Immobilization hypercalcaemia responding to intravenous pamidronate sodium therapy

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Summary: A 16 year old male developed symptomatic hypercalcaemia of immobilization on day 47 following a diving accident which had resulted in incomplete C4 tetraplegia. Following initial reduction in serum calcium with salmon calcitonin 100 U/day, symptomatic hypercalcaemia recurred. A single dose of 30 mg pamidronate sodium, given intravenously, caused serum calcium to fall within 48 hours. Initial mild, asymptomatic hypocalcaemia was followed by a return to sustained normocalcaemia. No major adverse reaction was encountered, and if further clinical experience confirms its efficacy, pamidronate sodium will warrant consideration as first-line therapy for immobilization hypercalcaemia.

Introduction

Hypercalcaemia may complicate prolonged immobilization of any aetiology, and is a relatively frequent occurrence in younger patients with spinal cord injury. We report a recent case in which a single dose of pamidronate disodium (previously designated aminohydroxypropylidene diphosphonate) proved effective in treatment of this condition.

Case report

A 16 year old male suffered compressive fractures of cervical vertebrae 4 and 5 as a result of diving into shallow water. Neurological examination revealed incomplete C4 tetraplegia, with complete sensory deficit below T6. Serum calcium corrected to serum albumin of 45 g/l (Ca. corr.) on admission was 2.19 mmol/l (ref. range 2.25–2.60). Other electrolytes were normal, and serum creatinine was 0.06 mmol/l (0.06–0.11).

On day 47 post-injury, he complained of worsening nausea, vomiting and constipation. Physical and radiological examination showed evidence of high faecal impaction. Chest radiograph was normal. Ca. corr. was markedly elevated at 3.20 mmol/l (Figure 1). Clinical examination showed a prepubertal male, height 156 cm, (<3rd centile for age) mass 39.4 kg (<3rd centile). Both his parents and his sister were of normal height, but his father had also experienced delayed puberty, commencing at 18 years of age and

Figure 1 Albumin-corrected serum calcium (Ca. corr.) from days 1–175 post-injury, showing the effects of treatment with salmon calcitonin 100 units/day (days 71–120), and of a single 30 mg intravenous dose of pamidronate disodium (APD) (day 120). (Reference range for Ca. corr. 2.25–2.60 mmol/l.)

progressing normally thereafter, with a final height of 170 cm. There was no clinical evidence of Addison's disease, thyrotoxicosis or sarcoidosis. Investigations were as follows: creatinine 0.07 mmol/l, urea 10.9 mmol/l, sodium 136 mmol/l, potassium 4.2 mmol/l, phosphate 1.42 mmol/l, alkaline phosphatase 132 U/l, parathyroid hormone level, (intact molecule by immunoradiometric assay; kit from Incstar Corporation, Stillwater, Minnesota) <1.0 pmol/l (1.0–5.5), free thyroxine 18 pmol/l (9–25), 24-hour urinary calcium excretion 9.3 mmol/day (2.5–7.5). Erythrocyte sedimentation rate was 12 mm/h, and

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serum protein electrophoresis was normal. Serum testosterone was 0.8 nmol/l (adult reference range 10–35), luteinizing hormone 2.0 U/l, follicle stimulating hormone 2.0 U/l. His delayed puberty was considered most likely constitutional in aetiology, and further investigation was not considered necessary at this stage. A provisional clinical diagnosis of immobilization hypercalcaemia (IH) was made, and treatment was commenced with 3 litres of intravenous fluids daily, with some initial symptomatic benefit. Symptoms recurred despite intravenous fluids, and salmon calcitonin 100 U/day subcutaneously was commenced on day 71. The Ca. corr. initially fell to 2.60 mmol/l, but subsequently again increased to 2.97 mmol/l (Figure 1), despite partial recovery of neurological function in all limbs and consequent improved mobility aided by intensive physiotherapy. Bony healing was slow, necessitating 6 weeks of external traction, followed by 9 weeks' treatment with a rigid external brace. The patient suffered some initial flushing and nausea with calcitonin injections, improved by the addition of metoclopramide 10 mg before each dose.

