Concise report

Sodium thiosulphate treatment of uraemic tumoral calcinosis

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Abstract

Objective. The objective of this study was to describe the efficacy of sodium thiosulphate (STS) in tumoral calcinosis (TC).

Methods. The methodology involved the reporting of four retrospective case reports of TC complicating end-stage renal disease (ESRD).

Results. We investigated STS treatment in four patients (two men; ages 46–70 years) with TC. ESRD was secondary to nephronophthisis (n = 1), membranoproliferative glomerulonephritis (n = 1), diabetic nephropathy (n = 1), and thrombotic microangiopathy (n = 1). TC developed 3–28 years after dialysis began and resulted in articular pain (n = 4) and stiffness (n = 1). It involved shoulders and hips and was diffuse in one patient. Several treatments were tried without success. STS 12.5–25 g was given intravenously after each dialysis session for 11–14 months. Pain and stiffness rapidly disappeared and TC showed partial or total regression. Side effects during infusion included increased blood pressure (n = 1), nausea (n = 1) and vomiting (n = 1). TC did not recur after treatment discontinuation with follow-up of 1.5–12 years.

Conclusion. STS showed promising efficacy in this short series of TC. Further studies are warranted.

Key words: tumoral calcinosis, sodium thiosulphate, calcification, apatite, dialysis, renal failure.

Introduction

Tumoral calcinosis (TC) is a rare metabolic disorder that was described for the first time by Giard in 1898. The disease is characterized by massive calcium phosphate microcrystal deposition in periarticular tissues usually around large joints such as the hip and shoulder. TC can induce local complications such as pain, joint stiffness, nerve compression, inflammatory reaction, cutaneous fistula and infection. TC can rarely result in systemic symptoms with relapsing fever and chronic inflammatory syndrome.

TC may have multiple origins: it can be hereditary, associated with sarcoidosis or any other granulomatosis and excessive production of active vitamin D metabolites, associated with end-stage renal disease (ESRD) or idiopathic. Cases of familial hyperphosphataemia with TC usually occur in African people and are associated with inactivated autosomal recessive mutations of two genes regulating phosphate metabolism, namely fibroblast growth factor 23 (FGF23) and glycosyltransferase 3 [1]. These mutations cause a reduced concentration of circulating FGF23 or non-functional FGF23, leading to hyperphosphataemia by at least two mechanisms: increased tubular reabsorption of phosphate and increased 1α-hydroxylase activity and synthesis of 1,25-dihydroxy-vitamin D [2].

TC related to ESRD is referred to as uraemic TC (UTC). It is a severe complication of ESRD, especially in patients undergoing haemodialysis (HD); the prevalence is 0.5–3% [3]. Several factors favour UTC formation, including hyperphosphataemia, both extremely low and high serum parathyroid hormone (PTH) concentrations, adynamic osteopathy, vitamin D intoxication, and aluminium overload [4, 5]. Many other systemic and local promoters, including inflammation, uraemic toxins and a decreased level of calcification inhibitors, can contribute to the occurrence of TC [5].
Several treatments have been used without clear efficiency. Sodium thiosulphate (STS, Na₂S₂O₃), an older drug used to cure cyanide poisoning, has been successful for several cases of UTC and calciphylaxis, an important complication of ESRD secondary to calcium phosphate deposition in arterioles. Here we report the efficiency of sequential i.v. STS in four cases of UTC.

Methods

Case reports

The patient features and UTC histories are summarized in Table 1. We investigated three Caucasian European patients (two men) and a Moroccan woman, ages 46–70 years, with UTC. The causes of chronic renal failure were nephronophthisis (n = 1), membranoproliferative glomerulonephritis (n = 1), diabetic nephropathy (n = 1) and thrombotic microangiopathy (n = 1). Three of the four patients had calcifications of the mitral and aorta valves as well as abdominal aorta, iliac, femoral and popliteal arteries. UTC developed after 28, 4, 3 and 3 years of HD in the four patients, respectively. It was symptomatic in all patients, causing joint pain (n = 4) and stiffness (n = 1).

Patient 4 had diffuse pain involving the shoulder and pelvic girdles, hands and feet. It involved the shoulder (n = 3) and/or hip (n = 2) joints and was associated with diffuse subcutaneous calcifications in patient 4. UTC was refractory to phosphate binders (n = 4), calcium channel blockers (n = 2), anti-vitamin K (n = 1), colchicine (n = 1) and subtotal parathyroidectomy (n = 1). Bisphosphonate treatment was not proposed because patients were on dialysis. After failure of these treatments, all patients gave their signed informed consent to receive STS. Each patient obtained specific authorization to receive the treatment from the French drug administration authority.

