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Original Article

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Can Resistance Be Resolved with Lanthanum Carbonate in the Treatment of Hyperphosphatemia? A Multicenter Experience

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ABSTRACT

Objective: Kidney osteodystrophy is a condition that both reduces the quality of life and shortens the life span in patients with chronic kidney disease. Lanthanum carbonate is a phosphorus-binding agent that forms very tight complexes with phosphate ions, has low systemic absorption potential, and does not contain calcium and aluminum. The aim of this study was to evaluate the efficacy of lanthanum carbonate in patients with resistant hyperphosphatemia.

Methods: One hundred four hemodialysis patients (44 females and 60 males; mean age: 59.5 ± 4 years) whose serum phosphorus level was above 6 mg/dL despite the use of phosphorus-binding drugs (calcium acetate, calcium carbonate, and/or sevelamer) were included in this study. The patients were followed prospectively for 6 months.

Results: Twenty (19.2%) patients included in the study could not use the drug regularly due to difficulties in using it and nausea, while 84 (28 females and 56 males) patients used the drug regularly for 6 months. Lanthanum carbonate was used at a dose of 3 × 750 mg in 37 patients and 3 1000 mg in 47 patients. While 72.6% of the patients used the drug by mixing it with food, the rest drank it with water. The most common side effects were nausea, constipation, and itching. Four different centers from 3 cities in Turkey participated in the study.

When the patients who used it regularly were evaluated, after lanthanum carbonate use, the mean phosphorus level decreased from 6.9 ± 0.7 mg/dL to 5.97 ± 0.9 mg/dL (P = .02). The levels of calcium–phosphorus products were 62.12 ± 9.89 before lanthanum carbonate treatment and 57.6 ± 11.52 after treatment (P = .023).The levels of. It was observed that the mean parathormone levels decreased from 657 ± 48 pg/mL to 521 ± 36 pg/mL after treatment (P = .031). While none of the patients could take vitamin D due to hyperphosphatemia before the treatment, 52 patients could use vitamin D together with lanthanum carbonate. When 36 patients whose serum phosphorus level decreased with treatment but did not fall below 5.5 mg/dL were examined, it was observed that the mean parathyroid hormone level (708 ± 27 vs. 558 ± 30 pg/mL, P = .041) and the rate of patients using cinacalcet were higher in this group (41% vs. 8%).

Conclusion: We found that serum phosphorus, calcium–phosphorus products, and parathyroid hormone levels decreased significantly with lanthanum carbonate treatment in patients with resistant hyperphosphatemia. As a result of our findings, we think that resistant hyperphosphatemia can be effectively treated with lanthanum carbonate in most hemodialysis patients without severe hyperparathyroidism.

Keywords: Chronic kidney disease, hyperphosphatemia, lanthanum carbonate

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INTRODUCTION

Bone structure and dysfunction seen in patients with chronic kidney disease (CKD) is called kidney osteodystrophy. Vitamin D deficiency, phosphate retention, hypocalcemia, secondary hyperparathyroidism (SHPT), deterioration in bone structure, vascular and/or soft tissue calcifications, and metastatic calcifications can be seen in this chronic complication of CKD.[1,2]

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Phosphorus is an element discovered in 1669 and is found in nature in the form of apatite and is vital for all living things. Gastrointestinal, urinary, and skeletal systems play a role in phosphorus balance. Approximately 1-1.5 g of phosphorus is taken orally per day, and 60%-70% of this amount is absorbed from the duodenum and jejunum. While some of the absorbed phosphorus enters the bone cycle, most of it is filtered by the kidney and 90% of the phosphorus that passes into the ultrafiltrate is reabsorbed. The decisive step in phosphorus balance is absorption from the gastrointestinal tract.[3]

When kidney failure develops, normal physiology is disrupted and according to the "trade-off" hypothesis, phosphorus retention and hypocalcemia develop due to decreased glomerular filtration and increases the release of parathormone (PTH). The increased PTH level both normalizes the serum calcium level and normalizes the serum phosphorus as a result of phosphaturia. Hyperphosphatemia stimulates PTH mRNA synthesis, leading to parathyroid cell growth. As a result of all these disorders, soft tissue calcification, calcification in the vascular structure, and bone diseases develop.[4]

