Reducing high phosphate levels in patients with chronic renal failure undergoing dialysis: a 4-week, dose-finding, open-label study with lanthanum carbonate

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Abstract

Background. The majority of patients with end-stage renal disease on dialysis are hyperphosphataemic. Lanthanum carbonate has been shown to be a highly effective phosphate binder in pre-clinical studies. A 4-week, open-label, dose-titration trial was conducted to assess the ability of lanthanum carbonate to control phosphate levels in patients with chronic renal failure.

Methods. This preliminary study was of 6 weeks duration: 2 weeks of washout followed by 4 weeks of dose titration. Patients (n = 59) were titrated on the basis of weekly serum phosphate levels from a daily dose of 375 mg lanthanum carbonate to a maximum dose of 2250 mg. Patients were maintained on the dose that controlled serum phosphate to between 1.30 and 1.80 mmol/l (4.03–5.58 mg/dl). Serum phosphate levels represented the main efficacy assessment. Safety was also evaluated.

Results. Most patients were successfully titrated to 1500 and 2250 mg lanthanum/day (mean dose at end of titration: 1278 mg). At completion of the study 70% of patients achieved a serum phosphate of ≤1.80 mmol/l. The use of lanthanum carbonate in patients undergoing continuous ambulatory peritoneal dialysis or haemodialysis was generally well tolerated.

Conclusions. Lanthanum carbonate, a new non-aluminium, non-calcium phosphate binder, effectively reduces serum phosphate levels. Results of longer-term efficacy and safety studies are awaited with interest.

Keywords: chronic renal failure; dialysis; dose titration; hyperphosphataemia; lanthanum carbonate; phosphate

Introduction

Hyperphosphataemia is an almost universal complication in patients with end-stage renal disease undergoing dialysis. It is now known to be associated with development of hyperparathyroidism, renal osteodystrophy and increased morbidity and mortality [1], and so active management is being given a higher priority. High serum phosphate levels have traditionally been controlled by the administration of either aluminium- or calcium-based phosphate-binding agents [2]. There have been a number of safety concerns, however, associated with the use of these conventional phosphate binders. The use of aluminium phosphate binders in patients with impaired renal function is associated with well-documented toxicity [3], and calcium salts, particularly if given with inappropriate calcitriol treatment, can give rise to hypercalcaemia and potentially lead to metastatic calcification [4,5].

The problems associated with the use of aluminium- and calcium-based agents have prompted research into reduction of dialysis fluid calcium levels [6] and alternative phosphate binders not containing aluminium or calcium. Sevelamer hydrochloride is the first alternative binder to become available. It does not appear to have the toxic effects of aluminium, nor is it associated with hypercalcaemia, and has been a positive step forward in this therapy area. However, there are some concerns that treatment with sevelamer may reduce bicarbonate levels, thus promoting acidosis [7].

Lanthanum carbonate (Fosrenol®, Shire Pharmaceutical Development, UK), a rare earth salt, has been shown to be a highly effective phosphate binder during in vitro studies. Pre-clinical and clinical data suggest that lanthanum carbonate is an effective phosphate binder with very low toxicity, minimal systemic absorption and a good safety profile [8–11].

In the first part of a dose-finding study, we investigated the ability of lanthanum carbonate to
control serum phosphate levels in patients receiving continuous ambulatory peritoneal dialysis (CAPD) or haemodialysis. During this time, we also evaluated safety and tolerability in these patients.

**Subjects and methods**

**Study population**

Patients were considered suitable for inclusion if they had received either CAPD or haemodialysis for chronic renal failure for at least 6 months (including patients who had previously undergone renal transplantation) and had serum phosphate levels consistently above 1.80 mmol/l (5.58 mg/dl) following washout of previous phosphate binders. Patients were excluded from the study if they did not respond to phosphate binders, were known to be non-compliant with oral medication, or if they had any medical condition or abnormal biochemistry (in particular severe hyperparathyroidism [parathyroid hormone (PTH) levels >500 ng/l]) that would interfere with the study results.

