

Calciphylaxis Responsive to Lanthanum Carbonate (FOSRENOL) Therapy

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ABSTRACT

Calciphylaxis is a rare and debilitating vasculopathy predominantly seen in patients with renal failure. The proposed mechanism of injury is active vascular calcification with associated elevated parathyroid hormone, hypercalcemia, or hyperphosphatemia. With improved pharmacologic agents including non-calcium containing phosphate binders, vitamin D analogues, calcimimetics, and bisphosphonates, targeted therapy on the mineralization process has been tried with varied success. We report a case of biopsy-proven calciphylaxis in a patient with acute kidney injury requiring dialysis that had persistently elevated calcium-phosphorus product refractory to treatment. The patient, however, responded rapidly to the initiation of lanthanum carbonate therapy and modified dialysis. This is the first known case reported in the literature utilizing this new non-calcium-based phosphate binder in the setting of calciphylaxis.

INTRODUCTION

Calciphylaxis or calcific uremic arteriopathy was first described by Bryant and White in 1898 in a child with renal failure.¹ In 1962, Hans Selye coined the term calciphylaxis with his animal studies of soft tissue calcium deposition that were “sensitized” to vitamin D, parathyroid hormone (PTH), high calcium and phosphorus and then challenged with iron salts and egg albumin.² The entity is a rare and debilitating vasculopathy predominantly seen in patients with renal failure, however also seen in patients without end-stage renal disease.³ Although all of these cases possessed a proposed etiologic mechanism of injury and vascular calcification in the form of elevated serum PTH, hypercalcemia, and hypercoagulable state, the pathophysiology remains

an elusive topic. The predominant theory is that it is a systemic syndrome that almost always affects the skin with characteristic calcification involving the media of small- to medium-sized arterioles. Much research and attention to date has focused on the internal milieu that causes the histologic findings of calcium-phosphate aggregation within blood vessels.

In order to treat calciphylaxis, multiple case series and cohorts have targeted the ectopic or dystrophic calcification of injured tissue and vessels. Elevated calcium-phosphorus product has been a major focus of experimental studies and the pharmacologic management utilizing non-calcium-containing phosphate binders and vitamin D analogues.⁴⁻⁵ Low-calcium dialysate and dietary modification, especially in patients on total parenteral nutrition and enteral feeding, have also been studied.⁵⁻⁶ Parathyroidectomy in the past had been a successful strategy for treating calciphylaxis, however not until recently have results been controversial.⁶⁻⁷ The extremely high mortality associated with the procedure and recent improved medical management of secondary and tertiary hyperparathyroidism has significantly diminished its role as a treatment regimen. Other novel and evolving treatment modalities cited in the literature include intravenous sodium thiosulfate, calcimimetics, bisphosphonates, tissue plasminogen activator, and hyperbaric oxygen.⁸⁻⁹

We report a case of biopsy proven calciphylaxis in a patient with acute kidney injury requiring permanent hemodialysis that had persistently elevated calcium-phosphorus product recalcitrant to longer dialysis treatments and low-calcium dialysate. The patient interestingly responded rapidly to the initiation of lanthanum carbonate therapy and continued dialysis. This is the first case reported in the literature utilizing this new non-calcium-based phosphate binder in the setting of calciphylaxis.

CASE REPORT

A 64-year-old man with a history of cryptogenic cirrhosis was transferred to the trauma and life support unit after worsening liver failure, hypotension, renal failure,

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Figure 1. Photograph of lower right leg showing violaceous necrotic skin lesions with black eschar.

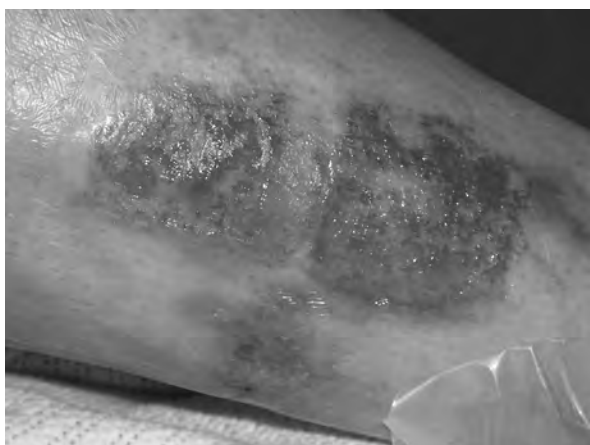


Figure 2. After 2 months of combination treatment with lanthanum and dialysis, there was significant healing with only superficial ulceration.

and encephalopathy. Prior to transfer, the patient was started on empiric antibiotics for presumed spontaneous bacterial peritonitis and septic shock, given aggressive crystalloid and blood products for fluid resuscitation and correction of coagulopathy, and eventually started on vasopressors for hemodynamic instability. The patient was transferred for renal failure thought to be due to hepatorenal syndrome and evaluation for liver transplantation.

On examination, the patient was diffusely jaundiced and had a pruritic, erythematous papular eruption over his trunk, abdomen, and lower extremities thought to be a drug eruption secondary to cephalosporin therapy he was receiving. He had pitting edema to his sacrum and no pain or hyperaesthesia over his lower extremities.