Serum phosphorus level in CKD is related to the amount of dietary phosphorus, residual kidney function, the use of phosphorus-binding compounds, the degree of phosphorus absorption from the intestine, the amount of calcium consumption, vitamin D deficiency and its treatment, the serum PTH and magnesium level, the use of phosphorus-containing enemas, dialysis efficiency, and the rate of transfer of phosphorus to the intracellular space. There are several important methods in the treatment of hyperphosphatemia, which has such a negative effect on mortality. These are primarily diet regulation, use of phosphorus binders, and effective and adequate dialysis. Phosphorus binders include aluminum-containing binders, calcium-containing ones such as calcium acetate and calcium carbonate, and new generation phosphorus binders without calcium and aluminum.[5]

Lanthanum is a trace element discovered by Mosander in 1839.[6] The trivalent cation, lanthanum, has a weight of 139 U and prevents phosphorus absorption by ionic binding to phosphorus. Lanthanum carbonate (LC) is minimally absorbed from the gastrointestinal tract and excreted primarily in the biliary tract. Although its effectiveness is not affected by the pH of the environment, the pH should be between 3 and 5 for its optimal effect.[5] It does not cause the conversion to adynamic bone disease and has positive effects on acidosis. The long-term side effects and toxicity of LC are still unknown.[7,8]

MAIN POINTS

- Lanthanum carbonate is a highly effective treatment option in resistant hyperphosphatemia.
- The use of lanthanum carbonate does not cause significant changes in calcium levels.
- Vitamin D usability increases with lanthanum carbonate and the use of lanthanum carbonate provides better PTH control.
- The use of lanthanum carbonate provides reasonable phosphorus control with less drug load.
- Basal PTH levels were significantly higher in patients whose phosphorus levels could not be reduced to the target range.

Hyperphosphatemia in dialysis patients is associated with increased both cardiovascular and all-cause mortality.[9] Despite all treatments used to control hyperphosphatemia, the rate of dialysis patients whose phosphorus level cannot be controlled is 70%.[10] Calcium-based phosphorus binders are inexpensive and well tolerated; however, these phosphorus binders can increase vascular calcification by increasing the calcium load.[11] The KDIGO clinical practice guideline recommends using calcium-based phosphorus-binding therapies at as low a dose as possible during phosphorus control.

In our study, we aimed to investigate the effectiveness of lanthanum carbonate in treatment-resistant patients who could not control phosphorus with other phosphorus-binding drugs.

METHODS

This is study is a multicenter prospective study and the study protocol was approved by the medical Ethics Committee of Necmettin Erbakan University (date: October 24, 2019; approval number: 2019/2134). Four different centers from 3 cities in Turkey participated in the study. Patients with resistant hyperphosphatemia despite the use of calcium acetate and/or sevelamer were included in this study. The patients used LC treatment as powder regularly for 6 months. The efficacy of LC on kidney osteodystrophy after treatment was evaluated. Written informed consent was obtained from all subjects included in the study.

A review of medical records (including information on age, sex, weight, height, disease duration, medications, and history of other diseases) was undertaken. Hemodialysis modality included conventional 4-hour HD 3 times a week with polysulfone dialyzers. A 250 mL/min (range 200-300 mL/min) of mean blood flow rate was obtained during dialysis sessions. Dialysate fluid composition included 140 mEq/L of sodium, 1-4 mEq/L of potassium, 3 mEq/L of calcium, 1.8 mEq/L of magnesium, and 33 mEq/L of bicarbonate.

Venous blood samples for biochemical analyses were drawn before the first dialysis of the week. All biochemical analyses were undertaken in the Central Biochemistry Laboratory of the Necmettin Erbakan University School of Medicine. Serum samples were used for detecting biochemical parameters and whole-blood sample were used to detect white cell and platelet counts. Serum creatinine levels were measured with the Jaffe method. In addition, phosphorus was determined using a Synchron LX 20 system (Beckman Coulter, Brea, CA, USA) with

original Beckman reagents, and serum PTH levels were measured at 3-month intervals.

