Multi-Modal Treatment Of Calciphylaxis With Sodium-Thiosulfate, Cinacalcet And Sevelamer Including Long-Term Data

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Key Words
Calciphylaxis • Calcific uremic arteriolopathy • End stage renal disease • Hyperparathyroidism • Sodium thiosulfate • Cinacalcet • Sevelamer

Abstract
Background: Calciphylaxis is a rare, yet life-threatening disease mainly occurring in dialysis patients. Traditional options of treatment remain unsatisfactory. Methods: Here we present a novel, combined approach, treating calciphylaxis with IV sodium thiosulfate, cinacalcet and sevelamer. In a case series five hemodialysis patients, have been successfully treated with this regimen. Treatment and survival data were analyzed using descriptive statistics. Results: In all patients, a rapid decrease in pain, improvement of general condition and wound healing within six months occurred. Side effects were low. Drug dosages: IV sodium thiosulfate initial dose 119.4 +/- 84.9 g/m²/week, maintenance dose 40.6 +/- 9 g/m²/week; cinacalcet: maintenance dose 36 +/- 32.9 mg/d and sevelamer maintenance dose 3320 +/- 1671 mg/d. One and two year survivals were 100 % and 80 %, respectively. We also report on long-term application of IV sodium thiosulfate of up to 52 months. Patient survival after diagnosis was 52, 84, 21, 36 and 30 months, respectively. Survival since initiation of hemodialysis was 76, 136, 89, 36 and 35 months, respectively. Conclusion: This novel combined approach, a multi-modal treatment of calciphylaxis with persistent hyperparathyroidism, using IV sodium thiosulfate, cinacalcet and sevelamer seems to improve the outcome of this devastating disease.
Introduction

Calciphylaxis is a rare disease mainly occurring in dialysis patients with renal hyperparathyroidism [1]. Additionally, calciphylaxis has been seen in other conditions, especially during coumadin treatment [2-4]. Medial and luminal calcification of small cutaneous and subcutaneous arterial vessels leads to vascular thrombosis and occlusion, consequent ischemia, necrosis, infection and – in most cases – death within weeks to months [5-7]. Mortality rates are estimated at 60-80 % [8]. Several variations of the disease may occur: cutaneous (necrotizing; including an acral subtype), subcutaneous (non-necrotizing) and systemic forms (involving vessels of internal organs, such as gut, heart and brain) [9, 10]. Apart from vessel calcification and tissue calcification, septal panniculitis can be found in a subgroup of patients [11].

For decades there has been speculation about pathogenetic factors and triggers of the disease [6]. Contributing factors include: end-stage renal disease, dialysis treatment, hyperphosphatemia, hypercalcemia, increased calcium-phosphate product, increased levels of parathyroid hormone, vitamin D supplementation, increased calcium load by calcium-containing phosphate binders, coumadin treatment, diabetes mellitus, tissue trauma, female gender, morbid obesity, rapid weight loss, malnutrition, low plasma albumin, steroid or immunosuppressive treatment, substitution of blood products and inflammation; for review see [12, 13]. It is as yet unclear, whether calciphylaxis follows a similar pathogenesis as the calcifying vasculopathy of patients with end stage renal disease, which includes an active transdifferentiation of vascular smooth muscle cells to an osteoblast phenotype [14].

Diagnosis usually is made clinically. Consideration of predisposing conditions, risk factors and alertness to ‘warning signals’ (extreme pain, livid cutaneous nodules and indurations, livedo sign, typical bizarre configuration of skin ischemia and necrosis) are generally sufficient to characterize the disease [15]. Skin biopsy, although desirable, frequently has been avoided, since progressive skin necrosis may be precipitated at the biopsy site.

Treatment up to now has been unsatisfactory. Different approaches have been suggested, including emergency parathyroidectomy [16], extensive dialysis against low calcium levels [17], bisphosphonates [18], cessation of steroids and immunosuppressants [19], optimum phosphate control using calcium and aluminium free phosphate binders [20] as well as use of prostaglandin and hyperbaric oxygenation [21].

