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*Case Report*

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# Encephalopathy caused by lanthanum carbonate

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**Abstract**
Lanthanum carbonate is a nonaluminum, noncalcium phosphate-binding agent, which is widely used in patients with end-stage chronic kidney disease. Until now, no significant side-effects have been described for the clinical use of lanthanum carbonate, and there are no available clinical data regarding its tissue stores.
Here we report the case of a 59-year-old patient who was admitted with confusional syndrome. The patient received 3750 mg of lanthanum carbonate daily. Examinations were carried out, and the etiology of the encephalopathy of the patient could not be singled out. The lanthanum carbonate levels in serum and cerebrospinal fluid were high, and the syndrome eased after the drug was removed. The results of our study confirm that, in our case, the lanthanum carbonate did cross the blood-brain barrier (BBB).
Although lanthanum carbonate seems a safe drug with minimal absorption, this work reveals the problem derived from the increase of serum levels of lanthanum carbonate, and the possibility that it may cross the BBB. Further research is required on the possible pathologies that increase serum levels of lanthanum carbonate, as well as the risks and side-effects derived from its absorption.

**Keywords:** chronic kidney disease; encephalopathy; lanthanum carbonate; phosphate-binding agent

## Background

Hyperphosphataemia is an established risk factor for cardiovascular mortality, renal osteodystrophy and secondary hyperparathyroidism in patients with end-stage chronic kidney disease (CKD) under renal replacement therapy. Limitations in the phosphate of the diet have been the cornerstone of the treatment, but this measure is not enough for the control of hyperphosphataemia, and the use of phosphate-binding agents (calcium carbonate, calcium acetate, aluminium hydroxide or sevelamer) is necessary [1]. The ideal phosphate-binding agent should offer a minimal absorption, few side effects, a minimal pill load and low cost. Aluminium hydroxide may cause encephalopathy, osteomalacia and anaemia [2]. Therefore, it must be used with caution. Calcium carbonate or calcium acetate increase vascular and valvular calcification. Sevelamer is a nonabsorbable ion-exchange resin that does not contain calcium or aluminium, and its use is only restricted by gastrointestinal tolerance, metabolic acidosis and the high pill load required for an adequate control of phosphate levels.

Two years ago, a new and powerful noncalcium nonaluminium phosphate-binding agent appeared on the market, lanthanum carbonate ($LaCO_3$), which allows for a potential improvement of the control of serum phosphate levels in patients with CKD, and no significant side effects have been described to date [3, 4].

We report here the case of a patient with end-stage CKD under periodic haemodialysis with confusional syndrome, probably secondary to $LaCO_3$ intake.

## Case report

We present the case of a 59-year-old male patient with a history of cystic thyroid nodules, arterial hypertension, portal hypertension of unknown origin with esophageal varices, Barrett's esophagus, left ventricular hypertrophy, secondary hyperparathyroidism and end-stage CKD of unknown origin, under haemodialysis since 1998 with cadaveric renal transplantation in 1999. The patient started haemodialysis again in April 2002 with Kt/V $>1.2$. His usual treatment included omeprazole (20 mg/day), prednisone (2.5 mg/day) and darbepoetin alpha (50 μg/14 days). For adequate control of secondary hyperparathyroidism, the patient was prescribed in stages, treatment with calcium acetate (3000 mg/day), paricalcitol (1 μg/48 h), cinacalcet (60 mg/day) and $LaCO_3$ (3750 mg/day) since September 2009, with poor gastrointestinal tolerance, which led to weight loss. The patient started treatment with $LaCO_3$ in November 2008 with a dose of 2000 mg/day, at which time analysis showed Ca 7.9 mg/dL, P 6.9 mg/dL, PTH 603 pg/mL; in July 2009, we increased the dose of cinacalcet to 90 mg/day, but the patient developed gastrointestinal intolerance and we decreased the dose to 60 mg/day and $LaCO_3$ was increased to 3500 mg/day because the patient had poor control of mineral metabolism with Ca 8.4 mg/dL,

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P 6.8 mg/dL and PTH 611 pg/mL, and drug dose was further increased to 3750 mg/day in September 2009 because the patient had poor control of phosphorus, 7.1 mg/dL.