Because of continuing symptomatic hypercalcaemia, he was treated with a single dose of 30 mg pamidronate disodium, given as an infusion in 0.9% saline over 4 hours, on day 120. He developed a fever of 39.2°C, but in view of concomitant urinary tract infection, this could not be definitely ascribed to the drug. There were no other adverse effects from the treatment. Figure 1 shows the fall in his serum calcium level following pamidronate therapy, with an asymptomatic Ca. corr. nadir of 2.04 mmol/l and subsequent return to normocalcaemia. Urinary calcium also fell from 11.1 mmol/day to 0.3 mmol/day with pamidronate therapy.

Discussion

Immobilization hypercalcaemia (IH) was first described by Albright,¹ and has been recognized as a relatively common complication of spinal cord injury in younger patients, affecting 11% of tetraplegic patients under the age of 21 years in a report by Maynard.² It is characterized by increased bone resorption, with radiological evidence of osteopenia,³ increased osteoclastic activity in cases undergoing bone biopsy⁴ and elevated urinary hydroxyproline excretion.⁵ Whilst resorptive hypercalcaemia is a near-universal finding after prolonged immobilization,³ it is unclear why only a small percentage of patients develop hypercalcaemia. The higher rate of bone

turnover in children has been invoked as an explanation for their increased incidence of this disorder.⁶ Parathyroid hormone levels have been variously reported as high, normal, or low in this condition,³ but parathyroidectomy has proven uniformly ineffective. Levels of plasma 1,25-dihydroxy-vitamin D (1,25-OH-D3) have been low when measured.³

Optimal therapy for IH has been even less well defined than aetiology. Dietary calcium restriction is irrational in the face of already-suppressed calcium absorption and negative calcium balance due to increased bone resorption.⁶ Mobilization reduces the calcium levels only slowly in most patients, and treatment is required for severe symptoms in the interim. Calcitonin therapy is of proven efficacy, but secondary 'escape', which is not necessarily improved by increased dosage, limits long-term utility,⁵ as in the current case. Glucocorticoids in relatively high doses (equivalent to 20–80 mg/day of prednisone) have also been shown to improve IH,⁵ but concomitant reduction of intestinal calcium absorption,⁵ inhibition of bone formation⁵ and well-known systemic toxicity make them far from ideal agents in this setting. Other traditional therapies for hypercalcaemia are of little clinical utility. Intravenous saline (with or without frusemide) is inconvenient in long-term treatment of hypercalcaemia. Phosphate therapy may aggravate morbidity due to extraskeletal calcification, already a problem in immobilized patients.⁵

In contrast, the diphosphonates are attractive agents for the treatment of IH on both theoretical and pragmatic grounds. They reduce bone resorption, putatively both by reducing access of osteoclasts to bony surfaces and by cytotoxicity to osteoclasts.⁷ Both etidronate^{6,8} and clodronate⁹ have been used effectively in IH, but the use of pamidronate sodium in this condition has not previously been reported to our knowledge. Etidronate has been reported to interfere with bone mineralization,¹⁰ and clodronate has not become widely available because of a possible (though disputed) association with acute myeloid leukaemia.¹⁰ Neither of these adverse effects has been noted with pamidronate, and its specific toxicity appears low, with transient fever and lymphopenia being the most frequently reported adverse effects.¹⁰ Guided by regimens commonly used to treat malignant hypercalcaemia we chose to administer a single 30 mg dose to this patient. This caused temporary, asymptomatic hypocalcaemia, and a lower dose may have been equally efficacious.

If further clinical experience confirms our findings, we believe that pamidronate disodium therapy, in conjunction with early mobilization where possible, should be considered first line treatment for IH.

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