Unequivocally, prognosis of this disease has been grim [22]. Two new principles of treatment have recently emerged: (i) control of hyperparathyroidism by treatment with calcium sensitizers (cinacalcet) [23, 24], and (ii) improving solubility of calcium and phosphate by sodium thiosulfate (STS) [25, 26]. This drug, known as antidote in cyanide intoxication, was first used to prevent recurrence of calcium containing stones of the urinary tract [27], then in tumoral calcinosis [28] and, more recently, has been used in calciphylaxis [29, 30]. STS as a complexator of divalent ions may increase solubility of calcium phosphate by formation of highly soluble calcium thiosulfate complexes and is able to chelate iron that might play a role in the complex pathophysiology of calciphylaxis as has been recently suggested [31]. STS has further been used to abrogate cisplatin toxicity, is an effective antioxidant and reverses endothelial dysfunction by increased nitric oxide production [7]. Furthermore Pasch at al. could show in an animal experimental model that STS can prevent vascular calcification [32]. In addition a vasoactive role by hydrogen sulfide generation has been proposed [33, 34]. Knowledge about pharmacodynamics of STS have been published recently [35].

Here we present five fully documented cases of calciphylaxis that were successfully managed with a novel triple treatment combining oral cinacalcet, sevelamer and intravenous STS, including long term treatment and survival data.
Patients and Materials

Ethical considerations

All patients gave informed consent concerning off-label use of the drugs applied and concerning scientific analysis of their data. This study was performed according to the Federal Laws and Regulations of Austria and Germany and is in accordance with the ethical standards of the local Institutional Review Board as well as adherent with the Helsinki Declaration of 1975, as revised in 2000.

Basic demographic data, comorbidities, classical cardiovascular risk factors, special risk factors associated with calciphylaxis and initial laboratory values are depicted in Table 1.

Case 1

In January 2005 a 58 year old male presented at our emergency room with severe pain of his abdominal wall and progressive immobilization. Abdominal subcutaneous adipose tissue was vastly indurated and extremely painful even upon light touch. There was no skin necrosis. He was first treated for ten days with broad spectrum antibiotics, since soft-tissue infection was suspected. No response, according to clinical condition and inflammation markers, was achieved. Due to multiple risk factors, including an extremely high parathyroid hormone (reported at >1200 pg/ml) a few weeks prior to admission, we suspected non-necrotizing calciphylaxis. Sodium thiosulfate was applied ex juvantibus for several days prior to skin biopsy to reduce the risk of biopsy site necrosis (see below); diagnosis was histopathologically ascertained. Treatment included: the use of high doses of IV STS (80 g) and cinacalcet (300 mg) per day, replacement of aluminum- and calcium-containing phosphate binders by sevelamer; intensive daily hemodiafiltration (6 hours) against low calcium, replacement of coumadins by IV heparin, combined analgesic treatment, treatment of acidosis by sodium bicarbonate, administration of calcitonin and IV ibandronate (2 mg used once) and cessation of all subcutaneous drug administrations.

The high initial doses of STS caused hypernatremia, and metabolic acidosis. Furthermore, the patient developed a gastric ulcer hemorrhage and one epileptic seizure.

Cinacalcet (initial dose: 300 mg per day), and sevelamer (initial dose: 4800 mg per day) had to be paused after three weeks for approximately three weeks due to anorexia and resulting incompliance. Cinacalcet was then reinitiated at 60 mg per day. STS was reduced to four times 30 g per week four weeks after start of treatment and dialysis frequency was simultaneously reduced. No further side effects (such as nausea, vomiting, seizures, hypernatremia, hemorrhage or acidosis) occurred after this dose reduction.

Within a few days from initiation of therapy, pain and inflammatory markers decreased and in the course of weeks, the vast indurations of his abdomen slowly resolved.

