Simulation-Based Sodium Thiosulfate Dosing Strategies for the Treatment of Calciphylaxis

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Summary

Background and objectives Calciphylaxis remains a poorly understood life-threatening disorder with limited therapeutic options. Sodium thiosulfate (STS) has reported efficacy, thought to be because solubilizing calcium deposits promote clearance by hemodialysis (HD). Lack of rigorous pharmacokinetic studies makes it problematic for determining proper STS dosing given the expanding range of dialysis prescriptions and intensities.

Design, setting, participants, & measurements The purpose of this study was to determine the dosing strategies for STS during different dialysis regimens. Given reported successes using an empiric 25 g, intravenous, 3 times per week after HD, simulations were performed to predict dosing guidelines for alternative, more or less intense dialysis to produce equivalent area under the curve drug exposure. The modeled prescriptions varied HD time from 12 to 40 h/week over three to six sessions (Qb 200 to 400 ml/min, Qd 300 to 800 ml/min), and continuous venovenous hemodialysis at low flow rates (Qb 100 to 200 ml/min, Qd 35 to 50 ml/min), using high-flux polysulfone hemofilters.

Results Simulations showed a marked variation in STS doses depending on HD frequency and duration. Blood and dialysate flows have a less prominent effect. Assuming no residual renal function, HD prescription permutations caused the dose to vary from 72 to 245 g/week (70-kg adult), and the simulations provide specific guidelines for clinicians.

Conclusions Based on the success reported for one STS dosing regimen and assuming area under the curve exposure of STS is proportional to its effect, pharmacokinetic simulations can be used to calculate the dose for alternative, higher or lower intensity dialysis regimens. These strategies are imperative to assure adequate treatment for this mortal disease, as well as to avoid toxicity from excess dosing.

Introduction Calciphylaxis (calcific uremic arteriolopathy) is an uncommon but life-threatening disorder typically associated with chronic kidney disease and ESRD in particular. It is characterized by vascular and other soft tissue calcification, intimal hypertrophy, and thrombosis of small vessels, which result in necrotizing nonhealing ulcers with a high risk of sepsis (1,2). Although the pathogenesis of calciphylaxis is not well understood, the contributing factors include hypercalcemia, hyperphosphatemia, hyperparathyroidism, use of calcium containing phosphate binders, hypercoagulability, and warfarin therapy. Historically, multifaceted treatment strategies have included medical and surgical (i.e., parathyroidectomy, skin debridement) interventions, but mortality rates remained high. Because there had been successful use of sodium thiosulfate (STS; Na2S2O3) in cases of humoral calcinosis or nephrolithiasis, it was tried (off-label) for calciphylaxis in light of this entity apparently sharing a pathogenic role of calcium. There have now been multiple reports of STS producing rapid and marked improvement or resolution of calciphylaxis. Although the mechanism of action of STS is not fully elucidated, it is proposed to increase solubility of the calcium deposits and thereby be efficacious whether in uremic or nonuremic cases (1,3–12).

STS has been administered both intravenously and intraperitoneally, and it has been used in both adults and children. Intravenous doses have varied from 5 to 75 g after or during hemodialysis in adults, with infusion times varying from 30 to 60 minutes. The most commonly reported dose has been 25 g after each hemodialysis session. Some have used body surface area–based dosing (especially in children) at 12 g/1.7 m2. The removal of STS by hemodialyzers is primarily diffusive and would be effected by patient and renal replacement therapy parameters (13). Because of the availability of a wide range of dialysis modalities and clearance intensities, however, we were thus concerned that the extent of STS removal
by the extracorporeal circuit would vary greatly and might compromise effective calciphylaxis therapy.

In the absence of either readily available assays for STS blood levels or rigorous studies of the pharmacokinetics of extracorporeal clearance, the variations in the extent of its removal under different dialysis conditions present a challenge for predicting drug elimination and adjusting dosing regimens. Our approach was based on the premise that STS efficacy is proportional to the patient’s “exposure” to the drug, e.g., the area under curve (AUC) for its blood concentration. We calculated this drug exposure for the reportedly successful and well-tolerated empiric regimen (25 g, intravenously, thrice weekly after high-flux hemodialysis [HD]) and performed mathematical pharmacokinetic simulations for a wide variety of alternative dialysis regimens (HD and continuous venovenous hemodialysis [CVVH]) to predict the STS dose that would achieve an identical AUC and hence the same anticipated therapeutic effect. We believe dosing guidelines could be especially helpful in unstable cases in which the dialysis modality, frequency, and intensity may change over the course of a single inpatient admission.

