

Treatment of Calciphylaxis: A Case for Oral Sodium Thiosulfate

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Calciphylaxis is a major cause of morbidity and mortality in end-stage renal disease (ESRD). Intravenous sodium thiosulfate (STS) is the mainstay of therapy for calciphylaxis. In peritoneal dialysis (PD) patients with calciphylaxis, intravenous STS poses logistic and financial challenges. Even though pharmacokinetic studies show poor bioavailability of oral STS, we report successful use of oral STS in 2 PD patients with calciphylaxis.

A 55-year-old Latina American woman with diabetes was initiated on PD after access failure and chronic hypotension. She developed painful ischemic lesions in the left middle finger and left big toe 4 months later. The ischemia in the left hand progressed, requiring amputation of two fingers. She later developed extensive painful calcific areas in the abdominal wall. She was initially started on oral STS 1500 mg twice daily that was subsequently increased to 3750 mg daily, which resulted in substantial pain relief and a decrease in the size of the calcific plaques.

Another diabetic patient with ESRD who was on PD presented with a painful ischemic finger for 2 years. He was treated with oral STS 1500 mg twice daily, resulting in prompt pain relief.

Oral STS can be an effective treatment for calciphylaxis.

Key words

Calciphylaxis, calcific uremic arteriolopathy, sodium thiosulfate, chronic kidney disease, chronic peritoneal dialysis

Introduction

Calciphylaxis is a painful and ominous complication of end-stage renal disease, associated with a 45% – 80% 1-year mortality (1,2). Treatment approaches

focus on reducing the calcium–phosphorus burden by avoiding calcium-containing phosphorus binders; minimizing or avoiding vitamin D analogs; using calcimimetic agents such as cinacalcet, intravenous or intralesional sodium thiosulfate (STS), or bisphosphonates; intensifying dialysis; applying hyperbaric oxygen; or judiciously using anticoagulants and tissue plasminogen inhibitor in patients with protein C deficiency or low antithrombin III activity (or both). Restoration of blood flow and pain management are also important aspects of managing patients with this complication.

Administration of intravenous STS can be arranged fairly readily in patients on in-center hemodialysis (HD), but nephrologists face logistic and financial barriers in arranging intravenous therapy outside of the center for patients on home dialysis modalities such as peritoneal dialysis (PD) and home HD. The intraperitoneal administration of STS comes with challenges such as risk of contamination, the need for the patient to come to the center, cost, sodium loading, and the intermittent nature of treatment for an ongoing pathology. Oral administration of STS offers the potential advantages of ease of administration, avoidance of peritoneal access, daily administration of treatment for an ongoing disease, and reduced cost.

We report our successful experience with oral STS in the treatment of calciphylaxis in 2 PD patients, and we review the existing relevant literature.

Case descriptions

Patient 1

A 55-year-old Latina American woman with diabetes and a history of multiple abdominal surgeries for ovarian cancer was initiated on PD after vascular access failure and chronic hypotension. She developed painful ischemic lesions in the left middle finger and the first toe of her left foot 4 months later. She also developed extensive painful calcific

plaques in the abdominal wall suggestive of calciphylaxis. Her mean serum calcium was 9.23 mg/dL (range: 8.3 – 9.7 mg/dL); mean phosphorous, 5.37 mg/dL (range: 3.9 – 9.4 mg/dL); and mean parathyroid hormone, 361.22 pg/mL (range: 101.5 – 622 pg/mL). In view of the logistic difficulties in obtaining intravenous access and transporting a patient with severe pain, off-label use of oral STS was started on October 31, 2013. The STS was obtained from a compounding pharmacy and was started at a dose of 750 mg, 2 capsules twice daily.

The ischemia in the patient's left hand progressed, requiring amputation of the middle and ring fingers on November 13, 2013. The incision healed, but was complicated by phantom limb pain. Histopathology of the amputated specimen showed ulceration with focal and acute inflammation and calcific atherosclerosis in the resected margins of the ring finger. For pain management, in addition to gabapentin and hydrocodone with acetaminophen, the patient applied topical lidocaine over the intact skin along the dermatomes shared by the calcified plaques. By January 30, 2014, treatment with topical lidocaine, gabapentin 300 mg daily, and acetaminophen 1500 mg daily resulted in analgesia in the abdominal wall and left hand and foot; the patient was therefore able to discontinue narcotics and return to work full time.

