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Sodium-Thiosulfate Induced Life-Threatening Metabolic Acidosis Limiting Treatment of Calciphylaxis

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Study Design A
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Statistical Analysis C
Data Interpretation D
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Patient: Male, 53-year-old
Final Diagnosis: Calciphylaxis
Symptoms: Non-healing skin ulcers • confusion • metabolic acidosis
Medication: STS
Clinical Procedure: Hemodialysis
Specialty: General and Internal Medicine • Nephrology

Objective: Rare disease

Background: Calcific uremic arteriolopathy (CUA) is a rare and incredibly painful cutaneous disorder secondary to microvascular involvement in which calcium dysregulation leads to stenosis of medium sized arterial blood vessels along with endothelial dysregulation and thrombosis. Ultimately, these patients are at high risk for non-healing wounds with risk of death from sepsis and multi-organ failure. It is a poorly understood condition with limited therapies that do not offer mortality benefit. Prevalence is about 4% in hemodialysis patients. Sodium thiosulfate (STS) can be used in hemodialysis patients but therapy is often limited by the development of high anion gap metabolic acidosis.

Case Report: A 53-year-old male who had end stage renal disease and who was on hemodialysis and taking warfarin for bio-prosthetic mitral valve replacement and atrial fibrillation presented with non-healing right lower extremity cellulitis which had failed outpatient treatment. A skin biopsy of the lesion was consistent with CUA. The patient failed to improve on calcitriol and cinacalcet and was started on intravenous STS. Subsequently, he developed life threatening metabolic acidosis requiring a bicarbonate drip. He died 12 weeks after his initial diagnosis of CUA.

Conclusions: This article seeks to describe how the treatment of CUA; a rare disease with high mortality, is limited by the development of metabolic acidosis when using STS therapy. There is an 80% mortality rate within 6 months from CUA with major adverse effect of a high anion gap metabolic acidosis. Further research is needed in the field of establishing optimal dosing and frequency.

MeSH Keywords: Acidosis • Calciphylaxis • Gold Sodium Thiosulfate • Kidney Failure, Chronic • Warfarin

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/919926

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Background

Calcific uremic arteriolopathy (CUA) lesions often appear purpuric and violaceous. As the area becomes more avascular, necrotic patches start to form. As these lesions form, patients become more susceptible to sepsis [1]. The pathophysiology of this condition is poorly understood. CUA usually occurs in end stage renal disease patients and is associated with hyperparathyroidism. Risk factors include hyperphosphatemia, calcium-phosphate product >70 mg^2/dL^2, erythrocyte sedimentation rate (ESR) >30 mm/hour, hypercalcemia, and hypoalbuminemia [2]. The overall involvement of warfarin induced calciphylaxis is rare but devastating, with the first appearance of rash at 6 months to 1 year after starting warfarin. Lesions are usually more proximal and severe. Pathologically, there is calcification of the vasa media in contrast to cardiovascular atherosclerosis where it occurs at the level of the intima [1].

