Interesting Case

Rapid resolution of calciphylaxis with intravenous sodium thiosulfate and continuous venovenous haemofiltration using low calcium replacement fluid: case report

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Introduction

The pathogenesis of calciphylaxis (calcific uremic arteriolopathy) remains to be fully elucidated, which makes treatment of this often fatal disease quite challenging. While controversial, vascular calcium deposition may play a secondary, if not primary, role in ongoing tissue ischemia. In cases that would not benefit from early parathyroidectomy, alternative strategies have been proposed to control calcium and phosphate homeostasis. The use of non-calcium based phosphate binders and intermittent haemodialysis with low calcium dialysate [1,2] has been of benefit in some but not all patients. One of the most recently suggested therapies is the use of sodium thiosulfate to increase the solubility of calcium deposits [3]. With its reported success in treating both nephrolithiasis [3] and tumoral calcinosis [4,5], Cicone et al. [6] described its efficacy when given after haemodialysis treatments in a single case of calciphylaxis. We hypothesized that the benefits of solubilizing calcific deposits in patients with ESRD would be severely limited by calcium clearance being dependent on intermittent dialysis sessions. To optimize removal, we devised a regimen combining intravenous sodium thiosulfate treatment with continuous venovenous haemofiltration (CVVH): a constant state of mild hypocalcaemia was maintained by a regimen involving zero-calcium replacement fluid, regional citrate anticoagulation and protocol-driven calcium repletion. We report here a case of progressive biopsy-proven calciphylaxis that responded rapidly to this new approach and which had an excellent outcome.

Case

A 46-year-old Caucasian woman with a history of cirrhosis due to hepatitis C underwent orthotopic liver transplantation in November 2003. After an episode of acute renal failure requiring dialysis, her kidney function recovered to a calculated GFR of 19 ml/min. As an outpatient she was maintained on an immunosuppressive regimen of cyclosporine and prednisone, without need for phosphate binders, calcium supplementation or vitamin D preparations. She subsequently became more uremic, had worsening liver function, thrombocytopenia and was admitted for a transjugular liver biopsy. Upon hospitalization, she gave the additional history of new painful bilateral lower leg skin lesions, which had evolved from an erythematous to violaceous colour. On examination she was noted to have multiple, extremely tender erythematous nodular as well as necrotic lesions on both calves, with the largest lesion being 10 cm in diameter. Her legs were very tender to touch, extending from her knees to her ankles bilaterally. On a pain scale from 0–10, she rated her pain 10/10 (described as 'shooting pain from a massive ant bite'). Peripheral pulses were normal. Skin biopsy demonstrated typical changes of calciphylaxis including small arteriolar intimal proliferation as well as medial deposits of calcium (confirmed by von Kossa staining). Laboratory findings on admission when the patient was felt to have dehydrated included a total calcium of 12.3 mg/dl, phosphate 5 mg/dl, calcium phosphate product of 60.3 mg²/dl²; BUN 103 mg/dl, creatinine 3.0 mg/dl, albumin 3.2 g/l; and intact PTH <10 pg/dl. The hypercalcaemia responded to volume repletion, and the calcium phosphate product decreased to 46.4 mg²/dl². During the first days of the hospitalization her mild hyperphosphataemia was treated with oral sevelamer...
replacement fluid was the calcium-free formulation of calcium levels at < 0.3 mmol/l. The haemofiltration was performed using a Diapact device (B. Braun, Bethlehem, PA), at a blood flow of 100 ml/min and using a high-flux polysulfone hemodialyzer (F160; Fresenius, Lexington, MA), and was not stopped during the sodium thiosulfate administration. Regional anticoagulation was accomplished in the extracorporeal circuit using sodium citrate (ACD-A; Baxter, Deerfield, IL), and the dose was titrated as needed so as to keep post-filter ionized calcium levels at <0.3 mmol/l. The haemofiltration replacement fluid was the calcium-free formulation of PrismaSate® (Gambro, Lakewood, CO), administered pre-filter at 31/ hour. The procedure and protocol orders were the same as that used for other renal failure illnesses, except that the central calcium chloride infusion was adjusted to maintain an ionized calcium level between 0.9 and 1.0 mmol/l instead of the usual 1.19–1.32 mmol/l. This high-dose filtration methodology also induces hypophosphataemia, which was treated using a continuous sodium phosphate infusion so as to achieve a low-normal level of ~2.4 mg/dl.