All but one patient were receiving calcium-based phosphate binders at screening (mean dose, 1.9 g) with Calcichew (calcium carbonate) the most frequently used product. The patient not on calcium-based treatment was not receiving any phosphate binder. Sixteen patients (27%) were receiving calcidiol and five (8%) were receiving calcitriol at the start of the study (typical dose, 1–4 μg/week).

**Study design**

The study reported here formed the first part of a longer dose-finding study. After patient screening, there was a 2-week washout period from previous phosphate binders, followed by a 4-week open-label titration period with lanthanum carbonate. At visit 1 (end of washout period/beginning of titration), the laboratory results from the screening visit were reviewed to ensure eligibility was maintained. A blood sample was taken for biochemical evaluation including phosphate and lanthanum levels. A 24-h urine sample was collected for determination of creatinine clearance. Throughout the study, patients returned for weekly visits and any change in their status was assessed. Table 1 indicates the schedule of the main study assessments. Standard practice for haemodialysis patients in the investigational centres was to take blood samples before dialysis and after the longest interdialytic period. At each visit during titration, serum phosphate results were reviewed and the dose of lanthanum altered as necessary (see below).

Patients who were receiving vitamin D treatments at screening were allowed to continue receiving them. However, initiation or dose alteration of such treatment was not permitted during the study because of its effects on serum phosphate and calcium levels.

**Dose titration**

Patients were titrated on a weekly basis, from a total daily dose of 375 mg lanthanum up to a maximum of 2250 mg. The aim was to achieve phosphate levels of 1.30–1.80 mmol/l (4.03–5.58 mg/dl). If serum phosphate levels were within this range or below 1.30 mmol/l after the first dose, it was possible to titrate down to 250 mg daily at subsequent visits. Patients were maintained on the dose that achieved target serum phosphate levels until completion of the titration period. Lanthanum carbonate was supplied as chewable tablets containing 125 or 250 mg of lanthanum, and patients were instructed to take the treatment in equally divided doses at meal times.

**Efficacy and safety variables**

Efficacy was assessed based on the achievement of phosphate levels ≤1.80 mmol/l. Other efficacy evaluations included measuring serum calcium and PTH. Safety evaluations included monitoring of adverse events, vital signs, laboratory evaluations and lanthanum levels. The final dose of lanthanum that each patient was taking at the end of the titration was recorded. Serum phosphate, calcium and plasma lanthanum levels were recorded at each visit. For the analysis of lanthanum levels, the limit of detection was 0.5 ng/g. PTH levels were recorded at screening, and at visits 3 and 5.

**Statistical analysis**

All data from the titration phase of the study were summarized for those patients who received study treatment. Biochemical data are given for all patients who were still in the study at the particular time point. Measurements of plasma lanthanum below the limit of detection were given the value 0.5 ng/g. Values are presented as means with confidence

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**Table 1. Schedule of main study procedures**

<table>
<thead>
<tr>
<th>Visit number</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Washout</td>
<td></td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titrationb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Full blood profile
- Interim blood profile
- Lanthanum levels
- Vital signs
- Adverse events

|   |   |   |   |   |
|---|---|---|---|
|   |   |   |   |

|   |   |   |   |   |
|---|---|---|---|
|   |   |   |   |

aWashout period was 2 weeks.
bTitration with lanthanum carbonate occurred over 4 weeks, with patients visiting on a weekly basis.
cOnly some of the patients had lanthanum levels assessed at these time points (10 at visit 3 and 11 at visit 5).
Results

Patients

In total, 59 patients (40 men, 19 women; mean age 54.7 ± 16.1 years) entered the titration phase. Of these, 66% (n = 39) were receiving CAPD and 34% (n = 20) were receiving haemodialysis. In total, 56 patients completed 1 week of treatment, 54 completed 2 weeks, 51 completed 3 weeks and 50 patients completed the titration period. Three patients withdrew as a result of adverse events and another two patients were requested to withdraw and did so because of adverse events. The remaining patients were withdrawn as a result of protocol violation (n = 1), high phosphate levels (> 3.0 mmol/l (9.3 mg/dl)) (n = 1), high PTH levels (> 500 ng/l) (n = 1) or a request to withdraw from the study (n = 1).

