Cinacalcet for the Treatment of Calciphylaxis

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Calciphylaxis is characterized by cutaneous ischemia and necrosis and is associated with a very high mortality rate. It usually affects patients who are undergoing dialysis or who have received a kidney transplant. There is no optimal treatment, but parathyroidectomy has shown some benefit. We report herein a case of a patient with calciphylaxis and secondary hyperparathyroidism who was successfully treated with cinacalcet hydrochloride, a calcimimetic.

REPORT OF A CASE

A 62-year-old man was admitted to the hospital for gastrointestinal bleeding and was found to have an elevated international normalized ratio. The patient had a medical history of chronic nephrolithiasis from long-standing Crohn disease that required an ileostomy and end-stage renal disease that had resulted in a kidney transplant 2 years prior to presentation. During his hospitalization, the dermatology department was consulted because the patient had painful bilateral thigh ulcers, which had developed 4 months prior to admission.

On initial examination, the patient had a 3.0 × 4.0-cm ulcer with eschar and surrounding induration and violaceous discoloration on his right thigh. On his left thigh, there was a 2.5-cm × 4.0-mm linear hemorrhagic crust. In addition, he had violaceous discoloration in a livedo reticularis pattern over his lower extremities bilaterally. Laboratory evaluation on admission included the following findings: his calcium level was 7.9 mg/dL (2.0 mmol/L); phosphorus level, 5.5 mg/dL (1.8 mmol/L); albumin level, 3.3 g/dL; urea nitrogen level, 39 mg/dL (13.9 mmol/L); creatinine level, 4.0 mg/dL (305.0 µmol/L); intact parathyroid hormone level, 1080 pg/mL (reference range, 7-53 pg/mL); 25-hydroxyvitamin D level, 10.0 ng/mL (25.0 nmol/L) (reference range, 20-57 ng/mL [49.9-142.3 ng/mL]); and 1,25-dihydroxyvitamin D level, 11.1 pg/mL (28.9 pmol/L) (reference range, 15.9-55.6 pg/mL [41.3-144.6 pmol/L]). The calcium-phosphorus product was 43.5 mg/dL. Findings from an excisional biopsy of the right thigh ulcer showed focal ulceration with fibrinoid and hemorrhagic exudate. There were also numerous small vessel thrombi and deposits of calcium present within the deep blood vessel walls. These histologic findings indicated a diagnosis of calciphylaxis.

The patient was treated with silver sulfadiazine cream twice a day with aggressive wound care for the ulcers, vitamin D therapy, and phosphorus binders. The patient’s hypocalcemia and hyperphosphatemia improved with therapy. Although his persistently elevated parathyroid hormone level improved, there was no improvement in his wounds. Parathyroid imaging was negative for parathyroid adenoma. His elevated international normalized ratio was corrected with vitamin K supplementation, and he was discharged from the hospital.

One month later, his wounds had increased in size, with the right thigh ulcer increasing to 5 × 9 cm and the left thigh ulcer to 3 × 6 cm (Figure 1). On his posterior calves bilaterally, there were tender, erythematous, and indurated plaques ranging in size from 1 to 3 cm.

Figure 1. Large ulcer on the left thigh with eschar and surrounding erythema and induration before treatment with cinacalcet hydrochloride.
Calciphylaxis is characterized by progressive vascular calcium deposition and cutaneous ischemia and necrosis and usually affects patients with end-stage renal disease who are undergoing hemodialysis or have received a kidney transplant. Although there is no optimal treatment for calciphylaxis, there have been several reports of beneficial treatment using different modalities. These include low-dose tissue plasminogen activator, parathyroidectomy, hyperbaric oxygen, wound debridement, intravenous sodium thiosulfate, low-molecular-weight heparin, increased frequency of hemodialysis, and using a zero-calcium dialysate.

Our patient presented with clinical and histopathologic evidence of calciphylaxis. He also had secondary hyperparathyroidism induced by his end-stage renal disease. His parathyroid hormone levels were as high as 1080 pg/mL. He was considered to be a high-risk surgical candidate for parathyroidectomy, and continued wound care did not halt the progression of disease.

Parathyroidectomy prolongs survival in some patients with calciphylaxis, but its role is still controversial. Parathyroidectomy both lowers parathyroid hormone levels and helps restore normal calcium and phosphorous homeostasis, helping to reduce known risk factors for calciphylaxis. Because this patient was a high-risk surgical candidate, medical treatment with cinacalcet, a calcimimetic that has lowered parathyroid levels in patients receiving hemodialysis, was started. The patient received a daily dose of 30 mg of cinacalcet hydrochloride.

Several weeks after the initiation of therapy with cinacalcet, the patient reported less pain associated with the ulcers, and his parathyroid hormone level continued to decline (Table). On physical examination, the right thigh wound showed dramatic improvement with re-epithelialization of the ulcer, and the left thigh wound also began to heal. Five months after he began treatment with cinacalcet, both ulcers continued to heal and the patient noted symptomatic improvement (Figure 2). During this time, the patient did develop 4 smaller 1- to 3-cm ulcers over his lower extremities. Three of these wounds healed, and the fourth did not become larger. After 5 months of treatment, the dosage of cinacalcet hydrochloride was increased to 60 mg/d, and his parathyroid hormone level continued to decline. His last measured value was 147 pg/mL (Table).