Treatment focuses on correcting the calcium-phosphorous-parathyroid axis. In patients undergoing hemodialysis, sodium thiosulfate (STS) can be used intravenously as was the case in our patient. STS functions as a chelating agent with the thiosulfate component forming soluble complexes with calcium, thereby lower the solubility product [3,4]. It also leads to vasodilation by favorably upregulating activity of nitric oxide synthetase. STS also has paracrine activity on neighboring endothelial cells leading to the regeneration of the glutathione stores; the proposed mechanism for its antioxidant effects. Additionally, elevated serum concentration of phosphorous induces change in intracellular expression of adipocytes such that they mimic osteoclast-like behavior worsening calcification. STS delays this progression by up to 3 days; and given the short half-life (ranging up to 3 to 4 hours) of STS, the function is suggestive of metabolite action. STS will degrade to hydrogen sulfide *in vivo* which independently is a stimulator of angiogenesis [4]. Hydrogen sulfide is renally excreted (95%) and thus the concern for metabolite buildup is high in chronic/end stage renal disease patients in which renal clearance is already significantly reduced [3]. The mechanism of acidosis is believed to be secondary to inhibition of the final step of the electron transport chain, the ATPase. Additionally, thiosulfuric acid can form *in vivo*. The high sodium content can also lead to volume expansion acidosis [3]. Although mild acidosis is desirable for the increased solubility of calcium-phosphate; the optimal frequency and dosing has not been established. It is usually started at 25 g intravenous (IV), administered at the end of hemodialysis session thrice weekly [5]. Large studies are limited by the rarity of the disease and toxic profile. Data that is available has been collected from case reports, series, and animal study models. Hence its dosing and frequency is determined on a trial and error basis. Surgical intervention has been debated as it can be used to remove necrotic tissue, eschar, and adjacent inflamed dermal tissue, however, this can trigger further deposition in that region [6]. In our patient, debridement was not pursued.

Additional measures include the use of cinacalcet. This may be temporarily related to the fact that it works to decrease the parathyroid hormone (PTH) levels by increasing the sensitivity of the Ca-sensing receptor on the surface of the parathyroid gland [4]. In our patient cinacalcet alone was ineffective. New studies are looking into serological markers for patients that may be at increased risk of CUA by looking at the concentration of PIVKA-II.

Case Report

This case describes a 53-year-old male who had multiple comorbidities including heart, lung, and end stage renal disease. Specifically, the heart disease included coronary artery disease with pacemaker placement for heart failure with reduced ejection fraction, atrial fibrillation, mitral valve repair and severe aortic stenosis. Lung disease included chronic obstructive pulmonary disease. The patient's end stage renal disease was secondary to IgA nephropathy. His first renal transplantation was performed in 1986. That renal transplant lasted 16 years and then failed. A second transplantation was attempted in 2002 but was unsuccessful. He had been on dialysis since 2003.

He presented to the emergency department for non-healing right lower extremity eschar after failing outpatient treatment with doxycycline for cellulitis. Computed tomography of bilateral lower extremities showed extensive soft tissue stranding of subcutaneous tissues and soft tissue ulceration of the right fore foot. No discrete abscess, osteomyelitis, or soft tissue gas was seen. Given that patient did not have a history of diabetes mellitus the pretest probability of a cellulitis was low and suspicion for CUA was high. The location of the violaceous lesions was unusual as CUA usually shows occurrence in areas with more adipose tissue (e.g., thighs, abdomen). However, given the uncontrolled hyperparathyroidism with PTH of 206 pg/mL and concurrent warfarin use, both of which are associated with CUA, treatment was started immediately with STS; denoted as Day 0. Skin biopsy was performed on Day 4 (after suspected CUA). Skin biopsy resulted on Day 12 which was consistent with CUA showing concentric calcifications of the subcutaneous capillaries. Unfortunately, he could not come off anticoagulation given his mitral valve.

High anion gap and low bicarbonate was presumed to be likely reflective of thiosulfate-induced anion gap acidosis. Patient was started on STS 25 mg thrice weekly after hemodialysis on Day 0. He received a total of 2 doses along with 2 sessions of dialysis before he developed severe high anion gap metabolic acidosis (HAGMA). On Day -1, prior to administration,

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Table 1. Electrolyte disturbances after STS initiation (day 0).

