ABSTRACT

Calciphylaxis is a rare but important cause of severe morbidity, which predominantly affects patients with advanced chronic kidney disease. It is associated with mortality in excess of 50% at one year, and this has changed little over the last 20 years despite advances in our understanding of its underlying pathophysiology, and evolving treatment strategies. Sodium thiosulphate has played a prominent role in the treatment of calciphylaxis since its first use in 2004, with reports of success both in improving the severe pain associated with the condition and in the healing of calciphylaxis lesions. The literature documenting the use of sodium thiosulphate in the treatment of calciphylaxis is reviewed here, along with a detailed summary of case reports and case series. While there is reason to be optimistic with regard to the efficacy of sodium thiosulphate within a multifaceted and multidisciplinary approach to treatment, there is clearly much yet to be learned.

Key-words:
Calcific uraemic arteriolopathy; calciphylaxis; sodium thiosulphate.

INTRODUCTION

Calciphylaxis, also known as Calcific Uraemic Arteriolopathy (CUA), is a rare, severe and indeed often fatal skin condition associated predominately, but not exclusively, with dialysis-dependent chronic kidney disease (CKD 5D). Its prevalence more than a decade ago was found to be approximately 4% in two case series of dialysis patients; however more recent data has suggested a prevalence of less than 1%1-3. Consensus has yet to be reached about the nomenclature of this condition, and there are problems with both of those mentioned above. Calciphylaxis, a portmanteau term combining calcium and anaphylaxis, was coined by Seyle in the 1960s when he found that inducing hyperparathyroidism or hypervitaminosis D in rats could ‘sensitise’ them to the development of soft tissue calcification when exposed to trauma or metallic salts4. The name was subsequently given to the syndrome of painful skin lesions associated with intimal vessel calcification increasingly being recognised in patients with CKD 5D and described in case reports later in the decade. More recently, given that hypersensitivity or IgE release is not implicated, CUA was proposed as a better description of the underlying pathological process. However, this is also problematic given the growing number of case reports of the condition in patients without renal failure5. ‘Calciphylaxis’ currently predominates both in the recent literature and in routine clinical use.

Calciphylaxis is characterised clinically by exquisitely painful, violaceous skin lesions, most commonly affecting the lower limbs or trunk6. The lesions tend to progress and enlarge rapidly from subcutaneous plaques, purpura or livedo reticularis in the early stages through to frank skin necrosis with deep, non-healing ulcers7 (Figure 1). The development of calciphylaxis is associated with a marked increase in mortality, with median survival from date of...
diagnosis of 2.64 months (range 0-7 years) and 45.8% 1-year survival in a retrospective study of 64 patients published in 20076.

A retrospective review of cases of calciphylaxis was recently undertaken in our unit, which provides renal services for a population of around 1.5 million. Between 02/04/2001 (when there were 486, 147 and 790 prevalent haemodialysis, peritoneal dialysis and transplant patients respectively attending our centre) and 29/05/2012 (when there were 644, 51 and 841 prevalent haemodialysis, peritoneal dialysis and transplant patients), a period of just over 11 years, 39 cases of calciphylaxis were identified using the electronic patient record. Only 7 patients remain alive. In 32, sufficient data is available to calculate a median survival from date of diagnosis to death of 39 days (range 4-976 days), and 6-month and 1-year survival of 37.5% and 31.25% respectively. Calciphylaxis was documented as directly contributing to death in 83.3%, sepsis in 37.5%, and withdrawal of dialysis in 20.8% (unpublished data).

The severity of skin involvement at presentation has been shown to influence survival, with 1-year mortality reported to increase from 41% in those with subcutaneous plaques to 67% if the skin was ulcerated. Furthermore, the subsequent development of ulceration increased mortality to over 80% at one year. While these figures are taken from a case control study of 36 patients published in 20022, which was before the routine use of some newer therapeutic modalities, more recent reports have failed to show a significant improvement in mortality8,9. With regard to location of lesions (proximal or distal to the knee/elbow), it has been suggested that proximal lesions confer a higher risk of mortality, though Weenig et al. found no significant difference in mortality based on position of lesions in a retrospective review of 64 patients with calciphylaxis diagnosed between 1992 and 20026. The loss of the protective epidermis/dermis layer substantially increases the risk of cutaneous and thereafter systemic infection; sepsis being documented as a contributing factor to death in 41% of cases, which is similar to our findings.
PATHOPHYSIOLOGY

Typical histological findings include small and medium-sized vessel microcalcification (best seen using the von Kossa stain), dermal and subcutaneous inflammation, microvascular thrombi and endovascular fibroblastic proliferation\(^7\). Vascular and extravascular calcification is a common consequence of chronic kidney disease (CKD) and secondary hyperparathyroidism, but only a minority of patients with such metastatic calcification will develop calciphylaxis. A number of inhibitors of vascular calcification have been identified which may be important, including fetuin-A and matrix GLA protein (MGP). Knockout mouse models for genes expressing fetuin-A and MGP exhibit extensive vascular and ectopic calcification\(^{10,11}\). Interestingly fetuin-A is down-regulated in inflammatory states, and inflammation is thought to play an important role in the development of calciphylaxis.

