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Off-Label Drug Uses

Sodium Thiosulfate: Calciphylaxis

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

Use of sodium thiosulfate in the treatment of calciphylaxis has been described primarily in case series and case reports and in a single retrospective review. Sodium thiosulfate demonstrated beneficial effects in most patients, with partial to complete resolution of skin lesions and reductions in radiotracer activity on bone scans. Additional data may be necessary to further define the role of sodium thiosulfate in the treatment of this condition.

RATIONALE

Calciphylaxis, also known as calcific uremic arteriolopathy, is a potentially life-threatening condition involving arteriolar media calcification, endovascular fibrosis, and subcutaneous tissue thrombosis. Intense pain, ischemia, necrosis, and nonhealing skin ulcerations often result. In addition to pain, morbidity can occur in the form of infections and organ failure. Calciphylaxis is most often observed in patients with end-stage renal disease (ESRD), but it has also occurred in patients with normal renal function with potentially predisposing risk factors (eg, hypoparathyroidism requiring use of calcium salts and vitamin D, obesity). Calciphylaxis has a mortality rate of up to 80%. Conventional therapy consists of intensifying treatment with a low calcium dialysate for those receiving hemodialysis, noncalcium phosphate binders, cinacalcet, selective vitamin D analogues, analgesics, or aggressive wound care techniques.[1-3]

Sodium thiosulfate traditionally has been used as an antidote in cyanide poisoning and as a nephroprotectant during cisplatin administration. It is thought to have both cation-chelating and antioxidant properties. The rationale for the use of sodium thiosulfate in calciphylaxis is the chelation of calcium to produce calcium thiosulfate, which may be more soluble than other calcium salts and, therefore, more readily cleared from the body.[4]

POPULATION

Adults with calciphylaxis.

DOSING STUDIED

Dialysis patients: 25 g intravenously (IV) diluted in 100 mL of sodium chloride 0.9% administered over 30 to 60 minutes 3 times per week during the last hour of or after the hemodialysis session. Therapy should continue until complete resolution of symptoms.[2,3,5-7]

Patients not on dialysis (normal renal function or mildly reduced glomerular filtration rate): 25 g 3 times per week.[1,4]

Optimal dose is not established. Because sodium thiosulfate is cleared by the kidney, the dose may be adjusted based on estimated glomerular filtration rate and the appearance of adverse effects (eg, metabolic acidosis, hypotension).

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DISCUSSION

Use of sodium thiosulfate in the treatment of calciphylaxis has been described primarily in case series and case reports. It demonstrated beneficial effects in most patients, with partial to complete resolution of skin lesions and reductions in radiotracer activity on bone scans.

Case Reports/Series

Dialysis Patients

A 69-year-old female patient with renal failure requiring continuous ambulatory peritoneal dialysis (CAPD) developed several subcutaneous plaque-like lesions on the calves and thighs consistent with calciphylaxis, which was confirmed by technetium Tc 99 bone scan to have increased radiotracer activity. Treatment with prednisone (40 mg every other day) provided transient modest pain relief but no clinical improvement after 4 weeks of treatment, and lesions continued to progress. Prednisone was gradually tapered over a 4-week period; 6 weeks later, IV sodium thiosulfate (25 g 3 times weekly administered over 30 to 60 minutes) was initiated, resulting in pain reduction within 2 weeks and resolution of pain and tenderness by 8 weeks. The subcutaneous plaques were reduced in size, and a repeat bone scan demonstrated a marked reduction of radiotracer activity. Total duration of sodium thiosulfate treatment was 8 months. During the last 6 months of therapy and for 4 months after completion of therapy, no analgesics were required for pain. A follow-up bone scan 4 months after therapy demonstrated no further changes. Subcutaneous plaques were still present but were smaller and nontender. No changes in serum calcium or phosphate occurred; however, significant increases in serum parathyroid hormone were noted. Adverse effects experienced during infusions included transient mild rhinorrhea, sinus congestion, and, rarely, nausea and vomiting. Mean serum sodium bicarbonate concentrations decreased from 19.8 mEq/L before sodium thiosulfate treatment to 15.4 mEq/L during treatment. Serum anion gap increased 8.7 mEq/L during treatment.[5]

A 35-year-old female patient with chronic renal impairment and morbid obesity developed calciphylaxis that manifested as painful subcutaneous nodules and elevated calcium and phosphate levels. Despite conventional therapy, the skin nodules enlarged, became necrotic, and spread until the patient was bed-bound and required large quantities of analgesics. Sodium thiosulfate therapy was initiated at a dosage of 25 g IV 3 times per week after hemodialysis. Pain resolved within 2 weeks, the lesions healed completely in 12 weeks, and sodium thiosulfate was discontinued. One month later, the lesions recurred and were accompanied by pain, signs of ulceration, and necrosis. Sodium thiosulfate therapy was resumed, and pain and skin lesions again resolved within 2 and 12 weeks, respectively. The patient's previously elevated serum calcium and C-reactive protein levels gradually decreased. Treatment with sodium thiosulfate was continued for 8 months. At the time of the case report, 18 months had elapsed since the infusions were discontinued, and the patient remained free of skin lesions. Based on the lack of recurrence with extended treatment, the authors suggested that the optimal duration of sodium thiosulfate therapy is several months.[2]