After five months of treatment, severe erysipelas of his left leg and sepsis occurred. The patient needed vasopressor treatment and intensive care management. After eight months, due to very low dietary and drug compliance as well as increasing pruritus, parathyroidectomy was performed and cinacalcet was stopped. A significant improvement of skin condition and pruritus resulted. After ten months he suffered from pneumococcal pneumonia and was on mechanical ventilation for three weeks.

Treatment with STS was never discontinued.

After one year of treatment, most of the subcutaneous indurations had vanished. The patient’s condition had remarkably increased. He had lost 30 kg of weight (prior to the severe infectious complications mentioned), did not need further insulin treatment and was well mobilized since four months after the start of treatment. He then was in a good condition and continued to receive STS treatment, since minor (non-necrotic) indurations of the skin never resolved. No further side effects occured.

After two years, upon dose reduction of STS from 30 g thrice weekly to 15 g thrice weekly, painful skin necroses of the calves occurred. The dosage was re-increased to 30 g thrice weekly and the ulcers healed within four weeks.

This patient died from sudden cardiac death following routine shunt surgery after having received continuous treatment for 52 months.

Case 2

A 61 year old male had undergone subtotal parathyroidectomy two years earlier, when suffering from a first attack of calciphylaxis on both calves. In February 2005 he presented with an extensive,
inflamed, severely painful skin necrosis of his left calf. Administration of cinacalcet (due to recurrent hyperparathyroidism) and switch from coumadin to heparin as well as intensification of dialysis treatment had already been started two months earlier at his external dialysis unit with unsatisfactory results. Upon admission to our hospital he was on coumadin treatment again. We continued cinacalcet and coumadin (due to the risk of aortic valve thrombosis on heparin treatment) and started daily treatment with STS (40 g), sevelamer (2400 mg) and intensified the pain regimen. He needed antibiotic treatment due to purulent infection of the necrosis. Careful wound management, avoiding tissue trauma was initiated. He was on continuous intravenous STS treatment for six months, while reducing STS infusions and dialysis frequency to three times a week after discharge. Due to anorexia and vomiting, STS dose was reduced to 25 g thrice weekly after three months. His skin necrosis continuously improved and the wound completely healed six months after initiation of STS treatment. From thereon, 10 g were administered twice a week and were continued for another two months. This patient suffered from intermittent recurrence of ulcerations in 2006 and 2007. He did not consent to reinitiation of STS treatment while continuing cinacalcet and sevelamer. He underwent percutaneous angioplasty in 2010 and was free of ulcerations since then. 84 months after initiation of STS treatment the patient died due to cardiac reasons, but without active calciphylaxis.

Case 3

In October 2005, a 60 year old female presented with intolerable pain of her right calf and rapidly progressive skin necrosis with secondary infection. Examination also revealed three ulcers of her left calf that had developed two months earlier. Treatment was initiated with low calcium daily dialysis, cinacalcet (30 mg per day) and STS (40 g per day). Antibiotic treatment was started due to purulent infection of the necrosis. Subtle, atraumatic resection of small parts of the necrosis was done to enable drainage of the pus. Within a few days, the primary necrosis increased in size despite treatment and her pain was difficult to control. Several livid, painful subcutaneous indurations on both calves and thighs developed, yet no further necrosis at these sites occurred. A continuous improvement was subsequently achieved. Eight weeks after the first admission, parathyroidectomy was performed and cinacalcet was stopped, since oral drug compliance was poor. Within six months of treatment, the leg ulcers were completely healed and her general condition was remarkably improved. In summary, the patient received continuous STS treatment for 16 months after which she requested that the treatment be stopped. Another six months later she died from acute cardiac death, without recurrence of the disease.