Statistical Analyses

Clinical and experimental data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows, Version 21.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics for each variable were determined. The suitability of the variables to the normal distribution was examined. The paired samples *t*-test was used to examine the change of parameters showing normal distribution. The parameters that did not show a normal distribution were evaluated using the Wilcoxon test. The Mann–Whitney *U*-test was used for comparisons between the 2 groups. A statistically significant difference was considered when the *P*-value <.05.

RESULTS

A total of 104 patients (44 females and 60 males; mean age: 59.5 ± 4 years) who received hemodialysis treatment and whose serum phosphorus level was consistently above 6 mg/dL in the last 3 months despite using calcium acetate and/or sevelamer were included in this study. Demographic and clinical characteristics and biochemical parameters of the patients are depicted in Table 1.

While 84 patients (28 females and 56 males) were using the drug regularly, it was observed that 20 (19.2%) patients could not use the drug regularly due to nausea and difficulty in use. Lanthanum carbonate was used at a dose of 3 × 750 mg in 37 patients and at a dose of 3 × 1000 mg in 47 patients. Most of the patients were using their medication by mixing it with food. While the most common side effects related to the gastrointestinal system were seen after LC use, side effects such as itching, rash, and dizziness were also detected (Table 2). It was observed that the average drug burden used for hyperphosphatemia decreased from 6.6 to 3.

A statistically significant decrease was found in mean phosphorus, PTH, and calcium–phosphorus (CaxP) product levels after treatment (6.9 ± 0.7 vs. 5.97 ± 0.9, 657 ± 48 vs 521 ± 36, 62.12 ± 9.89, and 57.6 ± 11.52, respectively). No significant change was observed in calcium levels before and after LC use (9.71 ± 1.3 vs. 9.5 ± 0.7) (Figure 1). Phosphorus levels decreased to the target range (*P* <5.5 mg/dL) in 48 patients, and vitamin D could be used together with LC in 52 patients who could not use vitamin D analog due to hyperphosphatemia before treatment, as a result of the decrease in phosphorus.

We also examined the patients whose serum phosphorus level decreased with treatment but did not fall below 5.5 mg/dL achieved phosphorus control after treatment. While there was no difference between the 2 groups in terms of age, duration of dialysis, and Ca levels, the basal PTH levels of the patients who did not respond to the treatment were found to be significantly higher (708 ± 27 vs. 558 ± 30 pg/mL, *P* = .041). In addition, it was observed that the use of cinacalcet was higher in the group with serum *P* >5.5 (41% vs. 8%). In addition, parathyroid adenoma was detected in 11 of these patients.

Table 1. Demographic, Clinical, and Laboratory Features of the Study Group

Parameters	Hemodialysis Patients (n = 104)
Age (years)	59.5 ± 4
Female/male	44/60
Body weight (kg)	71 ± 3
Dialysis vintage (years)	7.4 ± 2.3
Kt/V urea	1.7 ± 0.3
Albumin (g/dL)	3.9 ± 0.4
Hemoglobin (g/dL)	11.4 ± 0.5
Calcium (mg/dL)	9.71 ± 1.3
Phosphorus (mg/dL)	6.9 ± 0.7
Parathormone (pg/mL)	657 ± 48

Table 2. Characteristics of Patients Using Lanthanum Carbonate

	N (%)
Side effects	
Nausea	25 (30%)
Constipation	20 (24%)
Itching	12 (15%)
Stomachache	8 (9%)
Dizziness	5 (6%)
Diarrhea	3 (4%)
Dysgeusia	2 (2%)
Rash	2 (2%)
Meteorism	2 (2%)
How to use lanthanum carbonate	
Pouring it on food on a plate	32 (39%)
Pouring it on food on a spoon	19 (23%)
Other: pouring it between bread slices	10 (11%)
Other: pouring it into the mouth and then drinking water	12 (14%)
Mixing it with a liquid	11 (13%)
Drugs used at the start of lanthanum carbonate	
Calcium acetate	42 (50%)
Sevelamer	22 (26%)
Sevelamer + calcium acetate	12 (14%)
Calcium carbonate	5 (6%)
Sevelamer + calcium carbonate	4 (4%)