In another case report, a woman 45 years of age with chronic allograft nephropathy following a renal transplant 10 years earlier developed resistant, painful ulcers on her left leg. Symptoms progressed to septic shock despite treatment with analgesics and antibiotics, necessitating amputation of the left leg. One week later, ulcers developed on the right leg, and elevations in serum calcium and phosphate levels were noted. Calciphylaxis was diagnosed and treatment was initiated with conventional therapy and cinacalcet. When the ulcers continued to progress and the patient was found to have low serum intact parathyroid hormone levels, a low bone turnover or adynamic bone syndrome was suspected. Cinacalcet was discontinued, and sodium thiosulfate was started at a dosage of 25 g 3 times per week after dialysis. Pain decreased and skin lesions resolved within 2 weeks. Calcium and phosphate levels returned to normal. At 6 weeks, most skin lesions had completely resolved. At 8 weeks, sodium thiosulfate therapy was discontinued. At the time of the report, the patient was relapse free 4 months after completing her course of sodium thiosulfate.[6]

In a retrospective case review, 172 maintenance hemodialysis patients at a single center who received sodium thiosulfate for calciphylaxis between August 2006 and June 2009 were identified. Clinical, laboratory, and mortality data were obtained from the center's clinical database. Physician surveys regarding patient outcomes were obtained for 53 patients. The majority of patients (74%) were women, and mean age was 55 years. The median IV sodium thiosulfate dose was 25 g (in 100 mL of normal saline) administered during the last 30 minutes of each hemodialysis session. The median number of treatment infusions

was 38. Overall mortality for the entire group during follow-up was 42%; 1-year mortality was 35%. The authors noted that this was lower than the published 1-year mortality rate of 55% in patients not treated with sodium thiosulfate. For patients with survey-based outcomes available, complete resolution was achieved in 26.4%, marked improvement in 18.9%, improvement in 28.3%, and no improvement in 5.7%. For those who completed sodium thiosulfate therapy, these rates were 30.2%, 18.6%, 18.6%, and 7%, respectively. The clinical outcome was unknown in approximately one-fourth of the surveyed patient group.[3]

Nondialysis Patients

A 44-year-old female patient with obesity was hospitalized with painful subcutaneous nodules on the lower abdomen and thighs characteristic of calciphylaxis. Upon admission, laboratory screenings revealed normal renal function, labile serum calcium and phosphate levels, elevated serum C-reactive protein, and decreased parathyroid hormone levels. Medications upon admission included L-thyroxine, calcium, vitamin D, and warfarin. Over a 13-week period, the patient's condition significantly deteriorated, with extensive painful ulceration of the abdominal wall requiring up to 80 mg of IV morphine daily. Management included the substitution of heparin for warfarin, discontinuation of calcium supplements, continuation of alfacalcidol, daily wound care, and a trial of 7 infusions of pamidronate (30 mg each) that proved unsuccessful in reversing symptoms. At week 13 of the hospital stay, IV sodium thiosulfate was initiated (25 g 3 times weekly administered over 30 to 60 minutes). Within 2 months, analgesic use decreased from 80 to 5 mg daily and the patient experienced prolonged pyrexia-free episodes. At week 42, all wound lesions were resolved.[1]

Risk/Benefit Considerations

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Sodium thiosulfate is generally well tolerated. The most common adverse effects during sodium thiosulfate treatment for calciphylaxis were nausea and/or vomiting.[3,5,7]

Increased anion gap and, in some cases, severe anion gap acidosis have been reported in association with sodium thiosulfate treatment of calciphylaxis in hemodialysis patients.[3,8,9] The use of high bicarbonate dialysate may resolve sodium thiosulfate–induced metabolic acidosis.[8]

Because each 25 g of sodium thiosulfate in 100 mL of normal saline contains 4.8 g of sodium, the sodium load should be considered; increases in serum sodium levels have occurred during therapy.[3]

REFERENCES

1. Hackett BC, McAleer MA, Sheehan G, Powell FC, O'Donnell BF. Calciphylaxis in a patient with normal renal function: Response to treatment with sodium thiosulfate. *Clin Exp Dermatol*. 2009;34(1):39-42.

2. Subramaniam K, Wallace H, Sinniah R, Saker B. Complete resolution of recurrent calciphylaxis with long-term intravenous sodium thiosulfate. *Australas J Dermatol*. 2008;49(1):30-34

3. Nigwekar SU, Brunelli SM, Meade D, Wang W, Hymes J, Lacson E Jr. Sodium thiosulfate therapy for calcific uremic arteriolopathy. *Clin J Am Soc Nephrol*. 2013;8(7):1162-1170.

4. Baker BL, Fitzgibbons CA, Buescher LS. Calciphylaxis responding to sodium thiosulfate therapy. *Arch Dermatol*. 2007;143(2):269-270.

5. Cicone JS, Petronis JB, Embert CD, Spector DA. Successful treatment of calciphylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis*. 2004;43(6):1104-1108.

6. Ackermann F, Levy A, Daugas E, et al. Sodium thiosulfate as first-line treatment for calciphylaxis. *Arch Dermatol*. 2007;143(10):1336-1337.

7. Auriemma M, Carbone A, Di Liberato L, et al. Treatment of cutaneous calciphylaxis with sodium thiosulfate: Two case reports and a review of the literature. *Am J Clin Dermatol*. 2011;12(5):339-346.

8. 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(5):431-434.

9. Mao M, Lee S, Kashani K, Albright R, Qian Q. Severe anion gap acidosis associated with intravenous sodium thiosulfate administration. *J Med Toxicol*. 2013;9(3):274-277. ■