Nephrol Dial Transplant (2004) 19: 2130–2132
DOI: 10.1093/ndt/gfh305

Nephrology
Dialysis
Transplantation

Case Report

Rapid improvement of calciphylaxis after intravenous pamidronate therapy in a patient with chronic renal failure

Pierre Monney[1], Quan-Vinh Nguyen[1], Henri Perroud[2] and Eric Descombes[1]

[1]Dialysis Unit and [2]Department of Internal Medicine, Hôpital Cantonal, Fribourg, Switzerland

Keywords: bisphosphonates; calcific uraemic arteriolopathy; calciphylaxis; pamidronate; renal failure

Introduction

Calciphylaxis, also called calcific uraemic arteriolopathy, is a rare disease characterized by medial calcification of the small arteries and ischaemia of the subcutaneous tissue, often leading to necrosis of subcutaneous fat and skin. It affects mainly women with chronic renal insufficiency and/or obesity. According to recent studies, calciphylaxis seems to occur more frequently than previously believed, with an incidence of 1% per year [1] and a prevalence of 4% in dialysis patients [2].

The pathogenesis of calciphylaxis is poorly understood and its treatment is largely empirical and somewhat controversial. Recent studies have emphasized the crucial role of a multidisciplinary therapeutic approach focusing on the correction of the underlying abnormalities of the calcium and phosphorus plasma concentrations (using non-calcium-containing phosphate binders), local wound care with debridement of necrotic tissues and aggressive treatment of infectious complications [3]. The utility of parathyroidectomy, corticoid therapy and hyperbaric oxygen therapy remains controversial. However, despite intensive combined treatments, the prognosis of calciphylaxis remains poor: the overall 1 year survival is 45% and the 5 year survival is 35%, with a relative risk of death of 8.5 compared with other dialysis patients [4].

Bisphosphonates have a powerful inhibitory effect on osteoclast activity and bone resorption and are largely used in the treatment of osteoporosis, tumoral hypercalcaemia and Paget's disease. Some previous studies have shown that bisphosphonates also have beneficial effects on the evolution of experimental calciphylaxis [5,6] and tumoral calcinosis with systemic inflammatory response [7]. According to these latter observations, we decided to treat a woman with chronic renal failure and rapidly worsening calciphylaxis with pamidronate. This treatment brought a spectacular and rapid improvement of the patient's clinical condition and a rapid decrease of the inflammatory syndrome. We report this case, which is, to our knowledge, the first one in which a bisphosphonate has been used to treat a patient with calciphylaxis.

Case

A 59-year-old obese woman (body mass index: 40.1 kg/m^2) with a long history of type 2 diabetes and progressive chronic renal insufficiency was hospitalized in our hospital in May 2003 for uraemic pericarditis and extremely severe pain in the legs. The leg pain began several months prior to the hospitalization and increased progressively to such a point that it prevented walking and no longer responded to simple analgesic therapy. On admission, the patient's medication further included L-thyroxin 0.1 mg/day, furosemide 80 mg/day, epoetin-β 10 000 UI/week, insulin 12 UI/day and benazepril 5 mg/day. On clinical examination, we recorded a diminished general condition and generalized oedema. Body temperature was 37.3°C and blood pressure was 180/100 mmHg. There was a pericardial friction rub on cardiac auscultation. Examination of the legs showed several erythematous lesions of the skin and an induration of both calves and of the medial aspect of the thighs, which was exquisitely painful on palpation. Three 2–3 cm diameter necrotic ulcers with purpuric border were noted on the calves. The peripheral pulses were palpable and there was no sign of peripheral neuropathy. Laboratory results included glucose 6.6 mmol/l, urea 35.2 mmol/l, serum creatinine 628 μmol/l, sodium 138 mmol/l, potassium 6.3 mmol/l, ionized calcium 0.94 mmol/l, phosphate 2.85 mmol/l, intact parathyroid hormone 226 ng/l, albumin 28.7 g/l, C-reactive protein (CRP) 156 mg/l, haemoglobin 81 g/l, leukocytes 7.3 G/l, platelets 282 G/l and creatinine clearance 4 ml/min. Echocardiography

Correspondence and offprint requests to: Dr E. Descombes, Dialysis Unit, Hôpital Cantonal, CH-1708 Fribourg, Switzerland. Email: descombese@hopcantfr.ch