Day number	–1*	0 STS	1	2	3	4	5	6	13
Electrolyte									
Sodium [Ref. range 136–145 mmol/L]	139	134	136	137	137				
Potassium [Ref. range 3.5–5.1 mmol/L]	4.2	4.2	4.1	4	4.4				
Chloride [Ref. range 98–107 mmol/L]	99	95	91	90	88				
Bicarbonate [Ref. range 22–29 mmol/L]	24	19	17	17	18	14	15	20	25
BUN [Ref. range: 6–20 mg/dL]	17	27	16	24	17				
Creatinine [Ref. range: 0.4–1.0 mg/dL]	4.2	5.6	3.6	5	3.4				
Anion gap [Ref. range 8–15 mmol/L]	16	20	28	30	31	36	36	24	19

Day –1: denotes the day prior to initiation of STS; Day 0: denotes first day of STS administered; Day 1, 2... represent the days post-initiation of STS. Note on Day 4 Arterial blood gas was pH 7.28, pCO_2 39 mmHg, pO_2 47 mmHg; lactic acid 1 mg/dL. BUN – blood urea nitrogen. Reference ranges and units are written in parenthesis.

the patient had anion gap of 16 mmol/L with bicarbonate of 24 mmol/L. Post STS Day 1 the patient developed anion gap of 28 mmol/L with bicarbonate of 17 mmol/L. STS was held on Day 4 with subsequent dose reduction to 12.5 g thrice weekly post hemodialysis. Hemodialysis was postponed to Day 5 with planned treatment duration of total of 3 months. See the Table 1 regarding anion gap trend. The worsening HAGMA necessitated the need for dialysis on a higher bicarbonate bath solution. On Day 4 the patient's anion gap peaked at 36 mmol/L and his bicarbonate level was 14 mmol/L. Oral sodium bicarbonate 650 mg thrice daily was started on Day 4.

The patient had an episode of bloody emesis on Day 10. He underwent esophagogastroduodenoscopy (EGD) which showed gastropathy. He was started on pantoprazole 40 mg intravenously twice daily and warfarin was continued. The decision to avoid a change to a direct oral anticoagulant was made as end stage renal disease patients are at an increased risk of bleeding and apixaban is non-dialyzable.

On Day 11 Aranesp (erythropoietin stimulating agent 10 000 U subcutaneously thrice weekly) was started at 100 mcg subcutaneously weekly. Hyperbaric specialist was consulted for wound care.

For poorly controlled secondary hyperparathyroidism with PTH of 20 pg/mL, the patient was continued on Sensipar 30 mg daily. Sensipar had been administered to the patient for the past 2 years when his PTH was as high as 1679 pg/mL. No phosphate binders were given due to the patient's poor appetite.

The patient was discharged on Day 15 post STS administration with outpatient STS sessions scheduled post dialysis. Unfortunately, a concurrent problem was the inability of the patient to tolerate hemodialysis as an outpatient due to recurrent hypotension from severe aortic stenosis requiring total aortic valve replacement. In addition, transcatheter aortic valve replacement (TAVR) could not be performed due to poor surgical candidacy. Therefore, STS was not administered as outpatient treatment.

He was re-admitted Day 52 for high anion gap metabolic acidosis with anion gap of 28 mmol/L and bicarbonate of 18 mmol/L along with sepsis and multiorgan failure.

Despite dialysis inpatient and other measures patient became progressively encephalopathic and lethargic. He was placed on comfort care measures and expired on Day 64 after first initiating STS.

In summary: treatment with STS was started on Day 0. The patient developed severe acidosis on Day 4 after 2 doses of STS. He was discharged on Day 15 after started STS with improvement of his acidosis. Unfortunately, he was unable to receive STS outpatient treatment for the total duration of planned treatment due to recurrent hypotension sustained during hemodialysis. The cause of hypotension; severe aortic stenosis required TAVR procedure, but patient was poor surgical candidate. He continued to deteriorate and was readmitted this time with sepsis secondary to worsening cellulitis from open wounds due to the CUA.

Vital signs during the initial period of acidosis are described below. On admission vitals were: temperature 36.4°C, heart rate (HR) 74 beats per minute, respiratory rate (RR) 18 breaths per minute, blood pressure (BP) 103/63 mmHg. Significant

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laboratory results included: white blood cell (WBC) 6.1×10^3/uL, hemoglobin (Hb) 10.3 g/L and hematocrit (Hct) 30% and platelet count 930 000 per µL.

