

Sodium thiosulfate for the treatment of warfarin-induced calciphylaxis in a nondialysis patient

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ABSTRACT

Calciphylaxis or uremic arteriolopathy is a complex process typically seen in patients with end-stage renal disease, but has also been reported in patients with normal renal function. However, therapies for calciphylaxis are based on reports of traditional patients (i.e., end-stage renal disease). A mainstay of therapy, sodium thiosulfate (STS), has been shown to be effective for the treatment of calciphylaxis. Without a standardized therapy reported for nondialysis patients there is a need for evidence-based therapy. Here, we report a case of a 63-year-old woman with an acute injury on chronic kidney disease ($\text{CrCl}_{\text{Baseline}} = 48 \text{ mL/min}$, $\text{CrCl}_{\text{AKI}} = 36 \text{ mL/min}$), not requiring dialysis, with warfarin-induced calciphylaxis. After 4 weeks of therapy with STS, sevelamer, alendronate, and enzymatic debridement the patient subjectively reported slight improvement of the necrotic ulcers but developed cellulitis on her nonaffected limb. Additionally, after 12 weeks of therapy she was readmitted for renal failure and subsequently required dialysis.

Key words: Calciphylaxis, chronic kidney disease, nondialysis, sodium thiosulfate, warfarin-induced

INTRODUCTION

Calciphylaxis is characterized by painful, necrotic ulcerations that often manifest in small to medium sized arteries ($<0.6\text{-mm}$ diameter).^[1] The most commonly affected sites are the lower extremities but reports of calciphylaxis occurring in hands, fingers, tongue, abdomen, and buttocks have also been noted.^[2] Many reports have listed a series of factors that can contribute to this disease (e.g., obesity, female gender, Caucasian ethnicity, hypercalcemia, hyperphosphatemia,

and a calcium–phosphate product $>70 \text{ mg/dL}$).^[1-2] Medications may also contribute to the development of calciphylaxis (e.g., warfarin, prednisone, and methotrexate).^[2] Calciphylaxis is a challenging disease to properly treat with the majority of those diagnosed having an increased mortality rate of 60–80%, secondary to sepsis.^[1]

Differential diagnoses include vasculitis, cellulitis, coagulopathies, calciphylaxis, and cholesterol embolism syndrome.^[1-3] Traditionally, calciphylaxis is thought to occur in patients that have end-stage renal disease or hyperparathyroidism, although there have been accounts of calciphylaxis occurring in patients with normal renal function and hypothyroidism.^[1,3]

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Pharmacologically, there are several options to treat calciphylaxis. These treatments vary with the complexity of the disease. We report a case demonstrating the occurrence of complications with STS for the treatment of calciphylaxis in a patient with acute kidney injury on chronic kidney disease. Slight improvement of previous ulcerations and the induction of vasculitis on the alternate extremity were observed after 4 weeks of therapy. After 12 weeks of STS infusions, the renal function dramatically declined leaving the patient dependent on dialysis.

CASE REPORT

In the current report, a 63-year-old Caucasian female with an extensive past medical history of diabetes mellitus type II, hypertension, atrial fibrillation, a 12-year history of warfarin use, and congestive heart failure was directly admitted from an outside dermatology clinic after presenting with a 2-month history of non-healing, necrotic ulcers located on her right lower extremity [Figure 1]. Over the past 2 months, the patient reported worsening pain, swelling, and noticeable brown spots on her lower right extremity. A computerized tomography (CT) scan revealed no lower extremity osteomyelitis. An initial biopsy reports listed a diagnosis of calciphylaxis, and the pathology was confirmed upon admission to the University hospital.

Initial lab results yielded a slightly elevated parathyroid hormone (PTH) value (82.5 pg/mL) with normal phosphorus (4.0 mg/dL), calcium (9.2 mg/dL), and magnesium (1.8 mg/dL) values. Prior to admission the patient was placed on a phosphate binder, sevelamer 800 mg three times daily. Upon confirmation of calciphylaxis, the patient underwent enzymatic debridement with collagenase and alendronate 10 mg once daily was initiated, while sevelamer 800 mg three times daily was continued.

The etiology of calciphylaxis in this patient was focused on a 12-year history of warfarin use for atrial fibrillation.



Figure 1: Nonhealing, necrotic ulcerations on the right lower extremity

Anticoagulation panels revealed a supratherapeutic INR of 3.54, normal protein C activity (56%) and decreased protein S activity (58%), consistent with warfarin use. Perceived as the main causal factor, anticoagulation therapy with warfarin was discontinued.

Upon admission, the patient had an acute kidney injury on chronic kidney disease. At baseline, the patient's serum creatinine was 1.7 mg/dL (CrCl = 48 mL/min), whereas upon admission it was 2.25 mg/dL (CrCl = 36 mL/min). Hyperkalemia was also present upon admission (5.8 mg/dL). The patient was gently rehydrated and taken off her home medication, spironolactone, to improve renal function. Renal function improved and hyperkalemia resolved the 5-day hospital stay (SCr = 1.84 mg/dL and K = 5.2 mg/dL, respectively). Endocrinology and nephrology services were consulted to determine the appropriate STS treatment regimen. Treatment consisted of outpatient intravenous STS 12.5 mg twice weekly for 4 weeks.