Case 4

In June 2007, a 66 year old male patient presented with multiple, infected, painful ulcerations of both calves, that had started five months earlier, and end-stage renal disease (unknown glomerular disease with nephrotic range proteinuria) with edema and a pericardial effusion. Hemodialysis treatment was initiated and a skin biopsy was performed. Calciphylaxis was diagnosed. STS treatment (25 g thrice weekly) was initiated. Antibiotic treatment, had been started two weeks earlier and was continued for another two weeks. In addition, calcium carbonate was changed to sevelamer. Since the patient initially presented with uremic vomiting, cinacalcet was not prescribed first-line to reduce combined side effects. Upon further increase of PTH levels, the patient took cinacalcet for several weeks, but not over a prolonged period due to nausea. So in this patient, the contribution of cinacalcet to treatment may have been fairly low, due to poor drug compliance.

The ulcers and degree of pain continuously improved within three weeks. The ulcers healed within six months from start of treatment. Poor compliance concerning fluid restriction resulted in high interdialytic weight gains (which were well tolerated), and continued calf edema. Although this might have been aggravated by STS treatment, there was no change in interdialytic weight gains after cessation of STS infusions. This patient was on STS treatment for fourteen months with gradual dose reduction after ten months. Metabolic acidosis, requiring PO bicarbonate in addition to dialysis treatment was observed similar as in Case 1.

This patient was disease-free ever since and died from heart failure in December 2009. A metastatic colon cancer was found in autopsy.
Case 5

In November 2007 a 61 year old male patient presented to the dermatology unit with a painful ulcer of his left calf and was transferred to nephrology for suspected calciphylaxis. During the preceding months, hypercalcemia had repeatedly been documented by his dialysis centre. In our view, this was due to combined treatment of renal hyperparathyroidism with high doses of calcium-containing phosphate binders and calcitriol.

Skin biopsy was performed; coumadin, calcitriol and calcium-containing phosphate binders were discontinued. STS 25 g was administered thrice weekly after each hemodialysis treatment via his Cimino shunt. Cinacalcet was initiated at 60 mg per day and sevelamer was started. An initial episode of nausea was easily managed with metoclopramide. Furthermore, furosemide and calcitonin were administered for five days to treat hypercalcemia. Calcium free dialysis solutions were used initially and changed to low calcium after normalization of serum calcium levels.

Treatment was tolerated well with the only minor side effect being slight nausea. No changes of fluid, electrolyte or acid-base-homeostasis were found. Pain decreased rapidly and the calf ulceration healed within five months.

STS treatment was continued in decreasing doses for another six months and then stopped. No recurrence of disease occurred. This patient underwent aortic and mitral valve replacement because of endocarditis in October 2009. After an initially successful procedure, the patient developed recurrent aspiration pneumonias and died, probably caused by sudden cardiac death, in December 2009. There was no consent for autopsy.

Statistical methods

Descriptive statistics included computation of means and standard deviations. All analyses were done using SPSS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) and STATISTICA 10.0. (StatSoft, Inc. (2011). STATISTICA (data analysis software system), version 10. www.statsoft.com).

Results

An overview of demographic variables, risk factors and co-morbidities is given in Table 1, as well as a summary of characteristics of calciphylactic lesions (Table 1). A typical course of wound healing is shown in Figure 1. The histopathological lesion of calciphylaxis, calcification of small subcutaneous arterioles, is depicted in Figure 2.

Treatment measures and drug dosages, as well as overall STS treatment times, time to wound healing, recurrence and survival data are shown in Table 2.

In 4 patients (all presenting with the necrotizing, distal type), a complete remission was achieved and STS could be stopped. In 1 patient (severe, proximal, non-necrotizing type) a partial (near-complete) remission was documented, since very minor subcutaneous calcifications still could be found. Treatment was therefore continued for 52 months.

One and two year estimated survival probabilities were 100 % and 80 %, respectively.

Side effects of treatment are summarized in Table 3.

Laboratory values of calcium, phosphate, parathyroid hormone and bicarbonate in course of multimodal treatment are depicted in Figure 3.