The ulcer in the left first toe healed, and the patient had no side effects from the STS, other than persistence of diarrhea that had existed before she started on STS. Her mean anion gap was 25 during the 3 months before STS was started and 24.8 during the 11 months after STS start. With the exclusion of one anion gap measurement of 37 when the patient was hypotensive (systolic blood pressure < 70 mmHg during one of her visits 2 months after STS start), her mean anion gap was 23.6. During the next several months, the plaques softened and decreased in size. Figure 1 presents serial images showing improvement after oral STS start.

In December 2014, the patient presented with small-bowel obstruction requiring laparotomy and adhesiolysis. Her postoperative course was complicated by shock, with intestinal ischemia leading to death. Outside of her 2 hospitalizations, the patient was able to work during the last year of life. She and her husband were appreciative for the extra year of functional life with effective pain relief.

Patient 2

A 51-year-old diabetic man on PD after failed kidney transplantation presented with a painful ischemic finger 2 years after a complicated vascular access surgery, vascular access steal syndrome, and ligation of the arteriovenous graft without any pain relief. The patient had a painful ulcer in the right fourth finger. His mean serum parathyroid hormone was 436.23 pg/mL (range: 339 – 500.9 pg/mL); mean phosphorous, 3.55 mg/dL (range: 2.9 – 4.5 mg/dL); and mean corrected calcium, 9.58 mg/dL (range: 9.3 – 10.1 mg/dL).

The patient was treated with oral STS 1500 mg twice daily, resulting in prompt relief of pain 4 days after starting STS. The wound healed over a period of several months, and the patient experienced no side effects from the STS. His mean anion gap was 13.3 (range: 11 – 20) during the 6 months before starting STS and 14.5 (range: 9 – 19) during the 6 months after STS start.

The patient was relieved to finally be able to use the affected hand after 2 years of functional loss because of pain. Figure 2 presents serial images showing improvement after oral STS start.

Discussion

Vascular calcification is commonly seen in patients with chronic kidney disease, and cardiovascular events are responsible for almost 50% of the mortality in the HD population. Coronary calcification is an almost universal observation in patients on HD at 20 years of age or older, and the calcification progresses rapidly (3). In addition to a high prevalence of neointimal calcification of atherosclerosis, which is associated with a high prevalence of coronary artery disease in the general population, patients with end-stage renal disease also have medial calcification (Mönckeberg atherosclerosis). As shown by Moe and Chen, a high coronary artery calcium score is directly correlated with the risk of myocardial infarction (4). The same study also showed a high incidence of aortic or mitral valve calcification in end-stage renal disease and a direct correlation with dialysis vintage (4).

Causes of vascular calcification

Vascular calcification involves the transformation of vascular smooth muscle cells into osteoblast-like cells, which lay down a bone matrix of type I collagen and non-collagenous proteins. That framework acts as a nidus for mineralization, which results in

