SODIUM THIOSULFATE – A NEAR-FORGOTTEN CHELATOR

By

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Sodium thiosulfate (short STS) has a long history of medical use. It has been used as a chelating substance for cyanide and arsenic poisoning in the 1930s. The *World Health Organization's List of Essential Medicines* lists this antidote as the most effective and safe medicines needed in our health system. (WHO 2015) Synonyms for this relatively nontoxic substance are Sodium Thiosulphate Pentahydrate. Disodium Thiosulfate Pentahydrate. Sodium Hyposulfite Pentahydrate. Thiosulfuric Acid. Disodium Salt. Pentahydrate. The chemical formula is $Na_2S_2O_3$

STS is also employed as a food preservative, which is typically added to table salt at less than 0.1% and to alcoholic beverages at less than 0.0005%.

MEDICAL USES

Sodium thiosulfate is an inorganic sodium salt, also referred to as Sodium thiosulfate anhydrous, a colorless, water-soluble salt that has calcium-chelating potential and is useful in removing toxic substances from the body. Depending on the medical condition being treated, the salt can be applied intravenously, taken orally, or is applied to the skin.

CYANIDE POISONING

FDA approved STS for the treatment of cyanide poisoning, because sodium thiosulfate reacts with cyanide to form sodium thiocyanate, a nontoxic substance that is excreted renally. Sodium thiosulfate acts as a sulfur donor for the endogenous sulfur transferase enzyme rhodanese. (Lilly 1993) Sodium thiosulfate may also protect against nephrotoxicity in patients treated with cisplatin [FDA].

OTOPROTECTANT

Sodium thiosulfate has orphan drug designation as an otoprotectant esp. after platinum-induced ototoxicity [Brock et al 2012]. The mechanism by which sodium thiosulfate reduces the toxicity of platinum compounds is not fully understood. There are several postulated mechanisms. As a thiol, it is electrophilic and acts as a free radical scavenger. It may act by covalent binding and inactivation of the platinum compound; reacting irreversibly with cisplatin, forming Pt(S2O3)4. It is also hypothesized that there may be a direct interaction with the hair cells of the cochlea to rescue them from platinum that is already bound to these cells [Hirosawa 1989].

CISPLATIN ANTIDOTE

Uses in pediatric oncology include prevention of cisplatin nephrotoxicity and use as an antidote for extravasation of various chemotherapeutic agents (Nagai et al. 1995; Ener 2004); (Lyphomed 1992) Sodium thiosulfate, administered concurrently with cisplatin in the treatment of ovarian carcinoma has been reported to reduce the dose-related nephrotoxicity of Cisplatin, thereby allowing the dose of Cisplatin to be increased. (Hirosowa 1989; Goel 1989; Howell 1983)

CALCIUM CHELATOR

STS is known to be an anti-calcification agent with vasodilatory and antioxidant properties (McGeers 2016). It is sometimes used to treat calciphylaxis. The rationale behind is the chelation of calcium to produce calcium thiosulfate, which may be more soluble than other calcium salts and is therefore more readily cleared from the body (Baker 2007) Both tumoral calcinosis and calcific nephrolithiasis have been successfully treated with STS.

SKIN DISORDERS

Sodium thiosulfate demonstrated beneficial effects in most patients with partial to complete resolution of skin lesions and reductions in radiotracer activity on bone scans. (Generali 2015) It is used for the treatment of pityriasis, a skin disorder (PubChem 2019), as an antifungal drug in foot baths for prophylaxis of ringworm, and as a topical antifungal agent for tinea versicolor. To treat tinea versicolor, the salt is often combined with salicylic acid in a preparation that is applied topically to the affected areas.

ARSENIC INTOXICATION

In the 1930s, this antidote was used for the treatment of arsenic intoxication in laborers. In *The Journal of the American Medical Association* (1932), the use of STS was advised in a series of cases of dermatoses in laborers who sprayed potato plants with a combination of Calcium Arsenite and Paris green. The use of STS to treat arsenic is also mentioned in "Industrial Dermatoses: Treatment and Legal Aspects: Review of Recent Literature." published in the *Journal of Industrial Hygiene* (Downing 1936).

STS has been used to treat arsenic poisoning in animals. A study of arsenic-intoxicated cows in West Bengal indicates that STS significantly decreased arsenic load in milk, urine, and hair after 1 month. In milk, arsenic concentration was decreased significantly. (Ghosh 2011)

COPPER AND OTHER METALS

Chemically, STS has the potential to chelate copper and other metals and is used to dechlorinate water.