There were no signs, symptoms or electrocardiographic evidence of hypocalcaemia at any time during the 10 days of this therapy. There was no discernible effect of each thiosulfate infusion on any of the plasma chemistry values, nor any other adverse effects (such as alkalaemia or haemorrhagic complications). Approximately 2 days after CVVH and thiosulfate treatments were initiated the patient’s condition began to progressively improve. No new skin lesions appeared, and the existing ones began to become less erythematous, indurated and tender. At the conclusion of the 10 days of this therapy the pain had decreased to 2/10, and there was little evidence of inflammation around the stable eschars. The patient was then switched to daily 4 h haemodialysis treatments for 15 days with a dialysate calcium concentration reduced to 1.5 meq/l. This kept the pre- and post-dialysis ionized calcium values in the range of 1.0 and 0.8 mmol/l, respectively, without evidence of symptomatic hypocalcaemia. The plasma total serum calcium had decreased to 8.8 mg/dl, with a calcium phosphate product of 24 mg²/dl². The sodium thiosulfate was continued as before. Her pain remained at minimal levels, she began to ambulate and was ultimately discharged 1 month after admission. At that time the erythema circumscribing the skin lesions had disappeared and they were not tender. The subcutaneous nodules had nearly resolved, and at no time was any surgical debridement necessary. We recommended that as an outpatient she continue receiving sodium thiosulfate after each thrice-weekly dialysis session with the reduced calcium dialysate, for an anticipated duration of at least 6 months.

Discussion

Calciphylaxis occurs in ~1% of dialysis patients each year and has a mortality of up to 80% [7,8]. The classical presentation commences with tender violaceous or mottled skin lesions, as well as plaques and subcutaneous nodules. They progress to ischemic non-healing deep ulcers with subcutaneous fat necrosis and infection. The terminal event is usually hypotension with a clinical picture compatible with sepsis. Histological examination of these lesions demonstrates multiple abnormalities of the small arteries and arterioles, as well as involvement of venules. Arterioles have characteristic changes of intimal fibroplasia and medial calcification. Of great importance in determining effective therapy is whether the calcium deposits play a primary or secondary role in initiating or perpetuating the ischemic lesions. Indeed the earliest descriptions of this disorder in renal failure patients focused on a causative role for disorders of calcium homeostasis. Subsequently, there were multiple published series of individuals [8,9] with similar lesions who suffered from severe hyperparathyroidism and the associated hypercalcemia, hyperphosphataemia and elevated calcium phosphate product. More recently, however, some of the patients described in case series have not had abnormalities in calcium and phosphate levels, nor hyperparathyroidism. There are also many descriptions of patients with this disease who do not have end-stage renal failure, including cases of chronic kidney disease not yet dialysis-dependent, renal transplant recipients, cirrhosis, primary hyperparathyroidism, hyperphosphataemia due to parenteral nutrition excesses and hypercoagulability disorders [9,10]. This has led to further uncertainty with regard to the role of calcium in the pathogenesis of calciphylaxis. Nevertheless, in light of the high mortality most clinicians make every effort to normalize calcium and phosphate levels. In patients with elevated intact parathyroid hormone levels, parathyroidectomy can help stop the progression of calciphylaxis, especially early in the course of the disease. Other treatments for calciphylaxis include reducing phosphate levels with non-calcium containing phosphate binders and hyperbaric oxygen therapy. The use of low (or zero) calcium dialysate for patients on intermittent haemodialysis is intriguing [1,2]; however, the benefit would likely be limited by the anticipated small mass clearance of calcium afforded by short treatments, and the rebounding of plasma calcium levels to predialysis levels shortly after the session.