With regard to MGP, its activation is reliant upon vitamin K. Therefore coumarins such as warfarin, which inhibit the activation of vitamin K, consequently reduce the activity of MGP. Furthermore, chronic warfarin use has been associated with vascular calcification in human studies\(^{12,13}\). Warfarin, as well as hypoalbuminaemia (which can be a marker of inflammation) was found to be significantly associated with calciphylaxis in a recent retrospective case control study from Japan\(^{14}\). This study attributed less significance to some of the previously described risk factors (Table I). However, it remains likely that the aetiology is multifactorial, with uncontrolled hyperparathyroidism and elevated serum calcium×phosphate product, activation of inflammatory mediators, protein deficiency states and medication such as warfarin, calcium supplements and vitamin D analogues all being important to varying degrees. It has been suggested that one or more of these stimuli may trigger the activation of nuclear factor kappa-B, which plays a role in bone mineralisation, atherosclerosis and growth factor activation, among other functions, and may therefore be an important step in the development of microvascular calcification\(^{15}\).

More recently, retrospective review of biopsy specimens has identified deposits of iron within calciphylaxis lesions, predominantly within the wall of affected vessels, with no iron seen in unaffected areas\(^{16}\). Deposits of aluminium and gadolinium have also been noted\(^{17}\). Gadolinium was not only found in specimens where the pathological diagnosis was both calciphylaxis and nephrogenic systemic fibrosis, but also in specimens where the sole pathological diagnosis was calciphylaxis. The significance of metal deposition within calciphylaxis lesions is uncertain, but these findings have led some investigators to consider iron supplementation as a potential disease trigger or risk factor, and desferrioxamine has been used as an alternative to sodium thiosulphate (STS) as a chelating agent\(^{18}\).

DIAGNOSIS

Clinical suspicion should be aroused when assessing any patient with CKD and secondary hyperparathyroidism who develops skin lesions associated with severe pain. The pain can be exacerbated by haemodialysis, presumably related to relative hypoperfusion and ischaemia\(^{19}\). While late-stage calciphylaxis lesions with ulceration and necrosis are usually typical, early lesions (for example subcutaneous nodules with no overlying skin inflammation) can be nonspecific and more difficult to recognise clinically. Most senior nephrologists and dermatologists will be familiar with the condition, while it may be completely unknown to other specialists. This may be important, for example, following surgical procedures in patients with CKD being cared for outside a specialist renal ward, when failure of wound healing and the development of tissue necrosis might not initially be recognised as calciphylaxis.
The histological findings described above are very characteristic, but not pathognomonic, of calciphylaxis. There is variation in clinical practice with regard to seeking histological confirmation given the concern that biopsy of the lesions, particularly in the early stages, can provoke ulceration and thereby worsen outcome. On the other hand, it is important not to overlook other conditions, the cutaneous manifestations of which may resemble calciphylaxis, but which require different treatment (Table II).

Bone scintigraphy has been used as an aid to the diagnosis of calciphylaxis, and also to monitor response to treatment. Characteristically, there will be increased uptake of tracer within subcutaneous tissues, usually corresponding to the clinical location of lesions, although the sensitivity and specificity of this test has not been fully characterised.

| Table II |
| Differential Diagnoses |
| Nephrogenic systemic fibrosis |
| Necrotising vasculitis |
| Pyoderma gangrenosum |
| Herpes zoster infection |
| Cryoglobulinaemia |
| Ischaemic or atheroembolic peripheral vascular disease |
| Hypercoagulability |
| Coumarin necrosis |

**TREATMENT**

Given the relative rarity of the condition and uncertainty about aetiology, treatment strategies are based upon case reports or case series reporting success in calciphylaxis. They have been aimed at correcting or removing underlying reversible risk factors or addressing theoretical targets. There are no randomised controlled trials of current treatment strategies, and it is unlikely that there ever will be. Patients in most of the published case reports have received a number of different treatments making it difficult to know which, if any, has been effective. Also, as would be expected, significant publication bias exists, and there are very few case reports detailing treatment failure.

