Severe Hypercalcaemia Four Months After Acute Oliguric Renal Failure – Successful Treatment with Intravenous Clodronate

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Abstract

A 33 year old man developed acute oliguric failure lasting 66 days, eight days after admission with multiple gun shot wounds. On day 99 after admission, serum calcium was elevated mildly at 2.54 mmol/l (normal range 2.1-2.5 mmol/l). Serum parathormone was undetectable. He was discharged soon afterwards. He presented again on day 164 with nausea, vomiting and blurred vision. Fundoscopy revealed an ischaemic retinopathy and extensive keratopathy. Serum calcium was 3.48 mmol/l and serum creatinine 262 umol/l (normal range 40-110 umol/l). Repeat parathormone was undetectable and there was no evidence of myeloma, sarcoidosis or malignancy.

Following treatment with intravenous saline and frusemide, serum calcium fell to a nadir of 3.05 mmol/l. On day 168 an infusion of sodium clodronate 300 mg was given. Twenty-four hours later serum calcium was 2.65 mmol/l and 48 hours later calcium was 2.26 mmol/l. Normocalcaemia was maintained for 17 days and severe hypercalcaemia never recurred.

This is the first report in which biphosphonates have been successfully used to treat hypercalcaemia following acute renal failure thus obviating the need for further dialysis.

Introduction

Hypercalcaemia has been seen in the course of acute renal failure and is commonest when the latter is due to rhabdomyolysis[1-10]. It usually occurs during the early stage of the polyuric phase of the illness although it has also been reported in the oliguric period of acute renal failure. Hypercalcaemia occurring late in the course of the polyuric phase or after recovery of renal function is not well documented. The present report describes a patient with acute renal failure in whom hypercalcaemia developed three months after the onset of oliguria. Treatment with sodium clodronate was successful in producing normocalcaemia.

Case Report

A 33 year old man was admitted to the Intensive Care Unit after sustaining a series of gunshot wounds to the right arm, right chest, left chest, left groin region and left thigh. At laparotomy he was noted to have a perforation of the right diaphragm, a laceration to the right lobe of liver, entrance and exit wounds in the posterior and anterior walls of the stomach respectively, a perforating wound of the mid-transverse colon and lacerations to blood vessels in the region of the left renal pedicle. The perforations were repaired and a defunctioning colostomy was performed. On return from theatre his condition was stable with a pulse of 90 beats/min. and a blood pressure of 160/100. He was producing good quantities of clear urine. Renal function, electrolytes and phosphate were within normal limits. Serum calcium was low at 1.68 mmol/l. Eight days after admission he developed oliguria, serum urea and creatinine rising to 28.9 nmol/l and 484 umol/l respectively. Haemodialysis was commenced and continued for 66 days. He subsequently underwent three further laparotomies to remove his left kidney and to deal with bleeding from his gastrointestinal tract. His transfusion requirements during the course of his four month admission were substantial and consisted of 70 units of packed cells and 15 units of fresh frozen plasma. On day 99 after admission he was noted to have a serum calcium of 2.54 mmol/l. Parathormone was undetectable. It was noted that he was drinking two to three pints of milk per day while in hospital. He was discharged soon after with advice to avoid dairy products and other calcium containing substances such as antacids. On day 164 he presented to the Ophthalmology Department with blurring of his vision and severe nausea. Serum calcium was 3.48 mmol/l. On examination he was moderately dehydrated. Blood pressure was 155/95. Visual acuity was reduced to a level of counting fingers in both eyes. There was a band of keratopathy and a widespread proliferative retinopathy on the background of an ischaemic retina. Repeat parathormone was undetectable and there was no evidence of myeloma, sarcoidosis or malignant disease. Following rehydration with intravenous saline and frusemide, serum calcium fell to a nadir of 3.05 mmol/l over 24 hours. On day 168 he was given an infusion of sodium clodronate 300 mg in 500 mls of normal saline over three hours. Twenty-four hours later serum calcium was 2.65 mmol/l and 48 hours later calcium was 2.26 mmol/l. Figure 1 shows the serial calcium levels during the course of his admission. Normocalcaemia was maintained until day 187. At this stage he developed acute glaucoma with anorexia, nausea and vomiting. Serum calcium rose to 2.76 mmol/l. He was treated with intravenous saline and oral prednisolone from day 187 to day 210 and serum calcium fell to normal levels over five days. Six days after stopping prednisolone, serum calcium was normal at 2.49 mmol/l and