One of the most recent advances in the treatment of calciphylaxis is the use of the inorganic salt sodium thiosulfate in order to enhance the solubility of calcium deposits. Calcium thiosulfate is extremely soluble: 250–100 000-fold greater than other calcium salts such as that of oxalate or phosphate [3]. Oral sodium thiosulfate was first utilized to treat non-uraemic patients suffering from calcium nephrolithiasis [3], and there was a marked reduction in stone...
formation. The compound was later successfully used intravenously for up to ~2 years to mobilize calcium deposits in dialysis patients with tumoral calcinosis [4,5]. All cases had reductions in radiographic evidence of the masses and improvements in symptoms without any alteration in serum calcium, magnesium or phosphorus. Cicone et al. [6] have now reported the use of this agent to treat a single peritoneal dialysis patient with calciphylaxis, without any modifications to the dialysis prescription. Improvement was noted within 2 weeks, after other treatments (steroids and non-calcium based phosphate binders) had failed. Lesions were greatly reduced and pain completely disappeared after an 8 month course of this medication.

We believe our patient had a successful outcome due to intravenous sodium thiosulfate mobilizing the vascular calcium (enhanced by the constant state of hypocalcaemia with low-normal plasma phosphate levels), which was then cleared by the CVVH regimen. The diagnosis was confirmed by biopsy, as opposed to the clinical and imaging criteria described in the previously reported patient treated with thiosulfate [6]. Our case, not unlike many others with this illness, involved severe (and then dialysis-dependent) renal disease, immunosuppression for a transplant, mild hypercalcaemia, mild elevations in the calcium phosphate product, absence of hyperparathyroidism and progressive disease despite use of a non-calcium based phosphate binder. Importantly there were no symptoms or complications due to the induction of hypocalcaemia or caused by the thiosulfate infusions. We cannot ascertain the relative importance of each of the two simultaneous interventions (CVVH and sodium thiosulfate), or the combination of both therapies. Notably, alternative protocols for continuous therapies could be adopted to achieve similar plasma calcium and phosphate levels. Depending on the machine and fluid availability, one could devise regimens using low calcium dialysate for CVVHD and systemic heparin anticoagulation. It is tempting to speculate that the improvement in vascular calcium homeostasis from the systemic effects of our combined regimen explains the recently reported benefit from using bisphosphonates to treat this disorder. As described by Monney et al. [11], it is unclear whether pamidronate had an anti-inflammatory effect in addition to its influence on bone calcium resorption. The need for cautious dosing in patients with severe renal insufficiency, as well as a concern over long-term effects of these agents on bone metabolism, may favour use of the apparently non-toxic sodium thiosulfate.

Further investigations are needed to determine the kinetics of the calcium and phosphate clearance and to determine the optimal dosing regimen of sodium thiosulfate. Shea et al. [12] reported that in patients with a creatinine clearance of 42 ml/min ~28.5% was renally excreted as the unaltered drug. Most of the medication, however, appeared to be eliminated by metabolic conversion to an inorganic sulfate. The pharmacokinetics during renal replacement therapies has not been rigorously studied. Nevertheless, even with the small molecular weight of 248 and a 31/h pre-dilution CVVH regimen, the anticipated (extra-corporeal) clearance would be less than that described above for stage 3 chronic kidney disease patients. Lacking kinetic data, we thus believed it was reasonable to use the previously described dose. Also unclear is the total duration of treatment. The plan for continuing 25 g intravenously three times a week after each intermittent haemodialysis treatment for 6 months will need to be re-addressed depending on the clinical response.

In conclusion, after the marked success in our biopsy-proven patient, we advocate the simultaneous use of sodium thiosulfate and CVVH with low calcium replacement fluids for patients with progressive calciphylaxis and high risk for mortality. Future studies are needed to optimize the dosing and duration of both of these treatment modalities.

Conflict of interest statement. None declared.

References


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