CLINICAL VIGNETTE

Calciphylaxis Complicated STS-induced Anion Gap Metabolic Acidosis

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Introduction

Calciphylaxis, or calcific uremic arteriolopathy, is a rare disorder caused by the deposition of calcific precipitates within the peripheral vasculature. It has high morbidity and mortality due to vascular injury associated with thrombus formation which leads to tissue ischemia and necrosis. It is typically seen in patients with end-stage kidney disease, most commonly in patients on renal replacement therapy, especially those on peritoneal dialysis.[1] Sodium thiosulfate (STS) is one of the few targeted systemic treatments for calciphylaxis. It is generally well-tolerated but has been associated with a potentially life-threatening anion-gap metabolic acidosis.[2] Partially due to not fully defined mechanism of action, evidence is lacking to define ideal STS dosing in calciphylaxis treatment.[3] We describe a young woman on peritoneal dialysis with limb-threatening calciphylaxis treated with intravenous STS. She developed dose-dependent anion-gap metabolic acidosis associated with severe GI symptoms which improved with dose-reduction.

Case

A 29-year-old female with type 1 diabetes and end stage kidney disease on peritoneal dialysis presented with progressive necrotic skin lesions of her extremities. One month prior to admission to our department, she was hospitalized at a community hospital with several non-healing right foot ulcers. She was found to have diffuse calcified atherosclerotic plaques along the right superior femoral and tibial arteries. The affected areas were not amenable to lytic therapy or targeted revascularization and resulted in a below-the-knee amputation. A skin biopsy was unable to yield a diagnosis. She then underwent a left lower extremity angiogram with angioplasty of a severe superficial femoral arterial lesion. Similar painful, progressive, ulcerated, non-healing ulcers developed along the left lower and upper extremities. She was then transferred to our hospital for continued care.

At the time of transfer, she had severe pain in her extremities but no fevers, chills, nausea, vomiting, diarrhea, or abdominal pain. Laboratory studies included a venous blood gas and metabolic panel which showed a venous pH of 7.43, pCO2 of 45 mmHg, and serum bicarbonate of 29.3 mmol/L with an anion gap of 19. Extensive rheumatologic and infectious testing included anti-nuclear antibodies and subsets, anti-cardiolipin antibodies, antineutrophil cytoplasmic antibodies (ANCA) antibodies, hepatitis serologies, QuantiFERON GOLD ELISA assay for tuberculosis, were all unrevealing. Angiogram of the left lower extremity showed two-vessel run-off without any focal lesions.

Skin punch biopsy of the lower extremity showed full-thickness tissue necrosis with intravascular fibrin thrombi and foci of calcium staining consistent with calciphylaxis. Tissue fungal and bacterial cultures were negative and there was no evidence of vasculitis. She was started on IV heparin and transitioned from peritoneal dialysis to hemodialysis for increased clearance. Intravenous STS 25g three times weekly was given during the last hour of each hemodialysis.

During the following two weeks of STS therapy, there was a gradual increase in the anion gap which peaked at a value of 35 along with a venous pH of 7.32, pCO2 of 39mmHg, and serum bicarbonate of 19.5 mmol/L. This was associated with worsening, severe RUQ abdominal pain with oral intolerance and intractable vomiting. There was no evidence of an active infection, acute appendicitis, cholecystitis, or diabetic ketoacidosis. Lactate and BUN levels remained unremarkable.

HD was modified with a high bicarbonate buffer solution along with supplemental bicarbonate and earlier timing of STS administration during HD. Unfortunately, this did not resolve the anion gap nor the patient's symptoms. A trial of dose-reduced STS to 12.5g was initiated. Within three days of dose reduction, the patient's symptoms markedly improved and labs now showed a venous pH of 7.37, pCO2 42 mmHg, and serum bicarbonate 23.7 mmol/L with an anion gap of 19. The patient continued to tolerate the dose-reduced STS regimen. However, there was notable progression of her skin lesions on the reduced dose. She was transitioned back to STS 25g administered during the last hour of dialysis with close ongoing monitoring of acid/base status. After discussion and shared decision making with the patient, the higher dose was continued to maximize therapeutic benefit and minimize the risk of further limb loss.

During the weeks following discharge, the patient developed intermittent spells of severe nausea, vomiting, abdominal pain, as well as recurrent anion gap acidosis which required frequent hospitalization. These episodes occurred while she remained on STS 25g dosing for the following 3 months. Gastrointestinal symptoms improved after her wounds stabilized and allowed for discontinuation of STS therapy.

Discussion

Calciphylaxis is a rare, poorly understood disease that causes calcific skin lesions commonly deposited in the peripheral vasculature. The pathophysiology is thought to involve the reduction of blood flow due to calcium deposits which leads to endovascular fibrosis, vascular thrombosis, and hypertrophied blood vessels. This leads to complications including tissue necrosis, limb ischemia, non-healing ulcers, and secondary skin and bloodstream infections. Diagnosis can be confirmed through skin biopsy, preferably in a non-ulcerated peripheral limb. One year mortality rates for calciphylaxis patients have been reported as high as 45.8% with high associated morbidity.[4]

Treatment options are limited but are aimed at maximizing supportive care measures such as optimizing parathyroid hormone and serum calcium levels, aggressive wound care, infection prevention, and pain management. Intravenous sodium thiosulfate has emerged as the primary targeted systemic treatment option with reports of an associated increase in 1-year survival of up to 75%.[5] While generally well-tolerated, rapid administration of concentrated STS solutions has been associated with gastrointestinal symptoms such as nausea and vomiting, as well as sepsis and a high anion-gap metabolic acidosis as seen in our patient.[3,6,7]

STS is a calcium chelator and potent antioxidant.[8] There have been proposed theories on how STS induces acidosis but the exact mechanism is still unclear. STS metabolites such as thiosulfuric acid and hydrogen sulfite have a 95% renal clearance and can accumulate in patients on renal replacement therapy which likely contributes to acidosis.[2]

Tt is hypothesized that a *mild* acidosis may augment calcium solubility and promote healing which may support the most common dosing strategy of administering STS at the higher dose of 25g during the final hour of three times weekly dialysis.[2,9,10]

Historically, acidosis associated with STS has been treated with adjustments in the dialysate buffer or with supplemental bicarbonate dosing.[11] However, in our patient's case, these adjustments were made without significant improvement in acidosis of symptoms. It has also been reported that the acidifying effect can be attenuated by administering STS earlier during dialysis; however, this strategy is not always effective and may lead to reduction in clinical efficacy.[9]

Conclusion

Calciphylaxis continues to be challenging to treat due to its complexity, sudden progression, and lack of treatment guidelines. There is a paucity of data to support STS or any other specific therapies as efficacious and safe treatment options.[6]

Despite absence of data, STS remains as the most widely accepted targeted systemic therapy for calciphylaxis.[7] There remains a gap in knowledge on mechanism of action and a lack of consensus on optimal dosing strategies. With increasing prevalence of calciphylaxis, it is important for clinicians to be aware that individualized dosing strategies may be necessary to strike a balance between maximizing therapeutic effectiveness while minimizing toxic effects.[1]

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