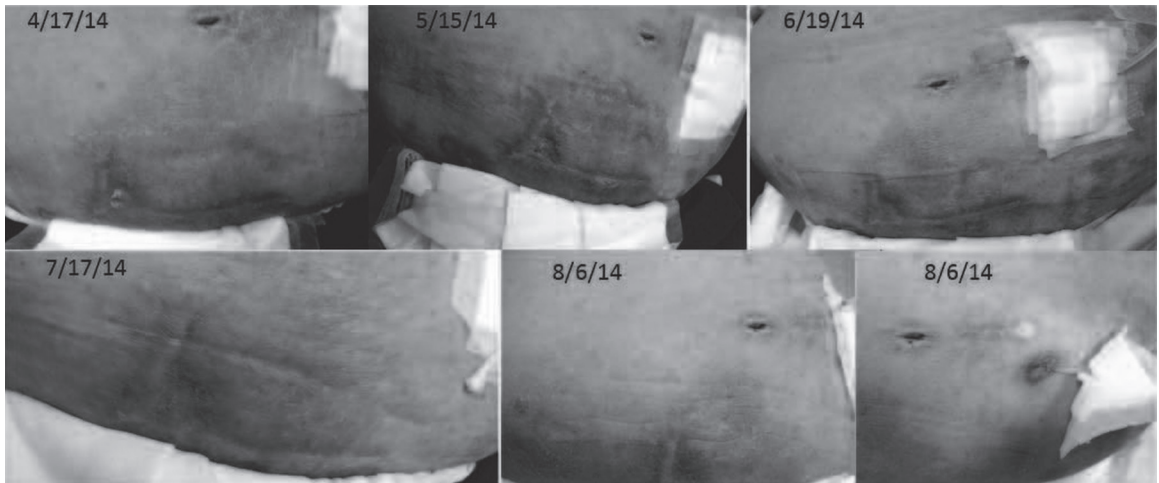


FIGURE 1 Response to oral sodium thiosulfate (started October 31, 2013) in patient 1.

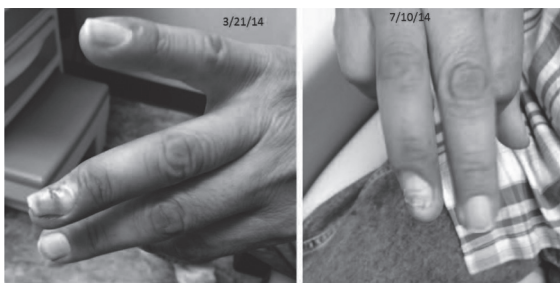


FIGURE 2 Response to sodium thiosulfate (started January 10, 2014) in patient 2.

calcification of the vessel and subsequent ischemia (4). The physicochemical properties of the mineral deposited into the blood vessels is believed to be the same as those of hydroxyapatite, the mineral compound of bone.

A host of factors are involved in vascular calcification in uremic patients, including hyperparathyroidism, oxidant injury, high levels of circulating calcium in patients with low parathyroid hormone levels, positive calcium balance during HD, alkalemia increasing the synthesis of amorphous calcium phosphate and its further conversion into apatite, decrease in the conversion of pyrophosphate into orthophosphate by increased alkaline phosphatase activity, decrease in gamma-carboxylation of matrix Gla protein, and vitamin K2 deficiency, among others.

A review of case-control series in adult patients demonstrated that hyperphosphatemia, not hypercalcemia nor hyperparathyroidism, was a risk factor in the development of calcemic uremic arteriolopathy (4). Other risk factors for calcemic uremic arteriolopathy include female sex, white race, hypoalbuminemia, and warfarin use.

Physical chemistry of medial vascular calcification

Calcification consists of noncrystalline (or amorphous) calcium phosphate, whitlockite [also called magnesium whitlockite, $(\text{Mg}, \text{Ca})_3(\text{PO}_4)_2$], apatite [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$], and hydroxyapatite [this is sometimes also called apatite, but is actually magnesium-substituted carbonate apatite, $(\text{Mg}, \text{Ca})_{10}(\text{PO}_4, \text{CO}_3)_6(\text{OH})_2$]. Apatite is the predominant crystalline form in blood vessels. Although formation of amorphous calcium phosphate is reversible, the formation of whitlockite, apatite, and hydroxyapatite is irreversible under physiologic conditions. Alkalemia that occurs after HD favors both conversion of Ca^{2+} and HPO_4^{2-} into amorphous calcium phosphate and formation of apatite. Pyrophosphate and gamma-carboxylated matrix Gla protein are inhibitors of the conversion of amorphous calcium phosphate into apatite. Magnesium inhibits the formation of apatite, but increases the formation of whitlockite. Those mechanisms have been reviewed in a simplified manner in a recent commentary (5). A recent study by Verberckmoes *et al.* (6) showed that whitlockite was present in the calcium deposits of

uremic vessels in rats treated with calcitriol and absent in uremic rats not treated with calcitriol.

Mechanisms of action of STS

Sodium thiosulfate is an effective anti-browning, reducing, and antioxidant agent, readily donating electrons to re-pair unpaired damaging electrons; it is also used as a chelator of cations such as calcium. In one of many possible antioxidant reactions, it scavenges reactive oxygen species and might be responsible for converting oxidized glutathione into glutathione.

Sodium thiosulfate is believed to bind to calcium, resulting in the formation of calcium thiosulfate. Although calcium phosphate is insoluble, calcium thiosulfate is highly soluble. Furthermore, STS is known to be a chelator of cations and has been used for more than a century as an antidote for cyanide toxicity and as a topical treatment for acne and tinea versicolor; more recently, it has been used as a chemoprotectant against carboplatin and cisplatin toxicity. Its use in the treatment of calciphylaxis has been described by many investigators (7–11).