Discussion

Calciphylaxis is a severe disease with a high mortality of up to 81% and a median survival of 2.64 months from the date of diagnosis [12]. Recently, with STS treatment Zitt et al found a 50 % survival of 3.3 months [30]. Classical treatment recommendations include: intensification of dialysis (increase of frequency and duration [20]) using a low calcium dialysate [17]; cessation of vitamin D preparations as well as calcium containing phosphate binders, steroids, immunosuppressants, blood products; application of bisphosphonates
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Since hyperparathyroidism seems to be one of the important factors in precipitating the disease, emergency parathyroidectomy has frequently been performed [16]. Several years ago, cinacalcet, a calcium sensitizing agent, was introduced as a novel drug to treat renal hyperparathyroidism [36]. Drug-induced decrease of PTH may circumvent the complications of surgery and anesthesia under high-risk conditions. In addition, bone metabolism can be altered at will to target levels of PTH, whereas parathyroidectomy may have irreversible results.

Yet all these measures did not substantially improve the grim outcome of the disease. Since hyperparathyroidism seems to be one of the important factors in precipitating the disease, emergency parathyroidectomy has frequently been performed [16]. Several years ago, cinacalcet, a calcium sensitizing agent, was introduced as a novel drug to treat renal hyperparathyroidism [36]. Drug-induced decrease of PTH may circumvent the complications of surgery and anesthesia under high-risk conditions. In addition, bone metabolism can be altered at will to target levels of PTH, whereas parathyroidectomy may have irreversible results.

Table 1. Demographic variables, risk factors and comorbidities at presentation. None of the patients revealed any signs of clinically relevant peripheral or cerebral artery disease at presentation.

| patient number | 1 | 2 | 3 | 4 | 5 |
|----------------|---|---|---|---|---|
| age at diagnosis | 57 | 61 | 60 | 65 | 61 |
| sex             | m | m | f | m | m |
| BMI [kg/m²]     | 46 | 26.5 | 30.4 | 40.5 | 24.1 |
| body surface [m²] | 2.42 | 1.88 | 1.88 | 2.51 | 1.98 |
| dialysis vintage [months] | 24 | 52 | 68 | 0 | 5 |
| dialysis dose (hours/week) | 15 hr | 15 hr | 15 hr | 12 hr | 12 hr |
| dialysis frequency per week | 3/wk | 3/wk | 3/wk | 3/wk | 3/wk |
| primary renal disease | DM | HT | WG | GN | HT |
| diabetes mellitus treatment | insulin | diet | - | - | - |
| hypertension treatment [number of drugs] | 3 | 4 | 0 | 3 | 2 |
| vascular comorbidities | CAD, AF | AV, AF | AV, AF | AF | AF |
| coumadin treatment | + | + | + | - | + |
| CRP [mg/dL] | 25.9 | 4.8 | 10.1 | 0.8 | 0.5 |
| total calcium [mmol/L] | 2.17 | 1.79 | 2.1 | 2.28 | 2.95 |
| ionized calcium [mmol/L] | 1.16 | 0.83 | 1.15 | 1.19 | 1.53 |
| phosphate [mmol/L] | 2.24 | 2.15 | 1.71 | 1.36 | 1.78 |
| intact PTH [pg/mL] at - 3 months to manifestation | 729 | 227 | 614 | 972 | 227 |
| intact PTH [pg/mL] | 242 | 199 | 301 | 1446 | 386 |
| alkaline phosphatase [U/L] | 167 | 118 | 125 | 129 | 227 |
| acual bicanenate [mmol/L] | 20 | 19 | 17 | 27 | 27 |
| phosphate binder | Al, CaAc 2.8 g | Al | CaAc 3 g | CaAc 6 g | Sev |
| 1,25-vitamin D3 [pg/week] | 3.5 | 0 | 0 | 0 | 7 |
| paricalcitol [pg/wk] | 0 | 0 | 0 | 0 | 0 |
| localization of lesions | abdomen, thighs | calf | calves | calves | calf |
| area (estimated) | > 2500 cm² | 180 cm² | 130 cm² | 400 cm² | 60 cm² |
| single necrosis | no | yes | yes | yes | yes |
| confluent necroses and ulcers | yes | yes | yes | yes | no |
| multiple, bilateral ulcers | yes | yes | yes | yes | yes |
| single necrosis | yes | yes | yes | yes | yes |