Four weeks post-discharge, and after a month of STS infusions, the patient was readmitted with left-lower extremity erythema and edema. At readmission, both calcium and phosphorus levels were found to be decreased compared to her initial presentation (8.7 mg/dL and 3.4 mg/dL, respectively). Laboratory and physical examination revealed new onset cellulitis. Slight improvement of the previously calciphylaxis-affected tissue was noted by the patient. At this time, although the frequency of STS infusions was increased from twice weekly to three times weekly, the dose remained set at 12.5 mg. Combination therapy with alendronate, sevelamer, and STS was continued throughout the hospital stay. Unfortunately, 15 weeks after the initial diagnosis of calciphylaxis the patient went into acute renal failure and became dialysis dependent.

DISCUSSION

The pathogenesis of calciphylaxis typically involves end-stage renal disease (ESRD) or chronic kidney disease but reports show that renal insufficiency is not required.^[4] In the presence of ESRD, secondary hyperparathyroidism contributes to an increased calcium-phosphate product (>70 mg/dL) that increases the risk of vascular calcification and thrombotic occlusion.^[4] However, this would not pose a significant risk to the patient in the current report who had a calcium-phosphate product of 36.8 mg/dL.

Warfarin-induced calciphylaxis has been noted in previous case reports.^[1] Warfarin is a nonspecific, vitamin K antagonist that blocks both vitamin K₁ and K₂. Vitamin K₁ is responsible for activating clotting factors while vitamin K₂ prevents the deposition of calcium in the vasculature. Not only does warfarin increase the amount of calcium in the vasculature but a review of literature found calciphylaxis to be associated

with decreased levels of protein C and S.^[4] These findings are also consistent with the present case.

Treatment consists of discontinuation of any medication contributing to the disease process. In the current case, a 12-year history of warfarin use in conjunction with a supratherapeutic INR warranted the discontinuation of warfarin. Alternative anticoagulants were considered; however, due to renal insufficiency and patient preference, antiplatelet therapy with aspirin 325 mg daily was initiated.

Enzymatic debridement and STS were utilized for the treatment of advanced calciphylaxis. Surgical or enzymatic debridement is of utmost importance in the treatment of nonviable tissue.^[5] Enzymatic debridement may be more effective than surgical debridement in an effort to minimize tissue damage to areas that have poor wound healing.^[5]

Although the exact mechanism is controversial, STS has been utilized for the off-label treatment of calciphylaxis. Studies propose that for the treatment of calciphylaxis, STS either works to form complexes that dissolve calcium–phosphate precipitations, or by direct extracellular effects. The use of STS was described by Raymond and Wazny.^[2] Literature suggests STS therapy should be initiated at 25 mg two to three times a week after hemodialysis; however, there is no standard dose or duration of therapy for the treatment of calciphylaxis.^[2,5] The majority of reports provide dosing for patients on dialysis but do not provide dosing recommendations for patients with normal renal function. In the previously reported cases involving patients with normal renal function, doses ranged from 12.5 to 25 mg three times a week and the duration of treatment ranged from 4 to 9 months.^[2]

Pharmacokinetically, STS has a half-life of 15 minutes in patients with normal renal function and 28.5% is eliminated unchanged in the urine.^[2] Drug parameters are significantly changed in patients undergoing dialysis (half-life = 478 minutes).^[2] Adverse effects related to STS include nausea, vomiting, infusion reactions, and metabolic acidosis.^[2,4]

Bisphosphonates are used to aid in treating calciphylaxis by inhibiting macrophages and proinflammatory cytokines. While long-term use of agents in this class (etidronate, pamidronate, ibandronate) have been used in combination with STS, the majority of patients that underwent bisphosphonate therapy were receiving hemodialysis.^[2] These reports may be skewed due to the number of case reports of calciphylaxis in patients requiring dialysis in the literature.

Another agent that has been used in combination with STS and bisphosphonates is the calcimimetic cinacalcet.^[6] The use of cinacalcet for calciphylaxis is reserved for patients with secondary hyperparathyroidism that present with elevated PTH

levels (269–2324 pg/dL).^[2] Treatment with oral cinacalcet is initiated at 30 mg daily; the longest duration of therapy reported was over a year.^[2,5]

The multifactorial pathogenesis requires supportive therapy to be the mainstay treatment. Utilization of alternative therapies such as hyperbaric oxygen therapy to theoretically promote angiogenesis or receiving a parathyroidectomy to restore calcium–phosphate balance have also been reported.^[1,2,4-6]

CONCLUSION

In conclusion, we report a case in which a woman with CKD, not requiring dialysis, was treated for warfarin-induced calciphylaxis with STS for a total duration of 12 weeks. Initial improvement of calciphylaxis on the right lower extremity was seen; however, cellulitis of the left lower extremity developed after 4 weeks of therapy. Combination therapy with alendronate, sevelamer, and STS regimen was similar to that reported in literature for patients receiving dialysis. Unfortunately, 15 weeks post initial diagnosis of calciphylaxis, the patient progressed to renal failure and is now dialysis dependent. Further investigation into treatment options and dosing regimens for nondialysis patients suffering from calciphylaxis is warranted.

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Conflicts of interest

There are no conflicts of interest.

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