Combined therapy with lanthanum carbonate and calcium carbonate for hyperphosphatemia decreases serum FGF-23 level independently of calcium and PTH (COLC Study)

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Abstract

Background. Increased blood levels of fibroblast growth factor-23 (FGF-23) are associated with increased mortality. We evaluated the effect of combined therapy with lanthanum carbonate (LaC), a new phosphate binder and calcium carbonate (CaC) on serum levels of phosphate and FGF-23.

Methods. This was a single-arm, open-label, multicenter study. Hemodialysis patients with a serum phosphate level >6.0 mg/dL despite CaC therapy were also given LaC for 16 weeks at a dose up to 2250 mg/day. CaC was given at a fixed dose throughout the 16-week period.

Results. Of 42 patients enrolled, 36 completed the 16-week study. The serum phosphate level showed a significant decrease from 6.9 ± 1.4 mg/dL at week 0 to 5.5 ± 1.2 mg/dL at week 16 (−20.0%, P < 0.05). The median FGF-23 level showed a significant decrease from 8250 ng/L at week 0 to 5000 ng/L at week 16 (−39.2%, P < 0.05). In contrast, corrected serum calcium and the serum parathyroid hormone level showed no significant changes. A significant positive correlation (r = 0.442, P = 0.007) was demonstrated between the percent reduction of serum FGF-23 and that of serum phosphate.

Conclusion. Both serum phosphate and FGF-23 levels were significantly decreased by treatment with LaC plus CaC.

Keywords: hyperphosphatemia; FGF-23; lanthanum carbonate; calcium carbonate; hemodialysis

Introduction

Disturbances of mineral and bone metabolism, including abnormal serum levels of phosphate, calcium and parathyroid hormone (PTH), are common in patients with chronic kidney disease (CKD). This condition has been named CKD–mineral and bone disorder (CKD–MBD), and it is associated with high levels of cardiovascular disease morbidity and mortality in patients with end-stage renal disease (ESRD) [1–3].

Fibroblast growth factor (FGF)-23 was recently identified as a circulating factor that regulates phosphate homeostasis, activation of calcitriol and metabolism of PTH. Recent studies have identified Klotho protein as a coreceptor that enhances the binding affinity of FGF-23 to the widely expressed FGF receptors. In CKD patients, FGF-23 levels increase as the glomerular filtration rate declines and phosphate accumulates, and it has been shown that a high FGF-23 level is associated with increased mortality [4–8].

Management of the serum phosphate concentration is one of the primary treatments for CKD–MBD since hyperphosphatemia is an independent risk factor for cardiovascular disease and cardiovascular mortality [1–3, 9, 10]. Calcium-containing phosphate binders are widely used to reduce serum phosphate levels. However, hypercalcemia frequently occurs as a result of dose escalation and prolonged administration of these binders, especially when used together with vitamin D receptor activators (VDRAs) [11]. Calcium overload may accelerate arterial calcification and arterial stiffening and thus could worsen the prognosis.

Lanthanum carbonate (LaC) is a non-aluminum, non-calcium phosphate binder that has been available in the USA and Europe. In 2009, it was also approved for use in Japan. Preclinical studies have shown that lanthanum binds phosphate throughout the gastrointestinal tract regardless of the luminal pH and is poorly absorbed from the gut [12, 13]. Clinical studies have indicated that LaC effectively reduces serum phosphate levels and treatment is well tolerated for up to 6 years [14–18].

We focused on hemodialysis patients whose serum phosphate level was not controlled by calcium carbonate (CaC) therapy and performed a prospective study in order to evaluate the clinical efficacy of combined therapy with LaC and CaC. The FGF-23 level was also measured before and after addition of LaC to investigate the mechanism of FGF-23 metabolism.

Materials and methods

Study design

This was a single-arm, open-label, multicenter study.
LaC was administered as add-on therapy to patients already receiving CaC for the treatment of hyperphosphatemia. The dose of CaC was not changed during the 16-week study period. The starting dose of LaC was 750 mg/day, which was adjusted stepwise based on assessment of serum phosphate levels and tolerability at 2-week intervals. The maximum dose was set at 2250 mg/day. The target of therapy was a serum phosphate level in the range recommended by the Japanese Society for Dialysis Therapy (3.5–6.0 mg/dL).

Prior to enrollment, each subject was given an explanation about the objectives of the study and then provided written informed consent to participate. The study protocol was approved by the Ethics Committee of Wakayama Medical University, and the study was implemented in accordance with ethical principles expressed in the Declaration of Helsinki.

Patients

The subjects were hemodialysis patients who met all of the following criteria: men or women aged ≥20 years, predialysis serum phosphate level >6.0 mg/dL, patients on hemodialysis for at least 3 months prior to enrollment and current treatment with CaC for hyperphosphatemia.