Materials and Methods
All calculations were performed based on treatments using high flux Fresenius Optiflux F160 polysulphone hemodialyzers (Fresenius Medical Care, Lexington, MA), which have a total luminal membrane surface area of 1.5 m² and well-characterized clearance characteristics.

Pharmacokinetic Calculations
Although there are no data describing STS kinetics for this off-label use in ESRD patients, there is information available pertaining to treatment of other disorders, primarily cyanide poisoning, in individuals without renal disease. Normally thiosulfate (negatively charged ion) elimination is primarily by glomerular filtration, with its clearance having been compared with that of creatinine. Gilman et al. (14) reported that the ratio of creatinine to thiosulfate in urine is in the range of 0.9 to 1.1, and that, unlike many other organic ions, it is neither reabsorbed nor actively secreted by renal tubules. Newman et al. (15) reported that the thiosulfate to inulin urinary clearance ratio is in the range of 0.7 to 1.3 (average 0.99 ± 0.08), and the ratio was independent of plasma concentration in the range of 60 to 600 μg/ml. Crawford (16) also confirmed the results of Newman et al., showing the thiosulfate/inulin clearance ratio in the range of 0.891 to 1.10 (average, 0.97). They further reported that the inulin and thiosulfate elimination is at the level of glomerular filtration and the average ratio of creatinine-to-thiosulfate clearance is 1.25 (1.14 to 1.48). Because STS has a molecular weight of 158.11 (similar to creatinine molecular weight of 113.12), for the purposes of modeling dialyzer clearance, we used KoA values for creatinine (672.66 ml/min for this hemodialyzer). Shea et al. (17) reported the kinetics of the thiosulfate after 6-hour intravenous infusion (12 g/m²) in female patients (with ovarian neoplasm) undergoing cisplatin therapy and observed that steady state was not achieved up to 6-hour infusion. Ivankovich et al. (18) reported that a two-compartment model best described the pharmacokinetics of STS after intravenous infusion in healthy volunteers. The observed volume of distribution of central and peripheral compartment for sodium thiosulfate was 0.15 and 0.33 L/kg in healthy subjects. The renal and nonrenal clearances were 0.09 and 0.0012 L/h per kilogram, respectively. These STS parameters, along with the hemodialyzer’s creatinine KoA value and the surface area, were used for pharmacokinetic profiling by commercial nonlinear mixed effect modeling software (NONMEM version 6.2; Icon Development solutions, Ellicott City, MD). Both the intra- and interdialytic intervals were simulated using NONMEM, with the clearance for STS modeled as:

\[ K = (K_{cr} + K_e) \]  

where \( K \) is total clearance, \( K_{cr} \) is creatinine clearance through the hemodialysis filter membrane, and \( K_e \) represents the clearance other than through hemodialysis, which includes residual renal clearance, if any, and hepatic or metabolic clearance.

A constant volume model as described by Smye and Will (19) for urea kinetics was used to define the pharmacokinetics of STS. The two-compartment open model used to fit the plasma concentration time profile using NONMEM was described by the following differential equations:

\[
dC_p/dt = C_pK_{in} - C_p(K_{cr} + K_e) - C_pK_c
\]  

\[
dC_p/dt = C_pK_e - C_pK_c
\]

where \( C_p \) and \( C_c \) are the concentration of STS in the central and peripheral compartment, respectively, \( V_c \) and \( V_p \) represent the volumes of distribution of central and peripheral compartments, and \( K_c \) is the intercompartment clearance. For our simulations, we used the reported mean parameters of STS for \( V_p \), \( K_e \), and \( V_c \) from healthy subjects (18).

This two-compartment model also includes the rebound in STS blood concentrations after hemodialysis.