PHARMACOKINETICS

STS taken orally is not systemically absorbed. Most of the thiosulphate is oxidized to sulphate or is incorporated into endogenous sulphur compounds; a small proportion is excreted through the kidneys. Approximately 20-50% of exogenously administered thiosulphate is eliminated unchanged via the kidneys. After an intravenous injection of 1g STS in patients, the reported serum half-life was approximately 20 minutes. However, after an intravenous injection of a substantially higher dose of STS (150 mg/kg, that is 9 g for 60 kg body weight) in normal healthy men, the reported elimination half-life was 182 minutes.

Passage across the blood-brain barrier is minimal (Anirban Das 2013)

STS breaks down (and inactivates) thiamine, therefore STS should not be given with this vitamin or thiamine-containing nutrients.

TOXICITY AND SIDE EFFECTS

The main adverse effect is hypernatremia. It occurs in 21 children out of every 100.

Different studies quote higher rates. However, hypernatremia is transient in nature and normalizes within hours of administration. Nausea and vomiting occur in 20% of children. Other rare events (<5%) include hypotension, contact dermatitis, and irritation if STS leaks from the vein during administration. No long-term adverse effects are known. There is insufficient data regarding safety in pregnant and lactating women.

CONTRAINDICATIONS

The only contraindication of using STS would be in patients with previous anaphylaxis. STS is not recommended in neonates because of the risk of hypernatremia and osmotic disequilibrium related to the immature renal function. Literature review suggests that hypotension is a relative contraindication.

SCOPE OF APPLICATION

PARENTERAL ADMINISTRATION

Sodium thiosulfate injection is supplied as a 10% (100mg/mL) and a 25% (250mg/mL) preservative free solution. Each ml contains sodium thiosulfate pentahydrate 100mg or 250 mg along with water for injection. The intravenous preparation is available as a part of the cyanide antidote kit.

It must be ensured that the drug is used within 24 months of its date of manufacture. It is to be stored at room temperature between 15-30C. The 10% preparation requires no dilution (Anirban Das 2013).

ORAL USE

After oral application, only 4% of STS was recovered in the urine of volunteers, reflecting a low bioavailability of 7.6% (0.8% to 26%). (Farese et al 2011).

Shetty and Klein report of cases using oral STS, providing relief from ischemia. One of these, a diabetic with calciphylaxis, a painful ischemic finger and end stage renal disease (ESRD). The patient, on peritoneal dialysis, was given 1500mg STS twice daily, resulting in prompt pain relief (Shetty 2016). The authors note that this inexpensive treatment is worthy of more research. Side effects encountered by one female patient were diarrhea, nausea and vomiting.

Albugami reported that oral STS was used and well tolerated as a maintenance treatment in patients with Calcific Uremic Arteriolopathy (Albugami 2013). The oral dose administered was up to 1200mg three times daily. ‘After 6 months of oral maintenance therapy, two patients had further regression of their calcific lesions with no new areas of involvement seen clinically or on the radionuclide bone scans. One patient had stabilization of the lesions with no new ones, and one patient had slight progression of the lesions. It was confirmed that this patient had not been taking the drug for at least 3 months.

The following is an excerpt from McGeers’ and Lees review, Medical uses of STS, published 2016 in the *Journal of Neurology Neuromedicine*. (McGeers 2016)

‘STS is generally available as a non-prescription oral product. One of the early medical uses of STS was in the successful treatment of arsenic, lead, mercury and bismuth poisoning. Halliday and Sutherland described using intravenous STS in a moribund case of arsenic poisoning. There was an immediate response with eventual full recovery. Shiels described the use of STS to treat chronic lead poisoning at the Mount Ina mine in Australia. It was then the largest single lead mine in the world. There were dozens of lead poisoning cases being diagnosed each year. Many such cases were successfully treated with intravenous injections of STS. Bertin et al. reviewed the outcome of treating arsenic toxicosis in cattle. The condition is typically fatal but a 50% survival rate was achieved with administration of intravenous fluids and STS. In these conditions, oral administration was ineffective. The lack of toxicity after intravenous administration emphasizes its safety. The ineffectiveness of oral administration suggests that relatively high doses are required to treat overdoses of poisonous elements.’

Dr. Ephraim Sulaiman MD of Kuala Lumpur, Malaysia recommends 7.5g/week of oral sodium thiosulphate as a secondary preventive treatment for calciphylaxis after NaMgEDTA infusions.

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Note:

This is an excerpt from the author's new book, *Evidence-based Clinical Chelation, A Textbook with Protocols for the Treatment of Chronic Metal Exposure,* MTM Publ. 2020.

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