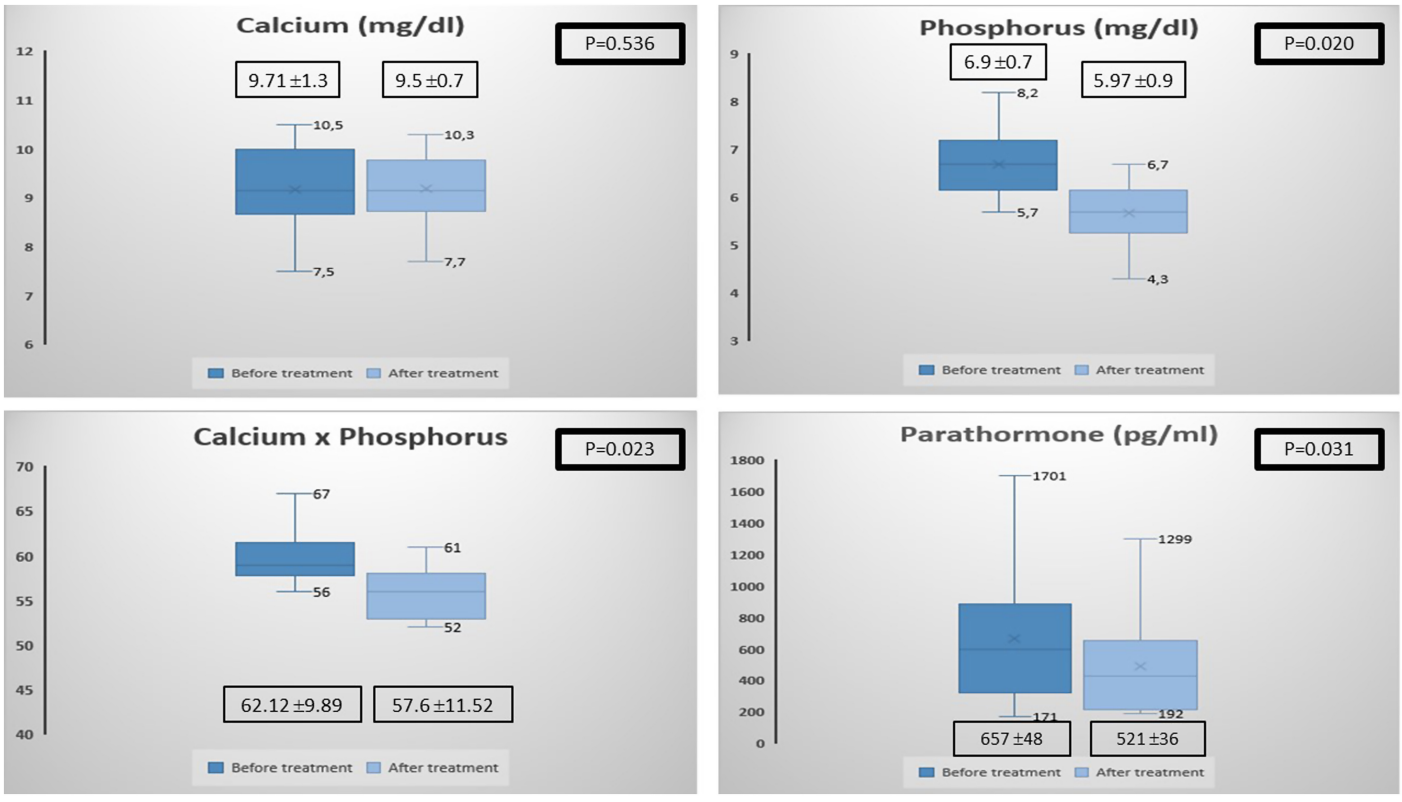

Figure 1. Change in laboratory features after treatment.

DISCUSSION

The main feature of our study is that it is a prospective study evaluating the use of LC in patients with refractory hyperphosphatemia. In addition, several important results were obtained as a result of the study. First, in patients with resistant hyperphosphatemia, serum phosphorus levels were found to be significantly reduced with lanthanum carbonate, while no significant change was observed in serum calcium levels. Second, it was determined that vitamin D usability increased with lanthanum carbonate, and PTH levels decreased significantly. Third, it was found that the basal PTH levels of the patients whose phosphorus levels could not be reduced to the target range were significantly higher. Finally, we found that the drug burden used for the treatment of hyperphosphatemia was reduced.