Abbreviations: AF: atrial fibrillation; Al: aluminum containing phosphate binders; AV: aortic valve replacement; CaAc: calcium acetate; CaCa: calcium carbonate; CAD: coronary artery disease; DM: Diabetes mellitus type 2; GN: chronic glomerulonephritis with nephrotic range proteinuria; HD: Hemodialysis; HT: hypertension; PTH: parathyroid hormone (ng/ml); Sev: Sevelamer; WG: Wegener’s granulomatosis.
In a case report prior to our first patient, STS was used to treat calciphylaxis [25]. Since then, a series of case reports has been published [26, 29, 37, 38]. Recently, we have participated in a study including 27 calciphylaxis patients receiving STS treatment, which showed a trend towards prolonged survival [30]. STS might dissolve calcium phosphate precipitates by formation of highly soluble calcium thiosulfate complexes [29, 32, 39]. This solubilising effect had been postulated earlier to result in the prevention of recurrence of calcium containing urinary stones [27] and of calcium deposits in tumoral calcinosis [28] as well as nephrocalcinosis [40].

These concepts of drug effect have been challenged by in vitro experiments of O’Neill and Hardcastle [41]. Thus, the exact mechanism of STS still remains elusive.

Here we present a novel concept to treat calciphylaxis. We believe that no single measure can sufficiently improve the outcome of this disease. Yet control of hyperphosphatemia and hyperparathyroidism and – as the most important measure – treatment with IV STS to improve solubility of the calcium-phosphate complex seem to give a realistic chance to significantly improve the prognosis of this devastating disease.

No standard dose of STS has yet been established. In our series, a wide range of doses was used. Generally, at least in cases of moderate disease activity and patients of average weight, a 25 g dose three times per week seems to be sufficient in the maintenance phase. This is in accordance with earlier case reports [25, 26, 38] and the data by Zitt et al [30], who reported an STS dosing range of 30 to 125 g per week with 81 % of patients receiving 75 (3 x 25) g per week. Similarly, 25 g/1.73 m² body surface area have been administered.
Table 2. Treatment measures and survival times; recurrence and death related to disease

| patient number | 1 | 2 | 3 | 4 | 5 | mean | SD |
|----------------|---|---|---|---|---|------|----|
| STS initial dose [g/week] | 560 | 280 | 120 | 75 | 75 | 222 | 206.9 |
| STS maintenance dose [g/week] | 120 | 75 | 75 | 75 | 75 | 84 | 20.1 |
| STS initial dose [g/m²/week] | 231 | 149 | 149 | 30 | 38 | 119.4 | 84.9 |
| STS maintenance dose [g/m²/week] | 55 | 40 | 40 | 30 | 38 | 40.6 | 9 |
| STS treatment time [months] | 52 | 8 | 15 | 14 | 11 | 20 | 18.1 |
| STS free time [months] | 0 | 76 | 6 | 22 | 19 | 24.6 | 26.9 |
| cinacalcet initial dose [mg/day] | 300 | 60 | 60 | 30 | 60 | 102.0 | 111.4 |
| cinacalcet maintenance dose [mg/day] | 60 | 60 | 60 | 0 | 60 | 36.0 | 32.9 |
| sevelamer dose [mg/day] | 4800 | 2400 | 2400 | 1600 | 5400 | 3320.0 | 1670.9 |
| bisphosphonate IV | once | no | no | no | no | yes |
| calcitonin SC | yes | no | no | no | no | yes |
| parathyroidectomy | after 8 | no | no | after 2 mo | no | no |
| calcium concentration (dialysate) [mmol/L] | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 |
| dialysis dose (hours x frequency/week) | 6 x 7 | 5 x 6 | 5 x 6 | 4 x 3 | 4 x 3 |
| vitamin D | no | no | no | no | no | no |
| bicarbonate PO | yes | no | no | yes | no | no |
| antibiotic treatment at manifestation | yes | yes | yes | yes | no | no |
| systemic anticoagulation after diagnosis | heparin | coumadin | none | none | none | none |
| time to wound healing [months] | - | 6 | 6 | 6 | 5 | 5.8 | 0.5 |
| recurrence [months after STS initiation] | 24 | 13,26 | -- | -- | -- | -- |
| survival after STS [months] | 52 | 84 | 21 | 36 | 36 | 36 (1) | 23-49 (2) |
| overall dialysis survival [months] | 76 | 136 | 89 | 36 | 35 | 76 (1) | 70-82 (2) |
| death related to calciphylaxis | no | no | no | no | no | no | -- |
| cause of death | acute cardiac | cardiac | acute cardiac | acute cardiac | aspiration pneumonia | -- | -- |