The patient was admitted to our hospital on the 1 April 2010, with acute confusional syndrome, conduct disorder and delirious ideas. At admission, the neurological examination was normal, with arterial pressure levels of 90/60 mmHg, similar to those registered during the last haemodialysis sessions. The predialysis analysis at admission showed urea 95 mg/dL; creatinine 11.12 mg/dL; Ca 9.9 mg/dL, P 4.1 mg/dL and the rest of the electrolytes were normal; GOT 69 U/L (GOT levels before the beginning of the treatment with $LaCO_3$ were normal); GPT 27 U/L, total proteins 4.6 g/dL; albumin 2.3 g/dL; C-reactive protein 2.3 mg/dL; procalcitonin was negative, PTH 186 pg/mL; ethanol <0.1 g/L and ammonium, ceruloplasmin, copper and aluminium levels were normal and haemogram: haemoglobin 9.3 g/dL with normal levels of mean corpuscular volume and mean corpuscular haemaglobina and leukocytes 6940/μL with normal formula and platelets 103 000/μL and normal coagulation. The cerebrospinal fluid analysis revealed protein levels of 102 mg/dL, with negative results for adenosine deaminase, culture, cytology and serology analyses. An emergency cranial CT scan was performed with normal results, and the electromyogram was compatible with mild-moderate sensory-motor polyneuropathy with predominance of desmyelinization, which was distal and symmetrical in both lower limbs. The electroencephalography showed normal bioelectrical activity, and the hepatic echo-Doppler revealed signs of diffuse hepatopathy and lack of signs of portal hepatic thrombosis. He was diagnosed with delirium of organic origin by the Service of Psychiatry. In view of the suspicion of $LaCO_3$-derived encephalopathy, the drug was removed on the 7 April 2010, and the patient showed a progressive improvement, and his behaviour as well as the arterial pressure levels became normal after 72 h. Afterward, $LaCO_3$ levels were determined in serum and cerebrospinal fluid samples from his admission with Perkin-Elmer Elan 6000 ICP-MS system, and the results were 49 μg/L in serum and 33.85 μg/L in cerebrospinal fluid. Levels of $LaCO_3$ in serum and cerebrospinal fluid were measured again on the 17 June 2010, when the patient was asymptomatic and his arterial pressure levels were 130/85. The results were negative, and proteins were still present in cerebrospinal fluid (118 mg/dL). The analytic control showed the following: urea 77 mg/dL; creatinine 5.1 mg/dL; normal ions; GOT 41 U/L; GPT 18 U/L; C-reactive protein 0.8 mg/dL; total proteins 6.7 mg/dL; albumin 4.2 g/dL and haemogram: haemoglobin 10 g/dL; leukocytes 5200/μL with normal formula and platelets 111 000/μL.

## Discussion

Lanthanum is an element that belongs to the rare earth elements. It is the first element of the lanthanides. $LaCO_3$ dissociates in the gastric area and the first stretch of the intestine, and it acts as a phosphate-binding agent [3, 4]. $LaCO_3$ is highly insoluble, and its absorption, which is enhanced in uraemic patients, is therefore minimal (0.002%). It shows a 99% binding to plasmatic proteins, and it is excreted biliary. Although it does not metabolize with hepatic enzymes, there are no data regarding cases of severe hepatopathy. Its elimination half-life is 53 h. Disorders that lead to a significant reduction of the bile flow, as portosystemic shunt, may be associated to a slower elimination of lanthanum, which would involve an increase of its plasmatic concentrations and a higher tissue deposition [6]. Experimental studies have detected the presence of $LaCO_3$ in several tissues, such as the alimentary canal, bones and liver [6, 7]. No brain deposit or cognitive disorders have been described.

The only significant adverse effects that have been found are gastrointestinal problems, in ~6% of the cases, whereas the main adverse reactions described for the central nervous system are nausea, headaches or taste alterations. At an experimental level, the impact of lanthanides on the central nervous system is not insignificant: they can cross the blood-brain barrier [8] (BBB) and accumulate on the hippocampus, the cortex and the cerebellum, with the subsequent risks of cognitive and conduct alterations [9]. $LaCO_3$ inhibits the activity of the $Ca^{2++}$-ATPase, it reduces the concentration of monoamine neurotransmitters [10] and it alters the function of the cholinergic system. There is limited experience of treatments for >2 years.

We present the case of a patient that was under treatment with $LaCO_3$ for 18 months. Gastrointestinal upsets derived from its intake led to anorexia, malnutrition, which was seen in retrospect, and an increase of the free fraction of the compound. This fact, together with a delay in the biliary excretion as a consequence of the portosystemic shunt, proved because the patient had portal hypertension of unknown origin with esophageal varices and led to increased levels of $LaCO_3$. Normal levels of ammonium ruled that the delirium was attributed to hepatic encephalopathy. We do not know if $LaCO_3$ altered the permeability of the BBB [10] or if it was previously altered, which would explain the spinal fluid protein concentration of our patient that could not be ascribed to any existing neurological pathology. Our clinical case showed that the high serum levels of $LaCO_3$ explain the fact that it crossed the BBB and led to confusional syndrome and hypotension, which disappeared when the drug was removed.

Although $LaCO_3$ seems a safe drug with minimal absorption, our work reveals the problems derived from the increase of $LaCO_3$ serum levels, after increasing the $LaCO_3$ dose in a patient with malnutrition and hepatopathy, and the possibility that $LaCO_3$ may cross the BBB. Further research is required on the possible pathologies that increase the serum levels of $LaCO_3$ and on the risks and side effects derived from its absorption.

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*Conflict of interest statement*. None declared.

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