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Short Communication

The Use of Sodium Thiosulphate in Patients Undergoing Dialysis

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ABSTRACT

Sodium Thiosulphate (STS) is an inorganic compound used for the treatment of acute cyanide poisoning. Its off-label use, though, is much more extended, since it has been widely administered, as a preservative measure, in the treatment of Calciphylaxis or Calcific Uremic Arteriolopathy (CUA). This short communication provides an overall frame of the use and latest data concerning studies on STS in patients undergoing dialysis.

INTRODUCTION

A common complication of Chronic Kidney Disease is secondary hyperparathyroidism. One of its most painful consequences is Calciphylaxis or Calcific Uremic Arteriolopathy (CUA), an uncommon skin disorder that occurs mainly in hemodialysis patients, characterized by cell death (necrosis) of fat and skin tissues In patients undergoing hemodialysis the prevalence is 1-4% and the male to female ratio is 1:3, indicating that hormonal factors may be involved in the onset of the disease [1,2]. Other risk factors include the uremic milieu, the high calcium / phosphorus product, warfarin treatment, metabolic diseases (diabetes, obesity) and the deficiency of S and C protein.

The modern theory of the pathogenesis of CUA is that it develops in 2 phases [3]. Initially, the expression of arteriolar calcium-producing factors such as bone morphogenic protein and core binding factor alfa is increased. They are involved in the differentiation of smooth muscle cells and their transformation into cells with osteoblast characteristics. Calcium is deposited in smaller vessels of the adipose tissue and the dermis, causing thrombosis, ischemia and necrotic lesions on the dermis and hypodermis. Patients with CUA suffer from severe pain secondary to ischemia, causing lesions which are rapidly converted into a grid. It is a rapidly deteriorating situation, with up to 50% mortality in the first year and significant comorbidity. Treatment of established CUA is limited but focused on reduction of a positive calcium load and the product calcium-phosphorus.

Even though no randomized controlled trials for the treatment of CUA are published yet, most common therapies consist in the use of Sodium Thiosulfate (STS), cinacalcet and bisphosphonates, surgical parathyroidectomy and hyperbaric oxygen therapy [4-6].

Sodium Thiosulphate ($Na_2S_2O_3.xH_2O$) is a mixture of sodium salt with thiosulfic acid, used in medicine for the treatment of acute cyanide poisoning [6]. Due to the sulfur molecules in the preparation, sodium thiosulfate binds heavy metals, toxins and

radionuclides naturally [4-6]. Although the mechanisms behind the therapeutic use of STS in treating CUA are not clear, STS have been proven to be effective in reducing stone mass in patients with severe nephrolithiasis and in resolving tumoral calcinosis deposits in dialysis patients [7,8]. Its off-label use in CUA is based on its ability to inhibit the formation and favor the mobilization of calcified plaques by producing thiosulfate of calcium (S_2O_3Ca) which is highly soluble and removed by dialysis [9,10]. Furthermore, STS is a potent antioxidant and vasodilator since it can donate electrons and react with superoxide and unpaired electrons, generating the potent antioxidant glutathione (GSH). It may also help to restore the dysfunctional endothelial in order to produce eNO and thus promote vasodilation [11].

Based on the clinical application of STS in the treatment of CUA, in 2008 Pasch et al. published the results of an experimental protocol for uremic rats treated with STS [12]. Their goal was to determine whether STS may prevent the development of vascular calcifications in patients suffering from chronic kidney disease. Indeed, it was demonstrated that STS prevented vascular calcifications in uremic rats, probably by enhancing acid- and/or chelation-induced urinary calcium loss. As an adverse event, it was noted that rat bone integrity was severely compromised, indicating the necessity of a careful risk–benefit analysis prior to the administration of STS in all patients suffering from CUA [5,12,13].

In 2011, a first attempt to investigate the pharmacokinetics of STS was undertaken. A small group of 10 patients undergoing dialysis was given STS intravenously while another group of 9 healthy volunteers was given STS both iv and orally. Nonrenal clearance was not significantly higher in volunteers in respect to anuric patients, while only 4% of the oral concentration was measured in the urines of healthy volunteers, suggesting a low bioavailability of the drug and thus, only intravenous and intraperitoneal administration of STS should be prescribed [12,13].