Elevated serum phosphorus levels in patients with reduced kidney phosphate excretion due to CKD predict worsening cardiovascular and all-cause mortality outcomes in both nondialysis and dialysis populations.[12] Therefore, lowering serum phosphorus concentrations through restriction of intake and/or extrakidney phosphate removal may be beneficial in reducing mortality.[13] In a study done by Hutchison et al,[14] the effectiveness of LC was evaluated and it was shown to be effective and well tolerated in the treatment of hyperphosphatemia. Similarly, in 2004, Finn et al[15] followed 145 patients for the use of placebo or LC for 6 weeks. As a result, they showed that LC is an effective agent for the short-term treatment of hyperphosphatemia in patients. In our study, LC was found to be effective in the treatment of hyperphosphatemia, consistent with the literature, and decreased phosphorus levels were observed in patients with resistant hyperphosphatemia.

An ideal phosphorus binding agent should be calcium-free or nonhypercalcemic and easy to use by patients. Phosphorus binders containing calcium can cause an increase in calcium levels, although they may decrease phosphorus levels. Therefore, the expected reduction in CaXP product may not be achieved. It has been shown that this undesirable increase in calcium levels does not occur with LC treatment and hence the targeted balance in the CaXP product is better preserved.[14] In this study, we found that similarly, there was no significant change in calcium levels before and after treatment.

Secondary hyperparathyroidism (SHPT) is common in most patients with kidney failure. Clinical manifestations of SHPT include increased bone and muscle pain, fatigue, and increased risk of bone fractures.[16,17] In a study done by Toida et al,[18] it was shown that PTH levels decreased with the use of phosphorus-binding agents and that the dose of vitamin D analogs could be increased more frequently in patients using LC. In the same study, it was stated that the decrease in PTH levels was more significant in patients using calcium-containing phosphorus

binders. In our study, on the other hand, we found a significant decrease in PTH levels after LC treatment. We also observed that the use of vitamin D analogs increased after treatment.

Sevelamer binds to bile acids and is not an effective phosphorus binder in acidic conditions. Lanthanum carbonate, on the other hand, has a high phosphorus-binding capacity both at acid pH in the stomach and at higher pH in the intestines.[19] Sevelamer hydrochloride is an alternative drug used for reducing serum phosphate, has no systemic absorption, and does not increase total body calcium load. However, sevelamer hydrochloride binds bile acids, is not an efficient phosphate binder in an acidic environment, and contributes to metabolic acidosis. Lanthanum carbonate is a potent and selective phosphate binder that retains high affinity for phosphate over a wide pH range, does not bind bile acids or contribute to metabolic acidosis, and has the potential to reduce drug burden and increase patient compliance compared with other phosphate binders. Consistent with these data, Martin et al[20] showed that phosphorus absorption was reduced more with LC compared to sevelamer. One of the most important causes of resistant hyperphosphatemia is the patient's inability to comply with the treatment. The increase in the patient's compliance with the treatment can be achieved by the high effectiveness of the treatment and the low drug burden. In other words, serum phosphorus levels and drug burden are inversely associated with adherence to treatment in patients on hemodialysis.[21] In a study done by Vemuri et al,[22] it was shown that the control of serum phosphorus levels with LC was provided with less drug burden. In our study, similar to the literature, the average drug burden used by patients decreased with LC treatment. Our study has some limitations. One of them is that the results cannot be universalized because all patients had the same ethnic origin. The small number of our patients is another significant limitation. In addition, the study was a single-arm study, which is another limitation of the study.

CONCLUSION

In conclusion, we found that in patients with refractory hyperphosphatemia, serum phosphorus and PTH levels were found to be significantly reduced with LC treatment. While 19.2% of the patients could not use the drug for various reasons, especially nausea, it was observed that the usability of vitamin D increased with LC treatment. It was determined that the basal PTH levels of the patients whose phosphorus levels could not be controlled after the treatment were significantly higher. Therefore, we think that resistant hyperphosphatemia can be effectively treated with LC in most hemodialysis patients without severe hyperparathyroidism.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Necmettin Erbakan University, Konya/Turkey (Approval no: 2019/2134, Date: October 24, 2019).

Informed Consent: Written informed consent was obtained from the patients/patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflict of interest to declare.

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