluminium drug alternatives that provide more normal phosphorus control without severe toxicity. Several new agents are available or are in development, including sevelamer

![Fig. 5. Mean serum phosphorus levels during titration and maintenance treatment (intention-to-treat) in Study 301.](image)

**Table 2. Serum PTH levels (ng/l) at screening and at the end of each treatment period in a randomized, open-label comparator study of lanthanum carbonate vs calcium carbonate**

<table>
<thead>
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<th>Screening</th>
<th>End of titration</th>
<th>End of maintenance</th>
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<tr>
<td><strong>Lanthanum carbonate</strong></td>
<td>507</td>
<td>449</td>
<td>226</td>
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<tr>
<td>n</td>
<td>218</td>
<td>257</td>
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<tr>
<td>Mean</td>
<td>244</td>
<td>268</td>
<td>240</td>
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<tr>
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<tr>
<td><strong>Calcium carbonate</strong></td>
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hydrochloride and lanthanum carbonate. Although sevelamer hydrochloride represents a step forward in the management of hyperphosphatemia, it has several drawbacks and is not the ideal phosphate binder.

Lanthanum carbonate is the most recent non-calcium, non-aluminium phosphate binder to be developed for the treatment of hyperphosphatemia and shows great promise. Preclinical studies have shown that it is as effective as aluminium, without the associated toxicity, and is minimally absorbed. In clinical studies, lanthanum carbonate has been shown to reduce serum phosphorus levels significantly, compared with placebo. It has a similar ability to calcium carbonate in controlling serum phosphorus levels, but at lower doses. In addition, lanthanum carbonate is at least as well tolerated as calcium carbonate, but is not associated with hypercalcaemia. Importantly, lanthanum carbonate seems to have a positive effect on bone histology, avoiding the evolution towards low bone turnover that is seen in calcium carbonate-treated dialysis patients. Lanthanum carbonate, therefore, represents a step closer to the ideal phosphate binder.

References

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