Laboratory findings on admission included a blood urea nitrogen of 106mg/dL, creatinine 3.1mg/dL, total calcium 6.7mg/dL, phosphorus 4.8mg/dL, calcium-

phosphorus product of 32.2mg²/dL², and an albumin of 1.3g/dL. The patient had numerous blood, urine, and peritoneal fluid cultures during his hospitalization that were negative. The patient was started on continuous venovenous hemofiltration (CVVHF) due to anuric renal failure, shock, and extreme volume overload that eventually necessitated intubation for hypoxemic respiratory failure due to pulmonary edema. Over the next several days, the patient continued on CVVHF with citrate regional anticoagulation secondary to a new internal capsule central nervous system bleed. Pre- and post-filter ionized calcium, as well as total calcium and phosphorus were managed without difficulty. The patient eventually was extubated, weaned off pressor agents, and tolerated intermittent hemodialysis 3 times weekly.

Due to severe malnutrition and failed swallow studies, he necessitated nasogastric (NG) tube feeds with low phosphorus Nepro™ enteral nutrition. It was noted on day 20 of his admission that his calcium (uncorrected) and phosphorus was 10.3mg/dL and 7.1mg/dL respectively with a calcium-phosphorus product of 73.1 mg²/dL². A low dialysate calcium bath at 1.25meq/L was initiated from 2.5meq/L and dialysis time was increased from 3.5 hours to 4 hours and 4 times weekly. Despite these measures, over the next few days calcium and phosphorus levels did not show improvement. Calcium-phosphorus product rose to a maximum of 135.7mg²/dL². An intact PTH was checked and normal at 26pg/mL. Calcium-based phosphate binders such as calcium carbonate or calcium acetate (Phoslo®) could not be used because of increasing calcium serum levels and calcium-phosphorus product. Sevelamer (Renagel®) could not be given due to the difficulty of crushing the tablets and the potential of obstructing the NG tube. Around this time, the patient developed extremely painful “tears” on the bilateral anterior lower legs. These lesions began as erythematous, indurated blisters/nodules that eventually ulcerated over approximately 2 weeks, resulting in necrotic eschar formation. Dermatology was then consulted (Figure 1) and a skin biopsy and cultures were performed.

Since sevelamer could not be used, dialysis was continued and lanthanum carbonate therapy (1000mg) was started 3 times daily. He also continued on low phosphorus tube feeds and meticulous wound care. Over the next 8 weeks, the calcium and phosphorus levels were much more manageable, with a product averaging 35.5 mg²/dL². His nutritional status improved with an albumin level of 3.8g/dL, and his intact PTH was still within normal limits at 27pg/mL. The patient’s skin lesions dramatically improved with these measures and the pain completely dissipated (Figure 2). The skin biopsy

revealed vascular calcification with intimal proliferation consistent with calciphylaxis (Figure 3).

The patient's functional status has improved with physical therapy and receipt of a successful kidney and liver transplant. No side effects in this patient have been observed with continued therapy with lanthanum carbonate.

DISCUSSION

Calciphylaxis has a prevalence rate of approximately 1%-4% in long-term hemodialysis patients, with 1-year survival of 45% and an 8-fold risk of death as compared to the general dialysis population.¹⁰ Sepsis is the major cause of death in these patients.¹¹ Clinical suspicion and the evolution of the classic skin lesion is the major clue to the diagnosis of this syndrome. Corresponding to the vascular nature of this disorder, patients typically present with a livedo reticularis pattern that progresses to exquisitely painful plaques. These plaques often have a stellate appearance, then ulcerate, and are covered in a black eschar. The lower extremities are the most common site of involvement.

Risk factors reported in the literature range from obesity and female gender to hypoalbuminemia and protein C or S deficiency (Table 1).^{3,7,12} These risk factors, in conjunction with key laboratory parameters of hyperparathyroidism, hypercalcemia, or hyperphosphatemia, should raise clinical suspicion of calciphylaxis. Levin et al described a mathematical formulation using some of these lab values as a surrogate in determining high-risk patients.¹³ Unfortunately, this has not been validated in subsequent studies. Skin biopsy is still the gold standard for diagnosis and shows calcification of the media of small cutaneous blood vessels with intimal hyperplasia, vascular thrombosis, cutaneous ulceration, and necrosis. Recently bone scintigraphy has emerged as a highly sensitive tool in diagnosing calciphylaxis and as an adjunct to track prognosis in treated individuals.¹⁴

Biomedical research has helped elucidate which cellular mechanisms are dysfunctional in patients with severe ectopic vascular calcification, ie, calciphylaxis. It has been shown that hyperparathyroidism is found in 82% of patients, hyperphosphatemia in 68%, hypercalcemia in 20%, and elevated calcium-phosphorus product in 33%.¹² What was once thought to be a passive deposition of calcium and phosphorus in blood vessels, now clearly points to an active and tightly regulated cell-mediated process.^{3,7} Many groups have shown that a complex set of endogenous factors may induce the increased mineralization of vascular beds much like bone formation, whether by up-regulation of calcium or phosphorus