Since 1946 the renal clearance of thiosulfate and the volume of distribution have been described by Newman and Gilman [14,15]. Ivankovich et al. [16] studied the pharmacokinetics of STS after intravenous administration to healthy volunteers and presented a two-compartment distribution model -central and peripheral- for sodium thiosulfate (renal and nonrenal clearances). Although there is no clinically determined dose and modality prescription protocol, the most empirically successful regiment is thrice-weekly 25 g, intravenous over the last hour of the hemodialysis treatment. Still a careful monitoring and dose adjustment may require, especially when dealing with unstable, catabolic patients whose Glomerular Filtration Rate (GFR), dialysis modality, frequencies, and durations may vary [4,13,17].

In 2017 a prospective single-center study in Findland assess the efficacy of intralesional administration of 1.5 to 15ml of STS once or twice /week in four patients suffering from cutaneous CUA, as an alternative administation procedure. The major side effect was the pain involving the administration of STS, but the results were encouraging since 3 out of 4 patients demonstared complete or almost complete remission while the forth patient who suffered also from lower limb arteriolopathy did not seem to benefit from the treatment [18].

In 2013 a single center retrospective cohort study was publiced by Nigwekar et al. They evaluated 172 patients undergoing dialysis and suffering from CUA, 85% of which were treated with STS between August 2006 and June 2009 at Fresenius Medical Care North America. The study concluded that the majority of the patients who received treatment with STS demonstrated from mild clinical improvement to complete remission [19].

In May 2017 a multicenter, randomized, double-blind, placebo-controlled clinical trial of Intravenous Sodium Thiosulfate in Acute Calciphylaxis Patients (CALISTA) started. This clinical trial, now on phase 3 [20], is due in May 2021 and the estimated enrollment is around 110 patients undergoing dialysis with calciphylaxis associated pain. Its purpose is to evaluate the efficacy and safety of intravenous administration of 25 grams of sodium thiosulfate at the end of each hemodialysis session (3 times weekly) during a 3 weeks period. The primary outcome to be measured will be the intensity of the calciphylaxis- associated pain and more specifically a reduction of the pain of more than 30%. The secondary end-points will be the number of patients achieving an improvement or stabilization of skin lesions during the 3 week period of administration, the time in days to achieve such improvement and the percentage of amputation or surgical skin lesion debridement.

In November 2019 the results of a double-blind, randomized, placebo-controlled study was published concerning the effect of STS on the progression of cardiovascular calcifications in patients undergoing dialysis. 60 patients with an abdominal aorta Agatston calcification score ≥100 were recruited, half of which received 25 g/1.73 m² of STS in the last 15 minutes of dialysis, while the other half received 100cc of 0.9% N/S. There was no difference concerning the progression of abdominal aortic calcification, but the group that received STS demonstated reduction of their iliac artery calcification score, reduced pulse wave velocity and heart valve calcification [21].

As there are no rigorously controlled studies evaluating the profile of sodium thiosulphate, the incidence of side effects reported in the medical literature cannot be estimated. Some of the most reported side effects are: sodium loading, metabolic acidosis, allergic reactions, hypotension, headache, disorientation, nausea, vomiting, prolonged bleeding time, salty taste in the mouth, diffused feeling of warmth and pain when introdusion intralesioanally. The rapid administration or administration of large doses of sodium thiosulphate was accompanied by a higher incidence of nausea and vomiting [5].

Although the results of the first randomized double-blind study on the efficacy of sodium thiosulphate in the treatment of CUA and more specifically on the reduction of the calciphylaxis related pain are not expected to be published before 2022, the clinical experience has made of the sodium thiosulphate as one of its most effective preservative measures in the treatment of CUA. More studies on the pharmacokinetics of STS and dose modifications for different dialysis regimes still need to be conducted in order to establish the best treatment protocol for different patients.

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