Dose of lanthanum

The majority of patients were titrated up from 375 mg lanthanum/day (Figure 1). Most patients were successfully titrated to either 1500 mg (22 patients) or 2250 mg (11 patients) lanthanum/day.

Control of serum phosphate

Mean serum phosphate increased from 1.80 mmol/l at screening to 2.26 mmol/l at visit 1 (Table 2) as the original phosphate binder was stopped. With the introduction of lanthanum carbonate, mean phosphate levels then decreased progressively over the study period to a mean value of 1.70 mmol/l at the end of the study (P < 0.05; Figure 2, Table 2). The mean reduction from visit 1 to visit 5 was −0.52 mmol/l (P < 0.05). The proportion of patients with serum phosphate ≤1.80 mmol/l increased from 7% at visit 1 (end of washout) to 70% (35/50) at visit 5 (end of titration). In five patients (14%) serum phosphate levels fell below 1.30 mmol/l.

Control of serum calcium and PTH

Mean levels of serum calcium did not change during the titration phase (Figure 3, Table 2). There were no clinically or statistically significant changes in PTH (Table 3).

Safety evaluation

In total, 59 patients received at least one dose of study medication and 50 patients received ≥4 weeks of treatment. The use of lanthanum carbonate was generally well tolerated. Altogether, three lanthanum carbonate-treated patients were withdrawn because of events believed by the investigator to be related to study treatment. One patient had treatment stopped because of nausea. Two patients experienced nausea and vomiting.

Lanthanum levels were detectable in 11 patients prior to initiation of oral lanthanum treatment. The mean level of plasma lanthanum at the end of washout was 0.54 ± 0.13 ng/g. The corresponding value after 4 weeks of treatment was 0.78 ± 0.45 ng/g. No clinically or statistically significant changes in other haematological and biochemical laboratory test results were observed.

Table 2. Phosphorus and calcium levels throughout the study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Screening (n = 59)</th>
<th>Visit 1 (n = 59)</th>
<th>Visit 2 (n = 56)</th>
<th>Visit 3 (n = 54)</th>
<th>Visit 4 (n = 51)</th>
<th>Visit 5 (n = 50)</th>
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<tr>
<td>Phosphorus (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.80</td>
<td>2.26</td>
<td>2.15</td>
<td>2.02</td>
<td>1.81</td>
<td>1.70</td>
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<tr>
<td>95% CI</td>
<td>1.68; 1.91</td>
<td>2.17; 2.34</td>
<td>2.04; 2.26</td>
<td>1.90; 2.13</td>
<td>1.71; 1.92</td>
<td>1.60; 1.80</td>
</tr>
<tr>
<td>Mean change from visit 1</td>
<td>−0.10</td>
<td>−0.23</td>
<td>−0.42</td>
<td>−0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.43</td>
<td>2.28</td>
<td>2.27</td>
<td>2.31</td>
<td>2.33</td>
<td>2.33</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.36; 2.51</td>
<td>2.22; 2.34</td>
<td>2.20; 2.34</td>
<td>2.25; 2.37</td>
<td>2.27; 2.38</td>
<td>2.27; 2.40</td>
</tr>
<tr>
<td>Mean change from visit 1</td>
<td>0.00</td>
<td>0.04</td>
<td>0.05</td>
<td>0.06</td>
<td></td>
<td></td>
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</tbody>
</table>