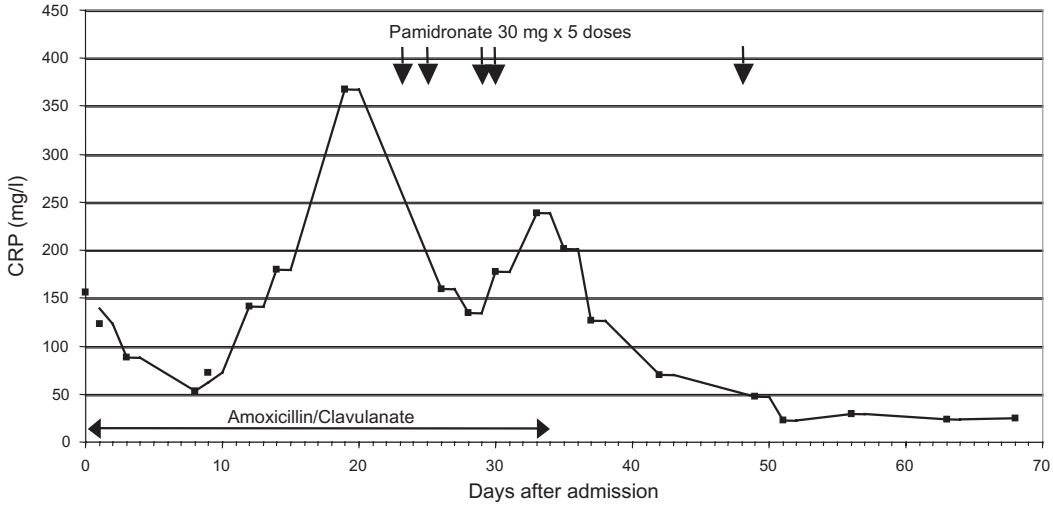

Fig. 1. Evolution of the CRP since admission. Each vertical arrow represents a single dose of 30 mg pamidronate. Antibiotic therapy was also given during the first 4 weeks of hospitalization (horizontal arrow).

showed a small pericardial effusion and Doppler ultrasound of the legs ruled out a deep vein thrombosis. The initial therapy consisted of intensive daily haemodialysis for 10 days, followed by 4 h dialysis three times a week (with a calcium dialysate of 2.5 mEq/l), antibiotic treatment for suspicion of skin infection [amoxycillin/clavulanic acid (Augmentin®)] and opiates for pain control. At the end of the first hospitalization week, we performed a plain X-ray of the thighs, which showed extensive vascular calcification of large and small arteries. A skin biopsy showed necrotizing panniculitis with medial calcification of small arteries, typical of calciphylaxis. In the following 2 weeks, despite normalization of the calcium–phosphate product, local wound care and antibiotics, the clinical condition continued to worsen, with exacerbation of pain and increase of CRP up to 368 mg/l. At that time we decided to start an intravenous pamidronate therapy (five 30 mg doses of Aredia® at days 23, 25, 29, 30 and 48 of hospitalization) without any other concomitant change in the therapy. The treatment was well tolerated and as soon as 48 h after the first dose of pamidronate, the clinical condition began to improve: the CRP values decreased rapidly to 20 mg/l (Figure 1) and the pain in the legs resolved simultaneously, allowing us to stop the therapy with opiates. The three ulcers healed within 1 month and the patient was discharged 5 weeks after the first pamidronate dose.

Six weeks after discharge, the patient noted a recurrence of pain in the legs ('the same pain as when calciphylaxis began' said the patient). Again, after an additional 30 mg dose of pamidronate, the symptoms disappeared in a few days. Thereafter, the patient remained totally pain-free, there was no recurrence of the skin lesions and the CRP remained stable at ~20 mg/l. A control X-ray of the calves made 6 months later showed no change in the degree of the vascular calcifications.

Discussion

Calciphylaxis is a painful symmetrical necrotizing panniculitis associated with medial calcification of small- and medium-sized arteries. According to the distribution of the lesions, we distinguish two forms of the disease: in the distal form lesions are limited to the calves and the forearms, while in the proximal form they also affect the thighs and the abdominal wall. A proximal distribution of the lesions and the presence of skin ulcers are associated with a very poor prognosis [1]. In the proximal form the survival rate is 23% (*vs* 63% in the distal form) [1] and if skin ulcerations develop it is only 11% (*vs* 79% in the non-ulcerating form) [8], the main cause of the high mortality being infection [4].

In the present case of biopsy-proven proximal ulcerating calciphylaxis, the most striking point was the rapid and spectacular improvement of the disease after pamidronate therapy. At the time calciphylaxis was progressing rapidly in our patient, with worsening of the clinical condition, exacerbation of pain and rapid increase of CRP despite dialysis with low-calcium dialysate, aggressive wound care and antibiotic therapy for 3 weeks. At that moment we decided to start pamidronate therapy and we ourselves were quite surprised to see that as soon as 48 h after the first dose of the drug was administered, the dramatic course of the disease suddenly changed. The clinical condition of the patient began to improve and the pain improved rapidly as well as the inflammatory syndrome. Thereafter, the ulcers healed also very rapidly, within only 4 weeks. This rapid change in the course of the disease occurred without any other concomitant change in therapy or in the dialysis prescription and strongly suggests a powerful effect of pamidronate.

