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CASE REPORT

Severe non-infective systemic inflammatory response syndrome, shock, and end-organ dysfunction after zoledronic acid administration in a child

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Abstract
Introduction Zoledronic acid is an intravenous bisphosphonate used to increase bone mineral density and reduce the risk of fractures. Its safety profile compares well with pamidronate in pediatric patients. We describe an acute, severe, life-threatening, inflammatory reaction in a child.
Methods A 7-year-old boy with complex medical problems and chronic ventilator requirements was admitted to the pediatric intensive care unit (due to ventilator needs) for zoledronic acid infusion and subsequent monitoring. His history was significant for osteoporosis secondary to immobilization with multiple fractures since 2 years of age, hypoxic-ischemic encephalopathy, quadriplegic cerebral palsy, seizure disorder, ventilator dependence, and pulmonary hypertension. He had previously been treated with four cycles of pamidronate without adverse events. He received 0.013 mg/kg of zoledronic acid infused over 30 minutes. Beginning 3 hours after completion of the infusion, he developed progressive tachycardia, fever, hypotension requiring vasopressor infusion, and increasing oxygen requirements. Laboratory studies revealed leukopenia, thrombocytopenia, elevated C-reactive protein, abnormal coagulation profile, metabolic acidosis, and negative cultures. The following day, he developed moderate acute respiratory distress syndrome and pulmonary hemorrhage requiring higher ventilatory settings, and subsequently diarrhea and abdominal distension. Initial clinical resolution was noted from the third day onward, and he was discharged on the sixth day after zoledronate administration.
Results Our pediatric patient demonstrated an acute, severe, life-threatening reaction to zoledronic acid requiring intensive cardiorespiratory support without an underlying pre-existing inflammatory disorder.
Conclusion Our case highlights the importance of careful monitoring of children following zoledronic acid therapy. We recommend inpatient observation after an initial infusion of zoledronic acid in medically complex children. Children and their parents should be thoroughly counseled on the potential risks of bisphosphonate treatment, which can sometimes be severe and life threatening.

Keywords Adverse drug reaction · Bisphosphonates · Inflammation · Low bone density · Osteoporosis · Serious adverse reaction

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Introduction

Bisphosphonates (BPs) are increasingly used for their beneficial effects for children with low bone density and fractures [1]. Zoledronate and pamidronate have a similar safety and efficacy profile in the treatment of pediatric osteoporosis and osteogenesis imperfecta [2–4].

Case report

A 7-year-old boy weighing 23 kg with a complex medical history and chronic ventilator requirement was admitted to

the pediatric intensive care unit for zoledronic acid infusion indicated for osteoporosis secondary to immobilization, multiple vertebral compression fractures, and multiple bilateral femur fractures since 2 years of age. He was monitored for the development of hypocalcemia and flu-like symptoms. His history was significant for hypoxic-ischemic encephalopathy at birth, quadriplegic cerebral palsy, seizure disorder, chronic aspiration, gastrojejunal tube placement, Nissen fundoplication, tracheostomy with ventilator dependence, pulmonary hypertension, and hypothyroidism. He was previously treated with four cycles of pamidronate at a prescribed dose of 9 mg/kg/year (divided into 3-day cycles) during the period of 2010–2012 without infusion-related adverse events. The day prior to zoledronic acid administration in April 2015, he underwent elective bilateral myringotomy with tympanostomy tube placement, microlaryngobronchoscopy, and submandibular gland botulinum toxin injection for sialorrhea. He tolerated the procedures well without apparent complication.

His home medications included but were not limited to baclofen, clonazepam, gabapentin, levetiracetam, levocarnitine, levothyroxine, and calcium carbonate. Family history was non-contributory.

He received 0.013 mg/kg (0.3 mg) of zoledronic acid the morning after the abovementioned procedures, diluted in 25 ml of normal saline over 30 minutes. In an effort to minimize side effects, a small dose was provided because this was his first dose of BPs in several years and his first dose of zoledronic acid. To minimize hypocalcemia, his home dose of calcium carbonate 1250 mg (500 mg elemental calcium) three times daily was doubled with a plan to continue the same for 2 weeks post-infusion. One day prior to infusion, his ionized calcium, phosphorus, and serum creatinine concentrations were normal. Three months prior to infusion, his 25 hydroxyvitamin D concentration was 47 ng/mL (normal, 20–50 ng/mL). His vital signs were normal except for baseline temperature that was generally between 34 and 36 °C without intercurrent illness.

Approximately 3 h after completion of the zoledronate infusion, he developed progressive tachycardia and rise in body temperature >2 °C from his baseline. He became hypotensive 9 h after the infusion with a nadir blood pressure of 40/20 mmHg. He received three boluses of 20 ml/kg of normal saline and subsequently required continuous infusions of dopamine, vasopressin, and epinephrine to maintain a mean arterial pressure (MAP) >50 mmHg. His oxygen requirement increased, and initial chest x-ray 12 h after infusion revealed a right-sided consolidation. Initial laboratory studies performed 9 hours after the infusions revealed leukopenia (3.4×10^9/L), thrombocytopenia (94×10^9/L), an elevated CRP of 50 mg/L (normal, <8 mg/L), metabolic acidosis (venous pH 7.34, PCO_2 29 mmHg, base deficit −9), and bicarbonate 15 mEq/L, with a normal lactate. Coagulation profile was abnormal with a prolonged PT of 21.3 s, elevated INR 1.9, a lengthening APTT from 42 to 171 s, and high fibrinogen greater than 400 mg/dL (normal, 200–375 mg/dL). Transaminases and bilirubin levels were within normal limits. The urinary output was 1.6 ml/kg/h with normal serum creatinine and a positive fluid balance of 1.6 L over 24 h. His ionized calcium concentration varied between 4.84 and 5.48 mg/dL (normal, 5.10–5.90 mg/dL). Intravenous hydrocortisone was started at stress doses given the presence of catecholamine-resistant shock and ongoing hemodynamic impairment. Blood and tracheal cultures were obtained, and empiric broad-spectrum antibiotics were started. Left femoral arterial line placement for ongoing management was complicated by an acute occlusive thrombus treated with unfractionated heparin.