With the above limitations in mind, many authorities advocate a multifaceted approach to the treatment of calciphylaxis. Therefore, while STS is the focus of this review, it is important to highlight the other treatment strategies commonly employed. Medication that may provoke or worsen the condition should be stopped, particularly warfarin and calcium-containing phosphate binders, as well as vitamin D analogues, although in some case reports vitamin D analogues have been continued, or started, in an effort to control hyperparathyroidism. Vitamin K supplementation may be considered, particularly in those patients in whom warfarin is a potential trigger.

In order to optimise calcium and phosphate balance, non-calcium containing phosphate binders such as sevelamer or lanthanum are often employed. For similar reasons, in those with CKD 5D the dose of dialysis is increased where possible – peritoneal dialysis patients are often switched to haemodialysis, and the frequency of haemodialysis is increased from the standard three times weekly to up to daily dialysis. A low calcium or calcium-free dialysate is often used.

Hyperparathyroidism is another treatment target. Urgent parathyroidectomy has been used with some reported success, perhaps related to the dramatic fall in serum calcium and phosphate sometimes seen after this procedure (the ‘hungry bones’ phenomenon), but no survival benefit was found in a retrospective case review. More recently, calcimimetics have been used as an alternative, or as a bridge, to parathyroidectomy. These can be very effective at reducing serum parathyroid hormone, as well as calcium and phosphate levels, and there are case reports of successful resolution of calciphylaxis following the introduction of cinacalcet. However, there are also reports of calciphylaxis not responding to cinacalcet, or developing in patients already being treated with this drug, sometimes with adequate biochemical control of hyperparathyroidism.

There have been promising reports of success using bisphosphonates, which reduce serum calcium levels by inhibiting osteoclastic activity and possibly preventing osteoblast apoptosis, as well as by inhibiting hydroxyapatite formation in vitro. There are concerns regarding the safety of bisphosphonates in advanced CKD, but, given the grave prognosis...
associated with uncontrolled calciphylaxis, their use may be considered to be justified. Hyperbaric oxygen therapy has been advocated in order to promote wound healing, with reported success in case series. However, its widespread use is hampered by cost, availability, and practicality. Prednisolone has also historically been used in the treatment of calciphylaxis. While there may be some benefit in the early stages, it is not recommended in the presence of ulcerated lesions, the increased infection risk being a major concern.

In addition to the above strategies, an emphasis on good wound care, surgical debridement of necrotic lesions (which has been shown to be associated with a survival benefit), and prompt use of antibiotics for bacterial infection are also likely to play an important role in improving the chances of healing calciphylaxis lesions.

**SODIUM THIOSULPHATE (STS)**

STS has been used as a therapeutic agent in medicine for over a century. It is a reducing and antioxidant agent, and has been described as a chelator of cations, although strictly speaking this is incorrect as it does not bind ions at more than one site. It was first used as an antidote for cyanide poisoning, for which it remains a third-line treatment to this day. In the middle of the twentieth century, STS was investigated as a potential agent to measure glomerular filtration rate (GFR) and extracellular fluid volume. However, it does not provide a reliable measure of GFR as it is produced endogenously and has significant and variable non-renal elimination. STS has also been used in oncology, both as an antidote for extravasation injury, and a means of preventing the ototoxicity and nephrotoxicity associated with platinum-based chemotherapies.

**Sodium Thiosulphate in Vascular and Extra-Vascular Calcification**

STS administration has been reported to reduce urinary tract stone formation in stone formers compared with a control period during which the same patients were treated with adequate oral hydration alone. It was postulated that this effect was the result of the high solubility of calcium thiosulphate in urine. STS was subsequently shown to reduce extravascular or tumoural calcification in dialysis patients.

These results led to the idea that the microvascular calcification seen in calciphylaxis might be improved by STS. In 2004, the first case report of successful use of STS in a patient with calciphylaxis was published. The clinical finding of subcutaneous plaques seemingly melting away following treatment gave weight to the idea that calcium salts were being dissolved by STS. Subsequently, uremic rats treated with STS were found to be protected from the development of aortic calcification, with an increase in urinary calcium excretion and development of metabolic acidosis noted.

Also, in a recent study comparing 16 haemodialysis patients treated with intravenous (IV) STS versus 16 controls matched for coronary artery calcification scores over 4-months, progression of coronary artery calcification was prevented in those treated with STS.