To our knowledge, this is first report of the use of a bisphosphonate in the treatment of a patient with

calciphylaxis. Why did we consider pamidronate? Two arguments were the basis of our decision. First, two studies in animals have shown that bisphosphonates can effectively prevent experimental calciphylaxis [5,6]. Of course, there are several differences between these animal models of calciphylaxis and the human disease, but in both studies the bisphosphonates were quite effective in preventing the necrotic lesions associated with the disease. Second, a recent paper [7] reported the successful treatment of a case of tumoral calcinosis associated with pyrexia and systemic inflammatory response for which the prescription of pamidronate (three doses of 30 mg) induced the disparition of fever within a few days and a normalization of the CRP within 2 weeks. In this latter case, the authors decided to use pamidronate with the hypothesis that the inflammatory syndrome might result from the local activity of osteoclasts and an associated release of proinflammatory cytokines. Actually, the inflammatory syndrome resolved rapidly but the calcified lesions remained unchanged, favouring the hypothesis of an anti-inflammatory effect of pamidronate [7]. In our case also, pamidronate induced rapid resolution of the inflammatory syndrome and of the local symptoms, while the follow-up X-ray of the legs did not show any significant change in vessel calcifications. This suggests that the mobilization of calcium salts from the arterial wall was not an important factor in the clinical improvement. Several studies have shown that, apart from their effect on bone, the bisphosphonates exert an inhibitory effect on macrophage activity and local proinflammatory cytokine production [9,10]. It is our impression that these cellular effects may have played an important role in the rapid improvement of our patient (i.e. rapid pain relief, rapid improvement of CRP and rapid healing of the necrotic ulcers). One may question whether other drugs with anti-inflammatory properties, such as steroids, might be useful. Fine and Zacharias [8] reported that steroids may be beneficial in some patients with non-ulcerating calciphylaxis, but at the present time most authors do not recommend their use.

In conclusion, the pathogenesis of calciphylaxis remains poorly understood and its treatment largely empirical. At the present time, the treatment is based mainly on a multidisciplinary therapeutic approach focusing on the correction of the abnormalities of calcium–phosphate metabolism, intensive wound care and aggressive treatment of infection. According to the present case, bisphosphonates may be an effective new alternative for the treatment of calciphylaxis. Of course, further studies are needed to confirm their efficacy in the treatment of patients with different types of calciphylaxis.

Acknowledgements. Presented in abstract form at the 35th Congress of the Swiss Society of Nephrology, Lucerne, Switzerland, 4–5 December 2003.

Conflict of interest statement. None declared.

References

1. Hafner J, Keusch G, Wahl C, Burg G. Calciphylaxis: a syndrome of skin necrosis and acral gangrene in chronic renal failure. *Vasa* 1998; 27: 137–143
2. Angelis M, Wong LL, Myers SA, Wong LM. Calciphylaxis in patients on hemodialysis: a prevalence study. *Surgery* 1997; 122: 1083–1090
3. Don BR, Chin AI. A strategy for the treatment of calcific uremic arteriolopathy (calciphylaxis) employing a combination of therapies. *Clin Nephrol* 2003; 59: 463–470
4. Mazhar AR, Johnson RJ, Gillen D *et al*. Risk factors and mortality associated with calciphylaxis in end-stage renal disease. *Kidney Int* 2001; 60: 324–332
5. Miller S, Vernon-Roberts E, McClure J. Cutaneous calciphylactic reactions in the mouse and the rat and the effects of diphosphonates on the reaction in the rat. *J Pathol* 1984; 142: 7–13
6. Price PA, Omid N, Than TN, Williamson MK. The amino bisphosphonate ibandronate prevents calciphylaxis in the rat at doses that inhibit bone resorption. *Calcif Tissue Int* 2002; 71: 356–363
7. Phanish MK, Kallarackal G, Ravanan R *et al*. Tumoral calcinosis associated with pyrexia and systemic inflammatory response in a haemodialysis patient: successful treatment using intravenous pamidronate. *Nephrol Dial Transplant* 2000; 15: 1691–1693
8. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. *Kidney Int* 2002; 61: 2210–2217
9. Cecchini MG, Felix R, Fleisch H, Cooper PH. Effect of bisphosphonates on proliferation and viability of mouse bone marrow-derived macrophages. *J Bone Miner Res* 1987; 2: 135–142
10. Pennanen N, Lapinjoki S, Urtti A, Monkkonen J. Effect of liposomal and free bisphosphonates on the IL-1 beta, IL-6 and TNF alpha secretion from RAW 264 cells *in vitro*. *Pharm Res* 1995; 12: 916–922

Received for publication: 29.3.04
Accepted in revised form: 15.4.04