Simulations were performed at different blood and dialysate flow rates to calculate the optimum dosing range. For HD, modeling was performed for \( Q_b \) of 200, 250, 300, or 400 ml/min and \( Q_d \) of 500 or 800 ml/min. For CVVHD, the \( Q_b \) was 100 or 200 ml/min, and \( Q_d \) was 35 or 50 ml/min. Creatinine clearance, which is used as a representative of STS clearance, was based on the mass transfer coefficient for F160 filters at all ranges of flow rates used. The creatinine clearance through the HD filter was calculated at different flow rates using the following equations (20,21):

\[ K = Q_b \left[ \left( \frac{K_{cr}Q_d}{Q_b} \right) \left( 1 - \frac{Q_d}{Q_b} \right) - 1 \right] + \left( \frac{K_{cr}Q_b}{Q_d} \right) \left( 1 - \frac{Q_b}{Q_d} \right) - \frac{Q_b}{Q_d} \]  

where \( K \) is the clearance of creatinine through the HD filter and \( Q_b \) and \( Q_d \) are the blood and dialysate flow rates, respectively.
where, \( Q_b \) and \( Q_d \) are the blood flow and dialysate flow rates, respectively, \( KoA \) is the mass transfer area constant for the dialyzer, \( K \) is dialyzer clearance of solute (creatinine clearance in this case), and \( A \) is surface area of dialysis hemofilter. For the purposes of the predicted dosing regimens described here, the residual renal function was considered zero, and the distribution parameters use a patient weight of 70 kg. The effect of weight on the distribution and elimination kinetics was not evaluated because of the absence of pharmacokinetic data in this regard.

### Results

The first simulation determined the AUC of the empirical 25 g, intravenous, STS 3 times per week given after HD to determine the target clearance for the alternative dosing regimens. This amounted to a weekly AUC of 78.5 h \cdot mg/ml.

Eight simulations were performed for the \( Q_b \) and \( Q_d \) ranges for HD and CVVHD, and the predicted STS (creatinine as surrogate) clearances are described in Table 1. The clearance values varied markedly, from approximately 35 to 290 ml/min, with the greatest impact caused by changes in blood flow. Using a goal of the AUC from the 25-g thrice weekly empiric prescription, the predicted doses are expressed in Table 2 as individual (after HD) and total weekly doses. Because of the substantial dialyzer clearance, single doses varied from 16 to 35 g, resulting in the weekly amounts as low as 75 and as high as 245 g. The simulated blood concentrations are graphically depicted in Figure 1, showing how the levels varied depending on whether the interdialytic interval was 20, 44, or 68 hours versus that of the continuous hemodialysis modalities.

### Discussion

Calciphylaxis, a potentially life-threatening complication, has been reported in up to approximately 4% of ESRD patients. With soft tissue and vascular calcifications causing expanding skin ulcerations, involvement of deeper structures, necrosis, and secondary local or systemic infection, the mortality rate can exceed 80% in severe cases. Devising appropriate therapy has been limited by a lack of a clear understanding of the disease pathophysiology. Although there are a number of cases in nonuremic individuals in which hypercoagulability or warfarin therapy have a contributing or causative role, most focus has revolved around chronic kidney disease patients with underlying mineral and bone disease. Strategies have addressed hyperphosphatemia, hypercalcemia, high calcium-phosphate products, exogenous calcium administration (i.e., calcium-based phosphate binders), and under- or overcontrol of hyperparathyroidism. Assuming a central role of calcium deposits (at least in the chronic kidney disease patients patients), a number of strategies have been based on correcting calcium abnormalities, including emergent parathyroidectomy (for severe hyperparathyroidism), withdrawal of pharmacologic suppression of hyperparathyroidism (in cases of oversuppression of PTH), non–calcium-based phosphate binders, and low-calcium dialysate. STS was an attractive therapeutic possibility because of its reported success in reducing stone burden in patients with severe nephrolithiasis or in resolving massive tumoral calcinosis deposits in HD cases (22,23). The proposed therapeutic mechanism was that of increasing the solubility of the calcium deposits by making thiosulfate salts of calcium. Based on in vitro studies, these have 250- to 600 times higher solubility than the calcium deposits in calcinosis deposits.
100,000-fold higher solubility than other calcium salts, such as those of phosphate and oxalate (22). Reported successes using STS for ESRD patients have used empiric doses, despite an appreciation that they would likely need to be altered with varying HD or continuous dialysis modality prescriptions. Because of the high mortality, many practitioners have combined therapeutic approaches. For example, in our prior publication (1), we administered STS and also induced carefully regulated mild systemic hypocalcemia: this was achieved by adjusting the dose of calcium repletion for the hypocalcemia induced by a continuous renal replacement therapy regimen that used citrate regional anticoagulation.