It has been suggested that STS has potent antioxidant and vasodilator properties, which could provide an explanation for the rapid pain relief described following STS treatment of calciphylaxis. However, recent laboratory work studying STS and vascular calcification has cast doubt on some of these ideas. While STS does appear to inhibit the calcification of injured or devitalised aortic tissue in vitro through direct extracellular actions, this is not specific for the thiosulphate salt, being seen also with sodium sulphate. The solubility of calcium sulphate is much lower than that of calcium thiosulphate, suggesting that increased solubility of calcium thiosulphate is not likely the reason for the beneficial effects of STS. Additionally, the antioxidant effect was challenged given that sulphate is the terminal oxidation phase of sulphur. It was also noted that STS did not inhibit hydroxyapatite formation in vitro.

While the mechanisms of its action remain unclear, interest in STS has flourished since 2004. We have identified 61 published case reports (including some small retrospective case series and conference abstracts) of STS in the treatment of calciphylaxis. Most of these document treatment success, with rapid resolution of pain within days or weeks, often
supported by impressive reductions in requirements for analgesia. Cessation of new lesion formation along with complete or partial wound healing or reduction in the size of subcutaneous plaques is also commonly reported. Table III summarises the cases and results published to date.

Although the case reports overwhelmingly document treatment success, it is difficult to attribute this directly to STS treatment for reasons previously described. In earlier cases, STS was often used as a final adjunct after several other treatment options had been trialled unsuccessfully. These treatments were usually continued while STS was being administered. It is often impossible to identify exactly how long after diagnosis, or how long after previous trials of treatment, STS was started in the case reports. More recently, STS has been used earlier in the course of treatment, but again, only as one of a number of changes to management instituted at the time of diagnosis. One case report goes some way towards substantiating the efficacy of STS, describing the recurrence of pain and early calciphylaxis lesions 1-month after the end of a 3-month course of STS. STS was restarted, and there followed a similar swift resolution of pain and healing of lesions. The treatment was continued for 8-months, with no further recurrence after 18-months follow-up60.

Despite their unavoidable weaknesses, the published retrospective case series are likely to be subject to less publication bias than individual case reports. While not being able to draw direct conclusions about the benefits or otherwise of STS in the treatment of calciphylaxis, it is interesting to note that patient survival in these studies is broadly similar to that reported prior to the routine use of STS and other more recent treatments (Table IV).

Table III
Case reports of calciphylaxis or calcific ur(a)emic arteriolopathy treated with sodium thiosulphate.
2004-2012
61 cases in 34 publications (including case series/conference abstracts); where data was not available for all patients, number of patients is stated.

<table>
<thead>
<tr>
<th>Patient details</th>
<th>Treatment &amp; outcome details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>Mean duration of treatment (n=32), (range) 13.7 weeks (0.3-80)</td>
</tr>
<tr>
<td>Female</td>
<td>Sodium Thiosulphate</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Other treatments used</td>
</tr>
<tr>
<td>Previous parathyroidectomy</td>
<td>Increased dialysis dose/freq. (n=38) 73.7%</td>
</tr>
<tr>
<td>Taking Warfarin at diagnosis</td>
<td>Low Ca**/Ca** free dialysate (n=29) 79.3%</td>
</tr>
<tr>
<td>Mean serum Ca** (n=32) 2.42 mmol/L</td>
<td>NCCPB (n=36) 69.4%</td>
</tr>
<tr>
<td>Mean serum PO4 (n=32) 2.01 mmol/L</td>
<td>Cinacalcet (n=47) 42.6%</td>
</tr>
<tr>
<td>Mean serum Ca**+PO4 (n=31) 4.87</td>
<td>Parathyroidectomy 13.6%</td>
</tr>
<tr>
<td>Plasma PTH &gt;1500 pg/ml or 1200 pmol/L (n=40) 33.3%</td>
<td></td>
</tr>
<tr>
<td>Mean serum albumin (n=14) 26.9 g/l</td>
<td></td>
</tr>
<tr>
<td>Incident RRT Status</td>
<td>Outcome</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>Pain relief</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>Yes 68.9%</td>
</tr>
<tr>
<td>Transplant (failing) 1.6% (1 patient)</td>
<td>No 8.2%</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Unknown 22.9%</td>
</tr>
<tr>
<td>Normal renal function</td>
<td></td>
</tr>
<tr>
<td>RRT Vintage in months (range) (n=29) 68.5 (1-360)</td>
<td>Healing/stability of lesions</td>
</tr>
<tr>
<td>Calciphylaxis Lesions</td>
<td>Yes 82.0%</td>
</tr>
<tr>
<td>Ulcerated</td>
<td>No 16.4%</td>
</tr>
<tr>
<td>Biopsy confirmed 67.8%</td>
<td>Unknown 1.6% (1 patient)</td>
</tr>
</tbody>
</table>