Discussion

In this patient case, warfarin was an important risk factor for CUA. He was taking warfarin for atrial fibrillation and mitral valve replacement. Warfarin will increase the rate of atherosclerosis due to the antagonist activity of warfarin against vitamin K which leads to a loss of function of the glycoprotein 1 A protein. Normally this protein works to inhibit arterial calcification. New studies are looking into serological markers for patients that may be at increased risk of CUA by looking at the concentration of PIVKA-II which is elevated in patients taking warfarin [7]. Primary treatment of warfarin induced calciphylaxis is to stop the warfarin; however, it could not be stopped due to valve replacement surgery.

The original article by Seyle (1962) [8] indicated that an elevated calcium phosphorous product led to precipitation known as calciphylaxis. However, calciphylaxis is still possible in the absence of an elevated product. In our patient, the calcium (7.6 mg/dL (corrected for albumin))-phosphorous (4 mg/dL) product was 30.4. mg^2/dL^2. As per the original study by Selye, precipitation occurred at levels greater than 70 mg^2/dL^2; with goal of <54 mg^2/dL^2 in chronic kidney disease (CKD) patients. Despite the absence of an elevated product; our patient did have significant secondary hyperparathyroidism with PTH of 206 pg/mL, and elevated inflammatory markers including ESR of 130 mm/hour and C-reactive protein (CRP) of 58 mg/L; along with mild hypoalbuminemia which are contributing risk factors.

Meta-analysis by Udomkarnjananun et al. showed that the average duration of thiosulfate treatment was for 20 weeks with an average dose of 56 g per week and total cumulative dose of 1155 g (equivalent to about 45 treatments of 25 g) [6]. In our case the patient received a weekly dose of 37.5 g. Higher dosing was prohibited by the development of a high anion gap metabolic acidosis. Arterial blood gas showed pH of 7.28, $paCO_2$ level of 39 mmHg, with bicarbonate of 21 mmol/L shortly after STS was started and subsequently dropped to 16 mmol/L within the next 4 weeks. The anion gap peaked at 36 mmol//L with mean range in the mid to high 20s. The patient was started on bicarbonate but failed to improve. The proposed mechanism of acidosis from STS is believed to be due the buildup of the metabolite hydrogen sulfide which is a known inhibitor of the terminal step in the electron transport chain [9]. This is particularly a problem in patients with chronic/end stage renal disease in which clearance is significantly reduced.

Unfortunately, our patient died 12 weeks after the first diagnosis of calciphylaxis. Our review of literature showed that different dosing strategies have been used including small daily doses as well as large bolus amounts dosed less frequently. Neither has shown benefit over the other and mortality remains high despite treatment. Furthermore, other treatment modalities including cinacalcet, parathyroidectomy, hyperbaric oxygen, and bisphosphonate therapy have shown no benefit when compared to STS [10,11]. Studies have relied largely on retrospective analysis. There are no randomized control trials investigating the use of STS.

In this case, the patient was unable to tolerate the treatment of CUA with STS because of life-threatening acidosis. When the acidosis had improved, unfortunately the degree of aortic stenosis was the limiting factor for hemodialysis to be performed in an outpatient setting as the patient became hypotensive and hemodynamically unstable and thus unable to tolerate hemodialysis. The duration of the planned STS therapy could not be given. Meanwhile the non-healing skin ulcerations served as a portal of entry for bacterial invasion and subsequent infection. As it has been well documented in the literature on CUA, the most common etiology of death is due to sepsis, as was the case with this patient.

Conclusions

Calciphylaxis is a disease with poorly defined pathology and treatment. At best, we have sodium thiosulfate that has limited ability to improve the severity of the cutaneous lesions but does not affect the rate of mortality. STS needs to be investigated more thoroughly to determine the optimal dosing schedule along with duration of therapy required to establish mortality benefit.

Conflicts of interest

None.

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