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Case Report

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A case of a severe reaction following the use of bisphosphonates in a patient with osteogenesis imperfecta

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Abstract: We present a case of an unusual delayed multi-systemic reaction, following treatment with pamidronate. Although serious adverse reactions have been reported with pamidronate use, such a severe reaction, late in the course of pamidronate treatment, has not been described before. An 11-month-old boy with severe and complex osteogenesis imperfecta (OI) presented with hyperpyrexia and respiratory distress 10 days after his fifth cycle of pamidronate. He had significant derangement of his biochemical parameters including a positive urine myoglobin. His respiratory distress was out of proportion to his chest radiograph changes. Bilevel positive airway pressure (BiPAP) and paediatric intensive care (PICU) admission were required. He was extensively investigated to exclude other diagnoses, but all of these investigations were negative. The reaction resembled rhabdomyolysis. He made a full recovery with only supportive management.

Keywords: bisphosphonates; osteogenesis imperfecta; rhabdomyolysis.

Background

Osteogenesis imperfecta (OI) is a group of disorders characterised by bone fragility in association with bone tissue hypermineralisation, often caused by mutations in genes involved in type I collagen synthesis, processing or transport. Bisphosphonates are drugs that reduce bone remodelling through the inhibition of osteoclastic activity, whilst allowing bone formation from modelling activity; so bone mass increases because newly formed metaphyseal trabecular bone is retained and new bone is added on the periosteal bone surface increasing cortical thickness. Bisphosphonates are widely used as first-line treatment of OI.

Serious adverse reactions have been reported with intravenous bisphosphonate use in adults including renal failure after several cycles, severe muscle and bone pain and dermatomyositis [1, 2]. Paediatric case reports have highlighted cases of respiratory distress following pamidronate infusions and also of multi-systemic disease in zoledronic acid use [3, 4]. We present a case of an unusual delayed multi-systemic reaction, following treatment with pamidronate. The reaction, resembling rhabdomyolysis and requiring paediatric intensive care (PICU) support, has not been reported previously to the best of our knowledge.

It has been found that there is a marked elevation of inflammatory cytokines and acute phase reactants after a pamidronate infusion at the dose used for osteoporosis in adults [5].

Case presentation

We present a case of an infant with severe and complex OI who had a life-threatening rhabdomyolysis-like illness episode 10 days after receiving a dose of pamidronate. He was known antenatally to have skeletal abnormalities and was subsequently confirmed to have a *COL1A1* mutation confirming the diagnosis of OI. He had a stormy neonatal course requiring respiratory support and at 6 months of age developed subdural haemorrhages initially managed with a sub-galeal drain, but subsequently requiring a ventriculostomy. He had four courses of pamidronate as an

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inpatient with gradually increasing doses, as per our local infant protocol [6]. There were no significant reactions noted with any of these.

Ten days after his fifth cycle of pamidronate, at 11 months of age, he presented with hyperpyrexia and respiratory distress, requiring bilevel positive airway pressure (BiPAP) and admission to PICU. His respiratory distress was out of proportion to the chest radiograph changes. He had significant derangement of his biochemical parameters (see Table 1). Notably there was evidence of hyponatraemia, hyperkalaemia, acute kidney injury, abnormal liver function tests, hypocalcaemia, a raised ferritin and lactate dehydrogenase, thrombocytopenia and abnormal coagulation. His serum 25-hydroxyvitamin D level was normal. Supportive management with fluids and electrolyte replacement was commenced. After a full septic screen, broad spectrum antibiotics were started.

Investigations for sepsis including a blood culture, cerebrospinal fluid (CSF) culture, urine culture, stool culture and nasopharyngeal aspirate were negative. Blood testing for hepatitis C, adenovirus, Epstein-Barr virus (EBV) and cytomegalovirus polymerase chain reaction (CMV PCR), HIV antibody, hepatitis B surface antigen and respiratory viral/Legionella PCR were also negative. The patient was not on any other medications prior to admission, making a diagnosis of malignant hyperthermia or other drug reactions unlikely. There was growth of *Enterobacter cloacae* in bronchoalveolar lavage. This was thought to be due to colonisation, not infection (low inflammatory markers, lack of white cells in sputum and previous colonisation). A liver biopsy and bone marrow aspirate were performed which excluded a diagnosis of aemophagocytic lymphohistiocytosis (HLH). Further investigations showed a positive urine myoglobin indicating rhabdomyolysis.

The patient gradually improved without additional treatment and biochemical parameters stabilised. As he improved clinically, it became obvious that he had decreased head movement, stiffness of limbs, poor interaction with carers and an anxious look. A computed tomography (CT) of the head and cervical spine was performed which excluded an acute fracture or intracranial bleed, thus raising the possibility of myalgia and bone pain as a cause of his symptoms. He showed an excellent response to morphine, which was successfully weaned over several weeks. By discharge, 5 weeks after his initial presentation, he had returned to his normal self.