The prevalence of calciphylaxis has been estimated to be approximately 4% in patients who are undergoing hemodialysis, and mortality estimates are as high as 87%. Prognosis has been shown to vary with lesion distribution, with survival rates ranging from 25% for proximal lesions and 75% for distal lesions. The pathogenesis of calciphylaxis (also referred to as uremic small-artery disease with medial calcification and intimal hyperplasia, uremic small-vessel disease, uremic gangrene syndrome, and calcific uremic arteriolopathy) is incompletely understood. Several risk factors have been identified, including secondary hyperparathyroidism, increased serum phosphate and calcium × phosphate product, female sex, diabetes mellitus, and protein C deficiency.

Parathyroid hormone, the main regulator of calcium homeostasis, is affected by calcium, phosphorous, and 1,25-dihydroxyvitamin D₃ levels. In patients with renal failure, there is an impaired ability to clear phosphorous and an impaired synthesis of 1,25-dihydroxyvitamin D₃, which result in hyperphosphatemia and decreased calcium absorption. These elements contribute to the development of secondary hyperparathyroidism, which is common in patients undergoing hemodialysis. In addition, a deficiency in vitamin D can exac-

Table. Patient Laboratory Values Over the Course of Several Months

<table>
<thead>
<tr>
<th>Date, 2005-2006</th>
<th>Parathyroid Hormone, pg/mL</th>
<th>Calcium, mg/dL</th>
<th>Phosphorous, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 1</td>
<td>1080</td>
<td>7.9</td>
<td>5.5</td>
</tr>
<tr>
<td>May 6</td>
<td>684</td>
<td>8.8</td>
<td>4.1</td>
</tr>
<tr>
<td>October 18</td>
<td>550</td>
<td>8.7</td>
<td>4.5</td>
</tr>
<tr>
<td>December 13</td>
<td>408</td>
<td>7.8</td>
<td>4.2</td>
</tr>
<tr>
<td>February 7</td>
<td>147</td>
<td>7.6</td>
<td>3.9</td>
</tr>
</tbody>
</table>

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; to convert phosphorous to millimoles per liter, multiply by 0.323.

*Therapy with cinacalcet hydrochloride was started in May. The reference range for parathyroid hormone is 7 to 53 pg/mL; for calcium, 8.5 to 10.1 mg/dL; and for phosphorous, 2.5 to 4.5 mg/dL.
erbrate secondary hyperparathyroidism. The medical treatment of secondary hyperparathyroidism includes control of hyperphosphatemia and therapy with calcitriol. Levels of parathyroid hormone are not uniformly elevated in patients with calciphylaxis, and some physicians have recommended parathyroidectomy only for patients with intractable secondary hyperparathyroidism uncontrollable by medical means. To treat the patient’s secondary hyperparathyroidism with very high levels of parathyroid hormone, therapy with cinacalcet, a class II calcimimetic that targets the calcium-sensing receptor of the parathyroid gland chief cells, was started. Cinacalcet induces conformational change in the calcium receptor, thereby increasing its sensitivity to circulating calcium. Cinacalcet has been shown both to lower parathyroid hormone levels and to improve calcium-phosphorous homeostasis in patients receiving hemodialysis in randomized, double-blind, placebo-controlled trials. It is indicated for both the treatment of secondary hyperparathyroidism in patients receiving hemodialysis and the treatment of hypercalcemia in patients with parathyroid carcinoma.

Cinacalcet is generally well tolerated, and nausea and vomiting are the most frequent adverse events identified. Hypocalcemia also occurs in approximately 5% of patients receiving cinacalcet (vs <1% in placebo group; P<.001). Hypocalcemia is rarely associated with symptoms and is treated by changing dosages of calcium-containing phosphate-binding agents or vitamin D sterols. Calcium levels should be closely monitored during therapy with cinacalcet.

Results in our patient demonstrated that cinacalcet may be a promising new approach to medically treat patients with calciphylaxis and secondary hyperparathyroidism. In addition to lowering the parathyroid hormone level, levels of calcium and phosphorus are also stabilized, which helps to correct potential risk factors that may be involved in the pathogenesis of calciphylaxis.

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5. Vassa N, Twardowski ZJ, Campbell J. Hyperparathyroidism: treatment of secondary hyperparathyroidism includes control by medical means. 15, 22

Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double-spaced with right margins nonjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPG files with each file numbered with the figure number. Material must be accompanied by the required copyright transfer statement (see authorship form [http://archderm.ama-assn.org/misc/auinst_cri.pdf]). Preliminary inquiries regarding submissions for this feature may be submitted to George J. Hruza, MD (ghruza@aol.com). Manuscripts should be submitted via our online manuscript submission and review system (http://manuscripts.archdermatol.com).