Abbreviations: STS sodium thiosulfate; LMW low molecular weight; PO per os; SC subcutaneous; IV intravenous.
Major treatment goals aim at decreasing the risk of calcium phosphate precipitation
(i) decreasing the calcium phosphate load (stop calcium containing phosphate binders and vitamin D; decrease oral phosphate uptake by dietary restriction and sevelamer; use low-calcium dialysate; increase dialysis intensity by daily, long-term dialysis).
(ii) decreasing hyperparathyroidism (using cinacalcet or surgical parathyroidectomy; yet the optimum target range of parathyroid hormone in calciphylaxis is currently unknown; PTH management should consider the risk of adynamic bone).
(iii) decreasing bone demineralization (e.g., treatment of renal acidosis). The use of bisphosphonates remains controversial.
(iv) administering STS, which, among other effects, may possibly increase the solubility of the calcium-phosphate complex.

Additional measures
(v) careful wound management avoiding trauma and performing subtle surgery primarily only in infection (there is a substantial risk of progressive necrosis at each new trauma site of ischemic skin [own unpublished data]; this must be kept in mind despite favourable reports of aggressive wound care, see [12, 20, 43]).
(vi) early treatment of infections (antibiotics, wound management),
(vii) effective pain management,
(viii) cessation of coumadins (which inactivate vitamin K dependent tissue inhibitors of calcification, such as matrix GLA protein) and, possibly, supplementation of vitamin K2.

Our new concept combines treatment of hyperparathyroidism by cinacalcet, improving calcium-phosphate solubility by STS and phosphate control by a non-calcium-non-aluminum phosphate binder (sevelamer). In addition to this, a high dialysis intensity (e.g., starting with 6 hours of treatment daily) and low dialysate calcium concentration, treatment of renal acidosis with sodium bicarbonate where needed, intensive analgesic and antiemetic treatment, careful and subtle wound management, avoidance of tissue trauma (including subcutaneous injections and surgery, if at all possible), early targeted antibiotic treatment (if infection should occur) and cessation of coumadins are necessary.

Need of parathyroidectomy should be re-evaluated regularly and should be considered (i) if no improvement should occur, (ii) if drug side effects of cinacalcet are intolerable and (iii) if compliance is poor. This is particularly important, since cinacalcet may cause severe gastrointestinal side effects, including anorexia and vomiting.

In our view, the use of bisphosphonates, as performed in case 1, should no longer be generally recommended, despite anecdotal reports of beneficial effects in calciphylaxis [18, 44]. This is due to the detrimental effects of bisphosphonates on uremic bone, which may result in adynamic bone disease and aggravation of calcium-phosphate disorder by blocking the buffering capacity of bone.

Table 3. Side effects of sodium thiosulfate

| Patient number | 1 | 2 | 3 | 4 | 5 |
|----------------|---|---|---|---|---|
| hypernatremia* | + | - | - | - | - |
| metabolic acidosis | + | - | - | + | - |
| gastric hemorrhage | + | - | - | - | - |
| seizure** | + | - | - | - | - |
| nausea, vomiting** | + | + | + | + | - |
| edema | + | - | - | + | - |

* This side effect (hypernatremia) was due to the high dose of sodium thiosulfate; ** This side effects of sodium thiosulfate (seizure, nausea, vomiting) may have been aggravated by a high dose of cinacalcet.
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As cases 2 (ineffective treatment with cinacalcet prior to combination with sodium-thiosulfate) and 4 (no long-term effective dose of cinacalcet achieved due to low drug compliance) demonstrate, the most important single measure in management of calciphylaxis is STS treatment.