References: 8,18,19,22,24,27-31,50,54-76

Pain relief was not explicitly stated as an outcome in a number of reports (hence pain relief < healing), but it is likely to have accompanied healing in most cases. PTH – parathyroid hormone; RRT – renal replacement therapy; NCCPB – non-calcium containing phosphate binder; Rx – treatment.
Dosing of Sodium Thiosulphate

The first report of STS in calciphylaxis by Cicone et al. used STS at a dose of 25g IV three times per week50. The reasons for choosing this dose were not specifically described, but reflect historical dosing for other indications. Most case reports have used a similar dosing regime, with the drug being given at the end of dialysis as an infusion over 30-60 minutes. This seems to be tolerated well, with the need for dose reduction being reported infrequently.

STS is predominantly excreted by the renal route, and during dialysis is removed by diffusion. Singh et al. devised a mathematical model to predict dose requirements for different modalities, doses and frequencies of haemodialysis, with the assumption that extracorporeal clearance of STS is similar to that of creatinine, given their similar molecular weights (158.11 vs. 113.12 Da)77. Using this model, if a total weekly dose of 75g STS IV is taken as effective in patients on haemodialysis for 4 hours, 3 times a week, an increase in the total weekly dose would be required to ensure a similar area under the concentration-time curve if dialysis frequency or dialysis dose is increased – up to a total of 90g STS weekly (in divided doses) for 2.5 hours haemodialysis five times a week, and much higher doses for continuous veno-venous haemodialysis.

There is no clear guidance about the appropriate duration of therapy, but most suggest continuing at least until lesions have healed completely, and the course is often extended for several weeks or months thereafter in an effort to prevent recurrence60. The mean treatment duration was 13.9 weeks (range 0.3-80 weeks) in the case reports referenced (Table III).

Side Effects of Sodium Thiosulphate

The most prominent side effect reported with STS is nausea and vomiting, and is usually described as mild, temporally related to the infusion, and responsive to antiemetics and/or prokinetics. Reducing the dose or rate of infusion can be helpful. A raised anion gap metabolic acidosis is also well recognised, and can be severe78. This is again less of a problem with a reduced dose, but is also relatively easily managed with bicarbonate supplementation or increasing the dialysate bicarbonate. Headache, hypotension, thrombophlebitis (when STS is given through a peripheral IV cannula), and hypersensitivity to smells with anorexia have been reported19,54,59,67. One patient developed five beats of broad complex tachycardia during STS infusion, which did not recur64.

With regard to longer-term adverse effects, there is some concern over the possibility of bone demineralisation, with a reduction in bone strength/bone mineral density (BMD) compared with controls reported in both animal and human studies of STS51,52. Adirekkiat et al. demonstrated a significant
reduction in total hip BMD and a trend towards a reduction in lumbar spine BMD in patients treated with 12.5g IV STS twice weekly for 4-months: a much smaller dose than is usually given in the treatment of calciphylaxis. The reason for this is unclear, but the metabolic acidosis induced by STS treatment could be a contributing factor. This may be clinically relevant in longer-term survivors of calciphylaxis.

**SUMMARY**

Calciphylaxis, while rare, is associated with severe morbidity and mortality. Over the last decade, significant advances have been made in understanding its underlying pathophysiology, but newer data appear to be dispelling previously accepted theories, and clearly more remains to be discovered. A low index of suspicion, early diagnosis, and a multifaceted approach to treatment is to be recommended in order to provide the optimum conditions to allow healing, and this has led to some success. STS, when used as part of this type of treatment strategy, appears to improve pain, and thereafter wound healing, but does not definitely improve mortality. Arguably, however, the swift and often complete relief of otherwise intractable pain achieved with STS treatment, along with its favourable side effect profile, appears reason enough to justify its use even when the extent and severity of calciphylaxis lesions and the overall condition of the patient make the situation apparently unsalvageable.

In order to improve the evidence base, well-designed multi-centre therapeutic trials on a scale large enough to be clinically useful would be the ideal, although it seems unlikely that this will be achievable. The UK Calciphylaxis Study is currently recruiting, with the aim of providing epidemiological insights. There are also national and international calciphylaxis registries, for example The UK Calciphylaxis Registry and Deutsches Calciphylaxie Register which, with sufficient participation, should help to guide future treatment strategies and improve our understanding of this challenging disease.

**Conflicts of interest statement.** None declared.

**References**


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