As bisphosphonates are the only current drug of choice that is suitable for treatment of severe OI, the decision was made to give further cycles of bisphosphonates at a reduced dose. A dose of 1 mg/kg of prednisolone was given on the day of the pamidronate infusion to reduce any immune response. The patient was reviewed a week later. He remained well and showed no changes in his biochemical parameters. Further doses of pamidronate have been given with prednisolone cover. These doses have been associated with episodes of pyrexia and periods of feeling unwell but there were no concurrent biochemical abnormalities. These episodes required symptomatic management with paracetamol only.

All data were anonymised and informed consent was obtained from all individuals included in this study.

Table 1: Blood results of the patient at initial presentation and then 1 week after the insult after supportive treatment only.

Blood	Result (initial)	Result (after 1 week)	Reference range
Sodium	154 mmol/L	139 mmol/L	135–145
Potassium	2.3 mmol/L	4.1 mmol/L	3.5–4.5
Urea	18 mmol/L	2.9 mmol/L	2.3–6.4
Creatinine	53 µmol/L	19 µmol/L	20–52
C-reactive protein	<4 mg/L	<4 mg/L	0–8
Creatinine kinase	30,553 IU/L	868 IU/L	24–195
Adjusted calcium	1.79 mmol/L	2.68 mmol/L	2.15–2.74
Phosphate	1.48 mmol/L	0.73 mmol/L	1.13–2.20
AST	994 IU/L	54 IU/L	15–58
ALT	310 IU/L	84 IU/L	9–36
Alkaline phosphatase	185 IU/L	530 IU/L	87–323
Lactate dehydrogenase	390 IU/L	–	500–920
Ferritin	2681 ng/mL	664 ng/mL	29–371

AST, aspartate transaminase; ALT, alanine transaminase.

Discussion

The acute presentation, absence of other underlying causes and temporal relation to pamidronate therapy raised the possibility of a pamidronate-associated adverse reaction. Differential diagnoses initially included sepsis/viral infection, other drug reactions, an intracranial bleed, fracture and HLH. All of these were excluded.

Our patient had a rise in creatinine kinase and myoglobin in urine fitting the criteria of rhabdomyloysis [7]. Myoglobinuria is pathognomonic of rhabdomyolysis and is highly sensitive for its diagnosis. He also suffered from the complications of rhabdomyolysis including hyperkalaemia, hypocalcaemia, hyperuricaemia, raised creatinine, acute kidney injury, acidosis, deranged clotting and volume depletion [7]. Treatment with early, aggressive, supportive therapy is also associated with excellent outcome as seen in our case.

Mild reactions to pamidronate are widely known. However, literature is sparse regarding acute, severe reactions. Trivedi et al. [3] reported a case of respiratory distress and multisystem involvement presenting as progressive tachycardia, fever, hypotension requiring vasopressor infusion and increasing oxygen requirements with zoledronate. However, this young boy already had long-term ventilatory requirements and went on to have a pulmonary haemorrhage [3]. Munn et al. [4] described four cases of respiratory distress following pamidronate infusions in children with OI. This always occurred after the first cycle. Two infants required intensive care.

Bisphosphonates are known to have side effects including a rise in body temperature and flu-like symptoms that resemble a typical acute phase response. The mechanism for this response appears to be associated with the release of tumour necrosis factor (TNF)-alpha and interleukin (IL)-6 [8]. It is possible that our patient had an extreme activation of this pathway when using pamidronate and that the use of steroids alongside the dose has dampened down any further reactions. Low doses of prednisolone appear to be beneficial, but higher doses do not further improve outcomes when used in sepsis [9] and may in fact be detrimental to long-term bone health, which was taken into consideration when giving steroid cover.

Our patient seems to have had an unusual, previously unreported, reaction to pamidronate treatment after several previous cycles being uneventful.

What is new?

We postulate that this was a severe, adverse reaction to pamidronate that has not previously been reported in the paediatric literature. It is important to include rhabdomyolysis in the list of possible adverse reactions to treatment with pamidronate in children. A yellow card has been submitted to the Medicines and Healthcare products Regulatory Agency (MHRA).

Learning points

1. Bisphosphonates are the first-line therapy in OI.
2. Significant adverse reactions have previously been reported in the form of respiratory distress, acute systemic inflammatory reaction and renal dysfunction.
3. The adverse reactions are usually with the first dose of the infusion.
4. A severe, adverse reaction with multisystem involvement occurred after the fourth cycle of pamidronate which has previously not been reported.

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