

Hypercalcaemia in osteogenesis imperfecta treated with pamidronate

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Abstract

The response to the bisphosphonate, pamidronate, is reported in a child with osteogenesis imperfecta who had recurrent symptomatic hypercalcaemia after immobilisation following fractures. Oral clodronate was effective in the prevention of immobilisation hypercalcaemia in the same child. The bisphosphonates may have other roles in osteogenesis imperfecta by decreasing bone turnover.

(*Arch Dis Child* 1997;76:169-170)

Keywords: osteogenesis imperfecta; hypercalcaemia; pamidronate; bisphosphonate.

Case report

A 13 year old boy sustained a fracture of the left femur; he had fractured his right leg twice before with minimal trauma. Radiography showed gross osteopenia. His sclerae were blue. He was treated conservatively with traction.

After four weeks he developed vomiting with nausea, anorexia, constipation, polydipsia, and polyuria. Investigations showed a grossly raised serum albumin adjusted calcium of 3.54 mmol/l (normal value 2.1-2.6 mmol/l), with mildly raised urea and creatinine. Hypercalciuria was demonstrated at 21 mmol/24 hours (<5 mmol/24 hours). Creatinine clearance was normal and parathyroid hormone (PTH) was appropriately suppressed. Other electrolytes including phosphate and alkaline phosphatase were normal. He was not on any medication and there was no history of vitamin ingestion.

Intravenous rehydration led to a fall to normal values of the urea and creatinine with little effect on the serum calcium concentration and he remained symptomatic. He was then treated with pamidronate disodium 15 mg infused intravenously over two hours and frusemide 20 mg orally twice daily. Informed consent was obtained from the parents and the patient as this drug is not licensed for use in children. The serum calcium concentration fell to a normal value of 2.54 mmol/l within three days and his symptoms improved. Over the next two weeks he was mobilised and the frusemide was discontinued. His serum calcium remained in the normal range. Repeat 24 hour urine excretion six months later showed a normal urine calcium excretion of 4.4 mmol/24 hours. Renal ultrasound scan showed no evidence of renal calculi or nephrocalcinosis.

Two years later he again fractured his right femur and was treated with skeletal traction. After 18 days he had symptoms of hypercalcae-

mia with a serum calcium of 3.27 mmol/l. All other electrolytes were normal as was the vitamin D concentration. PTH concentrations were appropriately suppressed and hypercalciuria again demonstrated with a calcium/creatinine ratio of 1.3 (<0.6 mmol/mmol). Treatment was started with intravenous fluids and frusemide 20 mg twice a day. After two days his serum calcium remained raised at 3.24 mmol/l so treatment with an intravenous infusion of pamidronate 15 mg was given. Within three days his serum calcium had fallen to normal with improvement of symptoms. The frusemide was continued.

Four weeks later, while still on traction, calcium concentrations began to rise again to a peak of 3.27 mmol/l when he was again symptomatic. A further dose of pamidronate 15 mg was given with good effect.

Five weeks later during mobilisation at home he refractured his right femur. Once again he was treated conservatively in a Thomas' splint. His serum calcium, which had been normal on admission, slowly rose to 2.73 mmol/l after two weeks. On this occasion prophylactic treatment with oral clodronate 520 mg twice a day was started. Serum calcium was checked weekly and found to remain in the normal range for the rest of this admission and for two weeks after discharge. He was discharged eight weeks after admission when beginning to mobilise, at which point the clodronate was stopped. No side effects were reported and the serum phosphate remained in the normal range.

Discussion

At the time of the first admission this boy had not been diagnosed as having osteogenesis imperfecta. However the presence of multiple fractures with minimal trauma, blue sclerae, radiological osteoporosis, and a family history make this diagnosis highly likely. Both his mother and his maternal aunt seem to have the same condition. He gives no history of easy bruising, abnormal scarring, hearing or dental problems. His height and weight were on the 50th centiles. There is considerable phenotypic heterogeneity in osteogenesis imperfecta but this case broadly corresponds to the Silience type IA.¹

Hypercalciuria is a common finding in children with osteogenesis imperfecta and may correlate with disease severity,² although its pathogenesis is not understood. Renal stones and renal papillary calcification were found in 7% of patients with osteogenesis imperfecta.³ However, increases in serum calcium are not characteristic and there is no evidence of a dis-

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Accepted 10 September
1996

turbance of calcium homeostasis in osteogenesis imperfecta. In this patient hypercalcaemia was likely to have been caused by the effects of prolonged immobilisation, the fractures, and the osteogenesis imperfecta, which can all lead to an increase in osteoclastic activity. The responses on each occasion to the use of pamidronate and the failure of the calcium concentration to rise during prolonged treatment with clodronate in the same situation would support this hypothesis.

Both of these drugs are bisphosphonates and are potent inhibitors of osteoclastic activity through not fully understood mechanisms. In vitro they bind strongly to hydroxyapatite crystals inhibiting their formation and dissolution. In vivo the inhibition of osteoclastic activity may, at least in part, be due to the binding of the drug to bone material as these drugs are analogues of pyrophosphate.⁴ Potential side effects of treatment with these drugs include decreased serum phosphate concentrations, gut disturbances, pyrexia, and lymphocytopenia. None were reported in our case.

Pamidronate has been used in the treatment of osteogenesis imperfecta with a reported increase in the radiographic bone mass⁵⁻⁶ using

an oral regimen. We would not on current evidence advocate routine use of bisphosphonates to this end. They should, however, be considered in cases of hypercalcaemia secondary to prolonged immobilisation. Prophylactic treatment with clodronate may also be considered in cases known to be at risk of developing hypercalcaemia. Where possible prolonged immobilisation should be avoided in at risk cases.

We acknowledge the help of the Orthopaedic Department, York District Hospital and of senior pharmacist Elizabeth McManus with this case.

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