The beneficial effects of STS are thought to be due in part to the enhanced solubility of calcium deposits in aqueous solution. Initial experiments by Yatzidis (12) demonstrated that calcium thiosulfate is 250, 1000, 3600, and 100,000 times more soluble in aqueous solution than calcium sulfate, citrate, phosphate, and oxalate respectively. Hence, the administration of STS in calciphylaxis could facilitate the mobilization of calcium from affected vessels.

Pharmacology of STS

Sodium thiosulfate ($\text{Na}_2\text{S}_2\text{O}_3$) has a small molecular weight of 248, and in patients with normal renal function, it has a serum half-life of 15 minutes. Animal data from normal and anuric dogs demonstrated that STS distributes rapidly throughout the extracellular space (13). Its volume of distribution was observed to double during renal failure, and its metabolic clearance rate declined drastically. In normal animals, STS had a half-life of 46.8 minutes, and 98% was cleared renally. However, in anuric dogs, the half-life was 239 minutes, and elimination occurred primarily through the biliary system. In 6 healthy humans (14), the average volume of distribution for STS was found to be 12.2 L (167 mL/kg); in edematous individuals, it was 18.2 L (240 mL/kg). Brucculeri *et al.* (9) measured the serum concentration of STS in a patient with end-stage renal

disease 15 minutes after infusion, before HD (52 hours after administration), and after a 4-hour HD session. The recorded STS levels were 110 $\mu\text{g/mL}$, 1.2 $\mu\text{g/mL}$, and 0 $\mu\text{g/mL}$ respectively, with a calculated half-life of 478 minutes.

Data about the pharmacokinetics of oral STS are limited. Farese and coworkers (15) studied 10 HD patients who received intravenous STS and 9 healthy volunteers who received 1 intravenous and 1 oral dose. Renal clearance was slightly higher in healthy volunteers at 2.25 ± 0.3 mL per minute per kilogram than in HD patients at 2.04 ± 0.7 mL per minute per kilogram. Urinary clearance was 2.62 ± 1.01 mL per minute per kilogram. After oral administration, only 4% of STS was recovered in the urine of volunteers, reflecting a low bioavailability of 7.6% (0.8%–26%). A dichotomy is evident between the foregoing data and data about the clinical efficacy of STS. Yatzidis (12) reported successful use of oral STS in preventing nephrolithiasis. Asplin *et al.* (16) also demonstrated that STS reduces calcium phosphate nephrolithiasis in rats, and Musso *et al.* (17) successfully used oral STS as a successful secondary treatment for calciphylaxis after initial therapy with intravenous STS. AlBugami *et al.* (18) reported a favorable experience of oral STS in 4 patients as maintenance therapy after initial intravenous therapy. Based on bone scans, 2 patients improved, 1 stabilized, and 1 progressed after 6 months of oral therapy. Despite successful reports supporting the efficacy of oral STS for calciphylaxis and other indications such as nephrolithiasis (12), tumoral calcinosis (19), and nephrocalcinosis (20), the pharmacokinetic studies of Farese *et al.* (15) showed poor and widely variable bioavailability (ranging from 0.8% to 26%) in 8 healthy volunteers. It is possible that oral bioavailability might be higher in uremic patients than in healthy human beings.

Our report is the first to describe the successful use of oral STS in patients on PD. Oral STS offers several potential advantages. Its cost is considerably cheaper. AlBugami *et al.* (18) reported that, in Canada, the average cost of intravenous STS is about CA\$12,000 per month; the cost of compounded oral STS is \$45 per month. We were able to obtain STS for our patients from a compounding pharmacy. Because oral STS is not commercially available, its retail price is unknown. Other benefits of oral STS include the avoidance of intravenous access and elimination of the logistics for in-center administration several

days each week. Potential side effects of oral STS are diarrhea, nausea, and vomiting. One of our patients had diarrhea before starting on STS, and her diarrhea persisted. She had 1 hospitalization for volume depletion, which could have been related to diarrhea caused by STS or by sevelamer.