Patients who fulfilled any of the following criteria were excluded from the study: prior treatment with sevelamer hydrochloride (within 3 weeks before the start of the study); gastrointestinal disorders including active peptic ulcer, ulcerative colitis, Crohn’s disease and intestinal stricture; severe hepatic dysfunction; suspected or confirmed malignancy; pregnant or breast-feeding women and women who wish to become pregnant.

During the study, the subjects were not allowed to change the dose of CaC or use any phosphate binder other than the study drugs. VDRAs or cinacalcet hydrochloride could be used concomitantly, but the dose had to be fixed during the study period.

Investigations

Serum phosphate levels were monitored at 2-week intervals to investigate whether the target serum level was reached. The corrected serum calcium (Ca) level was also determined at 2-week intervals. Furthermore, changes of the bone metabolism markers, intact parathyroid hormone (i-PTH) and FGF-23 were investigated. Serum i-PTH levels were measured at Weeks 0, 4, 8, 12 and 16, and serum FGF-23 levels at Weeks 0, 8 and 16. Serum intact FGF-23 was assayed by SRL, Inc. (Tokyo, Japan) (using a test kit from Kainos Laboratories Inc., Tokyo, Japan). Serum i-PTH levels were measured using electrochemiluminescence immunoassay. The normalized protein catabolic rate (nPCR) was calculated using Shinzato’s equation [19]. Other laboratory parameters were measured at the participating institutions. Blood samples for the measurement were collected before hemodialysis after the longest interval between the hemodialysis.

For assessment of safety, the occurrence of adverse events was investigated with respect to the relationship to LaC treatment.

Statistics

The serum phosphate levels, corrected serum Ca level and dosage of phosphate-binders were expressed as the mean ± standard deviation (SD). Serum levels of i-PTH and FGF23 were expressed as the median value with range (minimum–maximum). Serum phosphate levels and corrected serum Ca were analyzed using a repeated measures analysis of variance (ANOVA) model. i-PTH and FGF-23 were analyzed using Friedman repeated measures ANOVA on ranks test. If a significant difference was seen, a post-hoc test was performed [20]. Correlations were calculated by performing Spearman’s rank order analysis. The software employed was SigmaStat for Windows version 3.5 (Systat Software, Inc., Erkrath, Germany), and analyses were performed with the level of significance set at P < 0.05 (two sided).

Results

Patient profile

Forty-two patients from seven centers were enrolled, and all of them were included in safety analysis.

All patients were treated with LaC in addition to CaC. Thirty-six patients completed the 16-week study and six patients withdrew after starting LaC therapy. Two of these patients discontinued the study due to gastrointestinal symptoms (nausea and vomiting), which were suggested to be related to LaC therapy by investigators, and their symptoms resolved soon after withdrawal of LaC. The other four patients discontinued the study for reasons unrelated to LaC treatment by investigators judgment (constipation, gastrointestinal bleeding, surgery for bile duct stones and vascular graft surgery).

The baseline characteristics of the safety analysis set are shown in Table 1. Twenty patients (48%) had secondary hyperparathyroidism. Seven patients (17%) were using cinacalcet hydrochloride concomitantly and 16 patients (38%) used VDRAs. The mean daily dose of cinacalcet hydrochloride was 32.1 mg and that of oral VDRA was 0.31 μg. Dosages of these medications were fixed throughout the study period.

The mean hemodialysis duration was 4 h, and all patients had received hemodialysis three times a week. The mean dialysate calcium concentration was 2.9 mEq/L. The conditions of hemodialysis were fixed throughout the study period. No significant changes in the nPCR were seen before and after the study.

LaC was started at a dose of 750 mg/day. By Week 4, the dose of LaC had been increased in about a quarter of the subjects, and the mean dose was 993.1 ± 468.6 mg/day. The mean dose of LaC showed little change thereafter, with the mean dose at final follow-up (Week 16) being 1034.7 ± 474.9 mg/day. The mean dose of CaC was 3041.7 ± 1745.9 mg/day as the total amount of CaC at baseline and 2944.4 ± 1819.6 mg/day at a final follow-up (Week 16), showing almost no change throughout the study period (Figure 1).

Effects of LaC therapy

The baseline serum phosphate level was 6.89 ± 1.44 mg/dL and it decreased significantly after the introduction of

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n = 42; CGN, chronic glomerulonephritis; PKD, polycystic kidney disease; SHPT, secondary hyperparathyroidism.
LaC therapy to reach 5.52 ± 1.19 mg/dL in Week 16 (P < 0.05, Figure 2).

The baseline FGF-23 level was 8250 (115–40 200) ng/L. It showed a significant decrease after 8 and 16 weeks of add-on LaC therapy, being 5200 (38–31 400) ng/L in Week 8, 5000 (78–30700) ng/L in Week 16 (Figure 3a).