All patients received i.v. STS, 12.5–25 g, for 30–120 min after each HD session (three per week). STS treatment lasted from 11 to 14 months. STS was clinically effective: all patients showed pain relief after the first weeks of treatment. Moreover, all patients showed partial (n = 2, patients 3 and 4) or total (n = 2, patients 1 and 2) regression of periarticular calcium depositions (Fig. 1). Patient 4, who suffered from diffuse calcifications, had a significant reduction in hip and shoulder calcifications (Fig. 1, panel C), whereas wrist, hand and foot calcifications were unchanged. Similarly, calcifications remained unchanged in this patient. We observed no serious adverse effects, except for a slight increase in arterial blood pressure (n = 1), nausea (n = 1) and vomiting (n = 1) during infusions. STS was discontinued in patients 1–3 after pain relief and UTC regression, without UTC recurrence after 5.5, 1.5 and 12 years of follow-up, respectively. Patient 4 died after 14 months of treatment with STS because of a diffuse mesenteric infarction. We assumed that this event was not related to STS treatment. STS was effective in this patient, reducing large calcium deposits (Fig. 1) and relieving pain. Three other patients died during follow-up: patient 1 from a massive myocardial infarction, patient 2 from severe respiratory insufficiency and patient 3 from septicaemia.

At the onset of STS therapy, two patients showed increased serum calcium phosphate product: 8.14 (patient 1) and 5.94 (patient 3) mmol²/l². Elevated calcium phosphate product was secondary to hyperphosphataemia. Before STS treatment, anion gaps were 27.5, 21.9, 26.5 and 25.2 mmol/l for patients 1–4, respectively. STS therapy was associated with a significant decrease in serum phosphate levels in patients 1 and 3, with a subsequent reduction of serum calcium phosphate product (4.82 and 2.25 mmol²/l², respectively). After STS therapy, patient 1 showed increased anion gap, reaching 34.3 mmol/l at the end of treatment, which was unchanged for the other patients.

Discussion

These cases show that i.v. administration of STS in patients under chronic HD partially reduced or completely resolved UTC at the shoulder and hip joints after 11–14 months of treatment. UTC is a well-known complication of ESRD that appears at 3–5 years, on average, after dialysis onset; its incidence increases with dialysis duration. Accordingly, in our small series, UTC developed between 3 and 25 years and involved the shoulder joints in three patients and the hip joints in one. One of the mechanisms involved in UTC was hyperphosphataemia, associated with low bone turnover as in adynamic bone disease or high bone turnover as in secondary hyperparathyroidism [4]. Low bone remodelling in adynamic bone disease may negatively affect the buffering capacity of bone for calcium and phosphate, thus favouring increased serum calcium and phosphate levels and subsequent risk of soft-tissue calcifications.

UTC is difficult to treat. These masses are almost never completely resected and therefore are associated with a high risk of recurrence. Several medical measures used to prevent the increase of serum calcium phosphate product include counselling on lower dietary intake of phosphates, treatment with non-calcium- and non-aluminium-containing phosphate binders, improving dialysis efficacy by increasing the length or frequency of dialysis or the use of high-performance dialysis membranes and hemodiafiltration techniques as well as the use of low levels of calcium in dialysate solutions. Other measures include control of PTH levels according to the latest Kidney Disease Improving Global Outcomes recommendations and prevention of aluminium intoxication [6, 7].