Although it is often logistically straightforward to use the empirically successful thrice-weekly (e.g., 25 g, intravenous, after HD) regimens for stable inpatients or outpatients, a clinical dilemma arises when devising appropriate dosing strategies for other populations: unstable catabolic individuals whose dialysis modality, frequencies, and durations can vary over the course of an admission (i.e., for electrolyte, acid-base, or fluid volume control) or outpatients that undergo near-daily short dialysis treatments.

The major finding from this study is that the substantial dialyzer clearance of the small molecular weight STS necessitates dose modifications when varying dialysis modality, frequency, or intensity. STS has a small molecular mass (158.11 D) and is handled renally similarly to that of creatinine but without known reabsorption or secretion. Animal and human experiments (14–16,24–26) have reported a ratio of urinary STS-to-creatinine in the range of 0.9 to 1.13. This is also consistent with our using the hemodialyzer KoA value for creatinine as a surrogate for STS. Based on the empiric success of 25 g, intravenously, following each of thrice weekly high-flux HD treatments, one can model the pharmacokinetics to achieve identical AUC for alternative regimens. The effect of factors such as protein binding, volume of distribution, intercompartment transfer, molecular weight, and drug charges were kept constant as previously reported for healthy humans. A number of models have been reported to explain the elimination of the solutes (urea and creatinine) from the blood during hemodialysis (27–29); however, none of these models showed their applicability to predict clearance of other commonly dosed drug during HD under clinical settings. Recently Schneditz et al. (27) proposed a modified regional blood flow (diffusion assisted) physiologic-based pharmacokinetic model to explain the kinetics of creatinine and urea. The model explains the dialysis clearance of creatinine by incorporating a delayed intracellular and extracellular equilibrium of creatinine and introducing a $K_d$ to quantify this parameter. The classic two-compartment model used in this study assumes that the (extracorporeal) clearance through the dialysis hemofilter is similar to that of creatinine and the (intracorporeal) distribution parameters (intercompartment clearance and volume of distribution) are that of STS. Simulations included those for HD (from three to six times per week, blood flows 250 to 400 ml/min, dialysate flows 500 to 800 ml/min, durations from 2 to 8 hours) and CVVHD (dialysate flow 35 to 50 ml/min). These parameters lead to creatinine clearance varying from 183 to 290 ml/min for intermittent hemodialysis and from 35 to 48 ml/min for CVVHD. Table 2 shows the suggested dosing for these different hemodialysis regimens. The proposed doses vary from 75 g/wk for four dialyzes a week (3-hour sessions) up to 120 g/wk for five dialyzes a week (8-hour sessions), and as high as 168 g/wk for CVVHD. The effect of frequency of dialysis was most important, followed by dialysis duration and blood flow rates. Thus, as seen in the first four simulations (dialyzes from three to five times a week), the total weekly HD time is similar (12 or 12.5 h/wk), but the postdi-
alysis STS dose would need to vary from 25 to 18 g, yielding a weekly dose that would increase from 75 to 90 g.

Potential limitations of this study include the choice of creatinine as a surrogate for STS hemodialyzer clearance; however, we believe the impact on predicted doses would be minimal because 1) the use of a high-flux membrane would minimize differences in clearance for these small molecules of similar molecular weight, and 2) calculations are comparative in nature, using the empirically successful regimen as opposed to having to craft a de novo prescription. Other limitations of our calculations are because of using a “normal” 70-kg body weight and habits, with actual patients having different weights and proportions of tissue types (e.g., water, adipose) that would not be reflected in modeling parameters obtained from healthy subjects. Should patients have residual renal function, these equations could be used to devise alternative dosing regimens (i.e., using the K term as indicated above). Last, development of a readily available assay for blood STS levels would permit validation of modeling approaches and guide clinical usage over the diverse range of patient sizes and tissue characteristics.

In summary, the small molecular weight STS pharmacological is subject to substantial clearance by HD and CV-VHD modalities. Because of the high morbidity and mortality associated with calciphylaxis, it is imperative that dosing regimens be based on the intensity and frequency of the dialysis sessions. In the absence of readily available assays for STS blood levels, pharmacokinetic modeling, such as that presented here, can be used to devise practical prescription guidelines for clinicians and can result in up to threefold differences in weekly doses.

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Disclosures
None.

References

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