The baseline-corrected serum Ca level was 9.09 ± 0.69 mg/dL. It showed no significant change after the start of add-on LaC therapy and was stable throughout the study period (9.26 ± 0.76 mg/dL in Week 16, Figure 2).

Baseline i-PTH was 134.7 (12.0–379.3) pg/mL, and it also showed no significant change during add-on LaC therapy (Figure 3b).

The correlation between reduction of the serum phosphate and the change of serum FGF-23 level is shown in Figure 4. As the reduction of serum phosphate became more marked, the decrease of serum FGF-23 also became greater.

Safety of LaC therapy

Adverse events were reported in 17 patients (40.5%) and were related to LaC treatment in nine patients (21.4%). All of these events were non-serious gastrointestinal symptoms, such as nausea, vomiting, epigastric discomfort, abdominal distension and constipation (n = 4, 4, 3, 3 and 1, respectively). All of the events improved overtime.

Discussion

In the present study, LaC was administered as add-on therapy to patients with hyperphosphatemia uncontrolled by CaC. Add-on therapy with LaC significantly decreased the serum phosphate level and allowed control of phosphate within the target range of the Japanese Society for Dialysis Therapy Guideline (3.5–6.0 mg/dL) without any changes of serum Ca and PTH throughout the 16-week study period in most of the patients. The incidence of adverse events during combined LaC plus CaC therapy was similar to that during LaC monotherapy [18]. Thus, this study demonstrated good tolerability and efficacy of combined therapy with LaC and CaC in patients whose hyperphosphatemia was not controlled by CaC monotherapy.

FGF-23 is a phosphaturic factor produced by osteocytes that plays a vital role in normal phosphate and vitamin D metabolism, and it has been reported that FGF-23 secretion is enhanced in CKD patients to prevent phosphate accumulation [4, 5]. We previously reported that both serum
phosphate and FGF-23 levels were significantly decreased by coadministration of CaC and sevelamer hydrochloride compared with CaC monotherapy [21].

In the present study, we found the significant 40% reduction of the circulating intact FGF-23 level from baseline after 8 and 16 weeks of combined LaC plus CaC therapy. We measured intact FGF-23 with a Kainsos Laboratories assay kit, so the observed reduction of serum FGF-23 levels is thought to directly reflect a reduction of FGF-23 production in the bone. The percent reduction of the serum phosphate level showed a positive correlation with the percent reduction of serum FGF-23. Since phosphate has been reported to regulate FGF-23 [22], the observed reduction of FGF-23 presumably resulted from adequate control of serum phosphate achieved by the combination of two different phosphate binders, i.e. CaC and LaC. Because CaC was administered at a constant dose throughout the study, there were no significant changes of the serum Ca and serum PTH concentrations. Therefore, the change of serum FGF-23 was thought attributable to a decrease of the serum phosphate level or decreased intestinal phosphate absorption. The mean hemodialysis vintage of subjects was 6.9 years and most were anuric, so we assume that their residual renal function (RRF) was lost. Therefore, phosphatemia, serum FGF-23 level and calcitriol synthesis have not been influenced by RRF in this study. It has traditionally been considered that the kidneys, bone and parathyroid gland comprise the metabolic axis for bone/Ca metabolism. However, it seems reasonable to consider a new metabolic axis for phosphate metabolism that consists of intestine and bone in CKD patients undergoing hemodialysis, although this differs from the traditional concept. It is assumed that phosphate metabolism is markedly affected in ESRD patients undergoing hemodialysis as their kidney function is impaired. It remains unclear whether osteocytes in the bone, which are the site of FGF-23 production, recognize changes of the serum phosphate concentration and/or changes of intestinal phosphate absorption.

Gutierrez et al. investigated the association between serum FGF-23 and survival time in patients starting hemodialysis, and they reported that an increased serum level of FGF-23 was closely correlated with an increased risk of mortality that was independent of the serum phosphate concentration. Moreover, they found that the overall risk of mortality was increased to six times higher by an increased serum FGF-23 level, which was a far greater risk of death compared with the 20% increase in risk due to hyperphosphatemia [7].

The major limitation of this study is that it did not include a control group, in which patients were treated with CaC or LaC monotherapy. Further comparative studies are required to more clarify the potential benefits of LaC add-on therapy to CaC in hemodialysis patients.

In conclusion, adding LaC to CaC monotherapy not only decreased serum phosphate but also serum FGF-23. Thus, this combination phosphate binder therapy may also contribute to improving the survival of CKD patients through reduction of circulating FGF-23 as well as providing effective treatment of hyperphosphatemia.

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Conflict of interest statement. None declared.

References


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