*aP < 0.05.  
*bNot significant.
In this study we found that titration of lanthanum up to a maximum of 2250 mg/day can reduce serum phosphate to $\leq 1.80$ mmol/l after 4 weeks of treatment in 70% (35) of patients. Five of these patients experienced a reduction in serum phosphate to below 1.30 mmol/l, thereby taking them below the intended target range of the protocol, but not below the usual normal range. Given that positive lanthanum carbonate data have been reported involving haemodialysis patients only [10], the treatment appears to be effective regardless of whether patients were receiving CAPD or haemodialysis. No clinically significant effect was seen on PTH levels. Median PTH levels increased from screening, as would be expected when oral calcium-based phosphate binders are discontinued. Calcium agents reduce PTH levels both through the control of serum phosphorus and the direct action of calcium on the parathyroid gland. Patients with low/normal PTH levels are likely to have adynamic bone, and a rise in PTH to twice or three times the upper limit of normal is probably beneficial [12,13]. Rises beyond this range should, in routine clinical practice, be controlled by introduction of oral vitamin D metabolites. However, in this study most patients were not taking vitamin D at screening and no alteration or initiation of this treatment was permitted during the study as it was of short duration and would have influenced serum calcium and phosphate unpredictably.

The most common adverse events recorded during this short-term investigation were gastrointestinal in nature and resulted in withdrawal of three patients. Serum lanthanum levels were detectable in 11 patients prior to treatment, which is not surprising as it is present at very low levels in tap water. Mean values increased during the study, but remained low.

Lanthanum carbonate is an effective phosphate binder and appears to be a promising treatment for hyperphosphataemia. Data regarding the long-term safety and efficacy of this new phosphate binder are awaited with interest.

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**Conflict of interest statement.** Dr A. J. Hutchison has a paid consultancy agreement with Shire Pharmaceutical Ltd.

**References**


**Table 3.** PTH levels (ng/l) throughout the study (median and range provided because distribution is not normal)

<table>
<thead>
<tr>
<th></th>
<th>Screening (n = 53)</th>
<th>Visit 3 (n = 46)</th>
<th>Visit 5 (n = 43)</th>
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<tbody>
<tr>
<td>Range</td>
<td>5–947</td>
<td>5–2166</td>
<td>9–746</td>
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<tr>
<td>Mean</td>
<td>167</td>
<td>245</td>
<td>182</td>
</tr>
<tr>
<td>95% CI</td>
<td>118; 216</td>
<td>142; 348</td>
<td>133; 231</td>
</tr>
<tr>
<td>Mean change</td>
<td>81</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>from screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>117</td>
<td>185</td>
<td>143</td>
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<tr>
<td>Range</td>
<td>5–947</td>
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<td>9–746</td>
</tr>
<tr>
<td>Mean change</td>
<td>29.0</td>
<td>12.0</td>
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<tr>
<td>from screening</td>
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<tr>
<td>95% CI</td>
<td>−14.7; 72.7</td>
<td>−26.9; 50.9</td>
<td></td>
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</tbody>
</table>

*a*Non-significant ($P = 0.15$; Wilcoxon two sample test).

*b*Non-significant ($P = 0.37$; Wilcoxon two sample test).

**Discussion**

In this study we found that titration of lanthanum up to a maximum of 2250 mg/day can reduce serum phosphate to $\leq 1.80$ mmol/l after 4 weeks of treatment in 70% (35) of patients. Five of these patients experienced a reduction in serum phosphate to below 1.30 mmol/l, thereby taking them below the intended target range of the protocol, but not below the usual normal range. Given that positive lanthanum carbonate data have been reported involving haemodialysis patients only [10], the treatment appears to be effective regardless of whether patients were receiving CAPD or haemodialysis. No clinically significant effect was seen on PTH levels. Median PTH levels increased from screening, as would be expected when oral calcium-based phosphate binders are discontinued. Calcium agents reduce PTH levels both through the control of serum phosphorus and the direct action of calcium on the parathyroid gland. Patients with low/normal PTH levels are likely to have adynamic bone, and a rise in PTH to twice or three times the upper limit of normal is probably beneficial [12,13]. Rises beyond this range should, in routine clinical practice, be controlled by introduction of oral vitamin D metabolites. However, in this study most patients were not taking vitamin D at screening and no alteration or initiation of this treatment was permitted during the study as it was of short duration and would have influenced serum calcium and phosphate unpredictably.

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