Treatments with inconsistent results for UTC include bisphosphonates, calcium channel blockers, low-dose anti-vitamin K, probenecid, vimpotecine, cinacalcet as well as parathyroidectomy and renal transplantation [8]. STS has been used successfully in several cases of UTC [9–11]. More than 25 years ago, Yatzidis et al. [9] reported that STS was efficacious in curing UTC within 3 months in five patients. The literature contains reports of nine cases of UTC that were effectively treated with STS [9–11]. As in our four cases, STS was administered by infusion after each dialysis session. We also observed a
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years/sex</th>
<th>Ethnic origin</th>
<th>Cause of ESRD</th>
<th>Type of dialysis</th>
<th>Artery calcifications</th>
<th>Treatment</th>
<th>UTC clinical feature</th>
<th>Location</th>
<th>Aetiology</th>
<th>Time to onset of symptoms for dialysis, years</th>
<th>STS dose</th>
<th>Duration of treatment, months</th>
<th>Clinical outcome</th>
<th>Radiographic improvement</th>
<th>Adverse effects</th>
<th>Evolution after treatment</th>
<th>Duration of follow-up after treatment, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>56/F</td>
<td>Caucasian</td>
<td>Nephronophthisis</td>
<td>HD</td>
<td>Abd AO, iliac, femoral and popliteal arteries</td>
<td>Chelating phosphorus</td>
<td>Pain</td>
<td>Shoulders</td>
<td>HD</td>
<td>28</td>
<td>25 g x 3/week</td>
<td>14</td>
<td>Relief of pain</td>
<td>1</td>
<td>None</td>
<td>No recurrence</td>
<td>5.5 (death)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>46/M</td>
<td>Caucasian</td>
<td>Membranoproliferative glomerulonephritis</td>
<td>HD</td>
<td>Abd AO, iliac, femoral and popliteal arteries</td>
<td>Chelating phosphorus, calcium channel blocker</td>
<td>Pain</td>
<td>Lower limbs</td>
<td>HD</td>
<td>4</td>
<td>25 g x 3/week</td>
<td>11</td>
<td>Relief of pain</td>
<td>1</td>
<td>None</td>
<td>No recurrence</td>
<td>1.5 (death)</td>
</tr>
<tr>
<td>Patient 3</td>
<td>55/M</td>
<td>Caucasian</td>
<td>Nephroangiosclerosis + diabetic nephropathy</td>
<td>HD</td>
<td>Abd AO, iliac, femoral and popliteal arteries</td>
<td>Anti-vitamin K</td>
<td>Pain</td>
<td>Shoulders, hips</td>
<td>HD</td>
<td>3</td>
<td>25 g x 3/week</td>
<td>13</td>
<td>Relief of pain</td>
<td>1</td>
<td>NS</td>
<td>No recurrence</td>
<td>12 (death)</td>
</tr>
<tr>
<td>Patient 4</td>
<td>70/F</td>
<td>Moroccan</td>
<td>Thrombotic microangiopathy</td>
<td>HD</td>
<td>Abd AO, iliac, femoral and popliteal arteries</td>
<td>Chelating phosphorus, calcium channel blocker</td>
<td>Pain</td>
<td>Shoulders, pelvis, feet, hands, cervical spine</td>
<td>HD</td>
<td>3</td>
<td>25-12.5 g x 3/week</td>
<td>14</td>
<td>Relief of pain and stiffness</td>
<td>1</td>
<td>Blood pressure increase, asthenia, diarrhoea, nausea, vomiting</td>
<td>Death</td>
<td>0</td>
</tr>
</tbody>
</table>

Abd AO: abdominal aorta; NS: not specified.
GALNT3 mutation [12].

The observed adverse effects were nausea, vomiting, a slight increase in arterial blood pressure because of the sodium charge contained in STS and asthenia. These effects disappeared with reduced STS dose. Patient 4 died after 14 months of treatment because of mesenteric infarction. The temporal event suggested that this event was not linked to STS treatment. This patient had several co-morbidities, including severe Sjögren’s syndrome with pulmonary fibrosis and insufficiency, chronic heart failure and diabetes. According to their tolerance, the four patients had received 12.5–20 g of STS infusion, as reported by other authors [9–11]. One patient showed an increased anion gap with STS, which suggests metabolic acidosis, as was observed by Pasch et al. [13] in uraemic rats receiving STS.

The exact mechanisms by which STS dissolves UTC remain unclear. The previously believed hypothesis suggesting that STS might form calcium thiosulphate complex was recently rebutted by O’Neill and Hardcastle [14]. They showed that STS had very weak interaction with calcium and reduced ionized calcium in <4% of patients. Similarly, Asplin et al. [15] showed that STS was unable to reduce ionized calcium. Moreover, aortic calcification was still inhibited by STS even when the calcium concentration was increased to compensate for the STS chelating effect. They also showed that the inhibitory effect of STS was independent of a pH decrease or interference with apatite formation. Interestingly, STS only inhibited calcification of injured or devitalized aortas and not uninjured vessels. They suggested direct extra-cellular effects of STS on calcification initiated by cellular injury [14]. This could involve cellular fragments and breakdown products such as matrix vesicles and apoptotic bodies.

In addition, STS may have antioxidant properties by generating glutathione and improving endothelial cell function, which may have symptomatic effects [16].

Another plausible mechanism could be the transient metabolic acidosis after each STS administration, as suggested by one of our cases, which showed a significantly increased serum anion gap with STS treatment. These hypotheses need specific investigations.

In conclusion, our observations reinforce the promising role of STS as an efficient therapy for UTC. Further studies are warranted to confirm these observations and understand the mechanisms by which STS dissolves UTC.

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### Disclosure statement

The authors have declared no conflicts of interest.

### References