Summary

Calciphylaxis is a disease associated with high morbidity and mortality and poses therapeutic challenges. In the treatment of calciphylaxis, STS remains a mainstay. The present report of the successful use of oral STS in PD patients with calciphylaxis is, to the best of our knowledge, the first ever published. Oral STS is an economical, logistically appealing, feasible, and effective treatment option for affected patients. Larger studies are needed to better define oral STS as an alternative therapeutic option for calcemic uremic arteriopathy.

Disclosures

AS has a patent pending for “intradialytic use of sodium thiosulfate.” No other conflict of interest exists for either author.

References

- 1 Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. *Kidney Int* 2002;61:2210–17.
- 2 Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol* 2007;56:569–79.
- 3 Goodman WG, Goldin J, Kuizon BD, *et al.* Coronary artery calcification in young adults with end stage renal disease who are undergoing dialysis. *N Eng J Med* 2000;342:1478–83.
- 4 Moe SM, Chen NX. Calciphylaxis and vascular calcification: a continuum of extra-skeletal osteogenesis. *Pediatr Nephrol* 2003;18:969–75.
- 5 O'Neill WC. Vascular calcification: not so crystal clear. *Kidney Int* 2007;71:282–3.
- 6 Verberckmoes SC, Persy V, Behets GJ, *et al.* Uremia-related vascular calcification: more than apatite deposition. *Kidney Int* 2007;71:298–303.
- 7 Cicone JS, Petronis JB, Embert CD, Spector DA. Successful treatment of calciphylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis* 2004;43:1104–8.
- 8 Guerra G, Shah RC, Ross EA. Rapid resolution of calciphylaxis with intravenous sodium thiosulfate and continuous venovenous haemofiltration using low calcium replacement fluid: case report. *Nephrol Dial Transplant* 2005;20:1260–2.
- 9 Brucculeri M, Cheigh J, Bauer G, Serur D. Long-term intravenous sodium thiosulfate in the treatment of a patient with calciphylaxis. *Semin Dial* 2005;18:431–4.
- 10 Jain D, Yerram P, Khanna R. Renal transplantation after successful treatment of calciphylaxis with sodium thiosulfate [abstract 139]. *Am J Kidney Dis* 2010;55:B66.
- 11 Nigwekar S, Brunelli SM, Meade D, Wang W, Hymes J, Lascon E Jr. Sodium thiosulfate therapy for calcific uremic arteriopathy. *Clin J Am Soc Nephrol* 2013;8:1162–70.
- 12 Yatzidis H. Successful sodium thiosulphate treatment for recurrent calcium urolithiasis. *Clin Nephrol* 1985;23:63–7.
- 13 Braverman B, Ivankovich AD, Shah G. Thiosulfate pharmacokinetics in normal and anuric dogs. *Proc Soc Exp Biol Med* 1982;170:273–80.
- 14 Cardozo RH, Edelman IS. The volume of distribution of sodium thiosulfate as a measure of the extracellular fluid space. *J Clin Invest* 1952;31:280–90.
- 15 Farese S, Stauffer E, Kalicki R, *et al.* Sodium thiosulfate pharmacokinetics in hemodialysis patients and healthy volunteers. *Clin J Am Soc Nephrol* 2011;6:1447–55.
- 16 Asplin JR, Donahue SE, Lindeman C, Michalenka A, Strutz KL, Bushinsky DA. Thiosulfate reduces calcium phosphate nephrolithiasis. *J Am Soc Nephrol* 2009;20:1246–53.
- 17 Musso CG, Enz P, Vidal F, *et al.* Oral sodium thiosulfate solution as a secondary preventive treatment for calciphylaxis in dialysis patients. *Saudi J Kidney Dis Transpl* 2008;19:820–1.
- 18 AlBugami MM, Wilson JA, Clarke JR, Soroka SD. Oral sodium thiosulfate as maintenance therapy for calcific uremic arteriopathy: a case series. *Am J Nephrol* 2013;37:104–9.
- 19 Kyriakopoulos G, Kontogianni K. Sodium thiosulfate treatment of tumoral calcinosis in patients with end-stage renal disease. *Ren Fail* 1990;12:213–19.
- 20 Agroyannis BJ, Koutsikos DK, Tzanatos HA, Konstantinidou IK. Sodium thiosulphate in the treatment of renal tubular acidosis I with nephrocalcinosis. *Scand J Urol Nephrol* 1994;28:107–8.

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