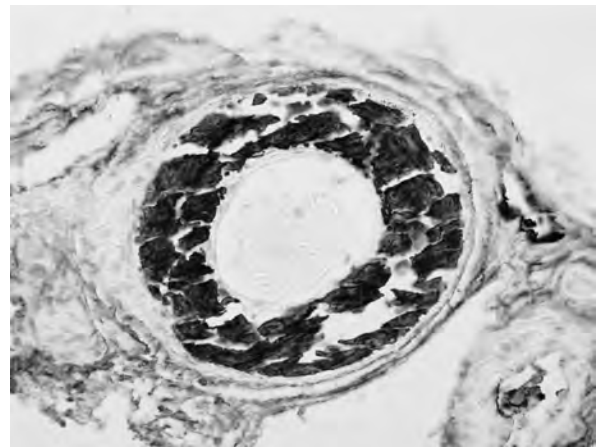


Figure 3. Von kossa stain showing calcium deposition of intima and media of vessel wall.

Table 1. Reported Risk Factors in Patients with Calciphylaxis

Calcium carbonate and acetate
Caucasian race
Cirrhosis
Corticosteroids
Crohn's disease
Diabetes mellitus
Elevated calcium-phosphorus product
Female gender
Human immunodeficiency virus
Hypercalcemia
Hyperparathyroidism (primary, secondary, tertiary)
Hyperphosphatemia
Hypoalbuminemia
Hypotension
Iron overload
Malignancy
Obesity
Protein C or S deficiency
Renal transplantation
Trauma
Vitamin D
Warfarin

deposition or down-regulation of inhibitors.

Matrix G1a protein (MGP), which originally was thought to promote calcification, has now been shown to be a potent inhibitor. In the MGP deficient mouse model, aggressive and uncontrolled vascular calcification occurs.¹² It has also been shown to be constitutively expressed in vascular smooth muscle cells and macrophages responsive to intimal injury.⁵ Experimental evidence also suggests that vascular smooth muscle may differentiate into a phenotype capable of inducing proteins of "osteoblastic" type activity. Both osteopontin and osteocalcin expression has been demonstrated to be up-regulated by a high phosphorus environment.⁵ Ahmed et al demonstrated in a controlled study of calciphylaxis

patients that osteopontin expression by vascular smooth muscle was seen in the setting of high phosphorus and calcium-phosphorus product.⁷ Moe et al further showed the importance of matrix Gla protein and $\alpha 2$ -Heremans-Schmid glycoprotein as inhibitors of vascular calcification in chronic kidney disease. $\alpha 2$ -Heremans-Schmid glycoprotein is an endogenous inhibitor of calcification that has been observed to be significantly lower in calciphylaxis patients.¹⁵ Based on experimental studies, elevated phosphorus levels seem to be the putative ion involved in elevation of calcium-phosphorus product and calciphylaxis.⁷ Lanthanum carbonate or FOSRENOL is a potent non-aluminum, non-calcium phosphate binder that was approved for use by the US Food and Drug Administration in October 2004. It is indicated to reduce serum phosphate levels in patients with end stage renal disease. It is not metabolized and is not a substrate or inhibitor of CYP450. It inhibits intestinal absorption of phosphate by forming highly insoluble complexes, thereby lowering serum phosphorus and calcium-phosphorus product. Well-designed studies have shown that doses of 375mg/day up to a maximum of 2250mg/day were effective in reducing phosphorus levels and calcium-phosphorus product as compared to placebo.¹⁶ Adverse effects were predominantly gastrointestinal, including nausea, vomiting, and abdominal pain, but in a majority of cases these doses were well tolerated. Pre-clinical data has shown minimal systemic absorption and, furthermore, bone biopsies in open-label active-controlled studies did not show differences in mineralization.¹⁶

Our patient's calciphylaxis developed over the course of weeks with no history of previous chronic kidney disease. The patient's laboratory markers were not typical of classic calciphylaxis with elevated serum PTH, and therefore pharmacologic measures such as cinacalcet or bisphosphonates could not be tried due to risk of adynamic bone. The need to control his calcium and phosphorus levels were critical due to excruciating pain and high risk for secondary infection of his skin lesions. In contrast to conventional treatment, lanthanum carbonate in combination with low-calcium dialysate and longer duration/frequency of dialysis provided a brisk response. More study is needed to determine whether the lanthanum carbonate was effective by decreasing the phosphorus levels or an active inhibitor of the mineralization process. Also, future therapeutic trials should investigate if treating an acute rise in phosphorus may mitigate potential detrimental effects such as vascular calcification.

CONCLUSION

In conclusion, our case report suggests an effective therapy for calciphylaxis in combination with modified hemodi-

alysis and meticulous wound care. The rapid response to treatment may hold promise for many patients suffering from this deadly and debilitating syndrome. Lanthanum therefore offers an exciting and new option for health care professionals, but more studies need to determine whether it can be used safely and efficiently in all forms of this enigmatic disease.

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