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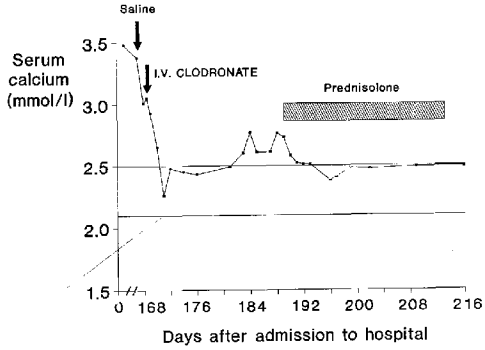

Fig. 1 – The effect of saline, clodronate and prednisolone on serum calcium levels

he was discharged in good clinical condition. His renal function remained moderately impaired with a urea of 9.3 mmol/l and creatinine 195 umol/l.

Comment

Hypercalcaemia developing during the course of acute renal failure has been reported previously and is usually associated with rhabdomyolysis. The hypercalcaemia occurs in the polyuric phase (85% of cases) and is commonest early in this phase. The latest reported time is 35 days after diuresis onset[3,5]. One further patient developed a transient hypercalcaemia 35 days after renal function returned to normal[1]. The hypercalcaemia is often short-lived and benign clinically. In the Feinstein series[1] (n=24) the duration of hypercalcaemia ranged from 1 to 35 days.

In the present patient, serum calcium was first noted to be elevated 91 days after the onset of acute renal failure and 36 days after the onset of polyuria. The patient was severely ill. Total duration of hypercalcaemia was 71 days.

In past reports the hypercalcaemia has generally been self-limiting or has been treated with a combination of glucocorticoids, frusemide and saline infusions[1-6]. Occasionally patients have been treated with haemodialysis using calcium free dialysate and there is one report of a patient being treated with Calcitonin[12]. To our knowledge this is the first report in which a biphosphonate has been used for the hypercalcaemia of acute renal failure. Sodium clodronate suppresses osteoclast mediated bone resorption without adversely affecting mineralisation and has been used successfully in malignant hypercalcaemia and in hyperparathyroidism[6,13-15].

A number of explanations have been proposed for the delayed hypercalcaemia found in some patients following rhabdomyolysis. These include mobilization of calcium from soft tissue, dehydration and autonomous secretion of parathormone[5-8,17]. In our patient hypercalcaemia persisted after dehydration was corrected while parathormone levels were undetectable on a number of occasions. Another suggestion is that vitamin D may play a role in the development of hypercalcaemia after acute renal failure. Llach *et al* (1981) studied six oliguric patients with rhabdomyolysis-induced acute renal failure and found a significant positive correlation between the levels of serum calcium and 1.25 dihydroxy vitamin D (1,25-$(OH)_2$ D) throughout the course of renal failure. Profound hypocalcaemia was associated with low levels of 1,25 $(OH)_2$ D during the oliguric phase while in the early polyuric phase hypercalcaemia was accompanied by a rise in 1,25 $(OH)_2$ D to levels above normal. Akmal *et al* (1986) in a similar series also found significant increments in 1,25 $(OH)_2$ D levels during the diuretic phase. The rise was significantly greater in the four patients who developed hypercalcaemia than in the three normocalcaemic patients. The source of the 1,25 $(OH)_2$ D is uncertain. However, it is known that vitamin D is stored in muscle and it is theoretically possible that rhabdomyolysis may result in the release of vitamin D into the circulation causing a rise in the serum levels of this hormone. Since one of the actions of 1,25 $(OH)_2$ D is to increase bone resorption it may be that clodronate lowered serum calcium levels by inhibiting this effect.

A further possibility for the aetiology of the hypercalcaemia in this case is prolonged immobilization. This has been documented in several reports and may take up to 10 weeks of immobilization to become fully developed[5,12,17,18]. The source of the late hypercalcaemia in these patients is probably increased osteoclastic bone resorption with a relative decrease in bone formation. Our patient was immobile and on a ventilator for 92 days. Even after discharge he spent most of his time in bed.

In summary, this case report illustrates a number of points. Hypercalcaemia occurring late after acute renal failure is probably under-recognized and can cause significant morbidity. The aetiology remains uncertain and is probably mulifactorial. This report demonstrates that biphosphonates by inhibiting osteoclast action can be successful in the management of hypercalcaemia occurring in this type of situation.

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