Additionally, our results show that IV STS can be used even for years without major side effects.

As the study by Zitt et al pointed out, STS as single measure may not be effective in all cases: 52 % of patients showed a complete remission and 70 % a partial or complete remission; 52 % of patients died after 101 days (3.3 months) [30]. Earlier studies reported one-year mortality rates of 45 – 55 % [12, 45].

The patients in this series were younger (60.8 vs 68 years) and had a higher dialysis vintage, (29.8 vs 12.4 months) when compared to the study by Zitt et al., whereas the co-morbidities were rather similar. They received higher initial STS doses (also due to increased dialysis frequency) and prolonged treatment times (20 vs 3.3 months).

Our five patients had a complete remission rate of 80 % and a complete or partial remission rate of 100 %. Similarly, the one- and two-year survival was 100 % and 80 % respectively.

To our knowledge, there is no clinical evidence in humans concerning a possible bone demineralising effect of STS or a potential increase in fracture rates. At least our patients - despite long term STS use - did not reveal any treatment-associated bone problems.

Clearly, our study has several limitations: Firstly, case number is low, as with any rare disease. Secondly, since patient recruitment was performed over several years, paradigm changes in calcium phosphate management have taken place and may have influenced target levels in our patients. Suppression of PTH or parathyroidectomy was considered beneficial at the beginning of our series to effectively control calcium phosphate metabolism. This may still be evaluated depending on the severity and refractoriness of calcium and phosphate derangements. Calciphylaxis patients may present with persistent hyperparathyroidism or with development of adynamic bone. STS treatment, on the other hand, tends to increase PTH (personal, unpublished observation). As a limitation of our results, use of cinacalcet is not encouraged in development of adynamic bone. Thirdly, not one drug used in isolation was proven to be effective. Despite a synergistic approach, not all patients could be treated with all three drugs continuously, due to side effects as well as patient incompliance. Yet these problems reflect the general complexity of severely ill, multi-morbid patients. We do not suppose, it will be possible to perform a randomized, placebo-controlled trial in such a rare and devastating disease as calciphylaxis in the near future.

Conclusion

We believe, that calciphylaxis has lost some of its threat. It still is a potentially lethal disease, requiring intensive and combined treatments. Evaluation of risk factors and early diagnosis of this disease should be encouraged. Since therapeutic measures minimising the risk of wound necrosis are available now, deep skin biopsy at the site of the suspected deep subcutaneous vessel (i.e. not at the ulcer margin, but at the estimated “circle midpoint of the supplying vessel”) should be encouraged. A combined treatment of cinacalcet (in cases with severe hyperparathyroidism), sevelamer and STS, as well as subtle, non-traumatic wound management, can increase patient survival.

In our five patients, one and two year survival was 100% and 80%, respectively. Survival times since initiation of dialysis reported here were in accordance with the general outcome of hemodialysis patients. This demonstrates the efficacy of the proposed treatment (see: Excerpts from the US Renal Data System 2009, Annual Data Report: 54 months for this age group [46]; and analysis of the Austrian Dialysis and Transplant Registry (OEDTR): median survival data (2005-2007) of incident hemodialysis patients, age group of 55 to 65 years: 56.9 months; [47].
The data reported here were provided by OEDTR. Responsibility for interpretation and reporting of these data lies with the authors.

Conflict of Interests

H.S. has received unrestricted research grants by Amgen Corp. and has received lecture honoraria from Amgen Corp, Roche Austria, Fresenius Medical Care and Genzyme. All other authors have declared no conflict of interest.

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