Chest radiograph (Fig. 1) performed 36 h after the infusion revealed bilateral airspace opacities. The presence of a PaO2/FiO2 ratio <200 in conjunction was suggestive of moderate acute respiratory distress syndrome (ARDS). Peak end expiratory pressure (PEEP) was increased to 10 cm H_2O. He developed bloody tracheostomy tube secretions concerning for pulmonary hemorrhage and subsequently received cryoprecipitate and platelet transfusions. His perfusion improved, inotropes and vasopressors were weaned off, hydrocortisone was tapered, and he developed brisk urinary output.

On hospital day 3, ventilator settings were weaned, body temperature was still above baseline, CRP peaked at 204 mg/L, tracheal secretions revealed mixed, usual flora, and blood cultures remained negative. Antibiotics were discontinued, as an acute inflammatory response to zoledronic acid infusion became the most likely diagnosis. He also developed abdominal distention and diarrhea. Stool studies were negative for vancomycin-resistant enterococci (VRE) and *Clostridium difficile*. Abdominal imaging showed bowel wall edema on ultrasound and a normal x-ray.

On the fourth hospital day, his temperature remained above baseline, his CRP was declining, and he was weaned to his home bilevel respiratory support settings and oxygen requirement. Full enteral nutrition was resumed. He was discharged home on the sixth day after zoledronic acid infusion.

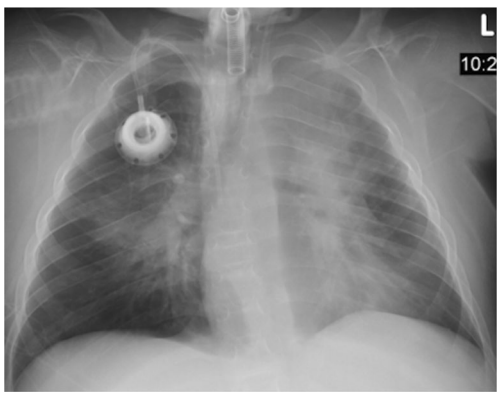

Fig. 1 Chest radiograph 36 h after zoledronic acid infusion revealed opacification of the left upper lobe, interstitial and airspace opacities within the left lung base, and patchy airspace opacities in the right midlung

Discussion

We report a boy who developed clinical features of a severe systemic inflammatory response following zoledronic acid infusion. To our knowledge, this is the first report of such a reaction to zoledronate in a pediatric patient.

Our patient demonstrated clinical features of a severe systemic inflammatory response with fever, tachycardia, and tachypnea within 12 h of a zoledronic acid infusion without an underlying pre-existing inflammatory disorder. We recognize the complexity of his underlying medical conditions, and procedures the prior day could have predisposed to the severe reaction under discussion. His condition progressed to secondary multiple organ dysfunction syndrome (MODS) including shock, moderate ARDS, coagulopathy, and thrombocytopenia. He had elevated acute-phase reactants in the absence of an identifiable pathogen on multiple blood cultures and a fairly rapid recovery after full supportive measures. Taken together, these data implicate zoledronic acid as a likely initiator of this overwhelming systemic inflammatory response and represents the first reported case. Previous studies have demonstrated elevation of inflammatory cytokines (IL-6 and TNF-α) and CRP after BP infusion that may explain his clinical presentation [5].

Systemic inflammatory response syndrome (SIRS) is the clinical manifestation of dysregulated inflammation in which there is a possibility of a massive and uncontrolled release of inflammatory mediators that initiate a chain of events leading to widespread tissue injury causing MODS with an associated high mortality [6, 7]. The term SIRS has routinely been associated with both infectious processes and non-infectious insults. When non-infectious inflammation results in organ dysfunction, it is termed as severe non-infectious inflammatory response syndrome (SNISIRS) [8]. This syndrome has a similar mortality as severe sepsis but has a higher rate of central nervous system failure. The time to peak organ dysfunction, episode length, and ICU stay are reported to be significantly shorter in patients with SNISIRS [9].

Our patient presented with quadriplegic cerebral palsy and low bone mass secondary to immobilization. The severe reaction in our patient was unexpected in the context of prior uncomplicated treatment with another intravenous bisphosphonate, pamidronate. It is possible the 3-year interval between bisphosphonate infusions was a contributing factor. Intravenous pamidronate has been studied in patients with cerebral palsy in small controlled and uncontrolled trials [10–14]. Transient hypocalcemia, rise in parathyroid hormone, and hypophosphatemia have been reported after its use [15, 16]. In 2004, respiratory distress had been described in children with osteogenesis imperfecta who were under 2 years of age during the initial cycle of pamidronate. All had pre-existing respiratory conditions and none were reported to develop hypotension or MODS [17]. Zoledronic acid is a third-generation BP that is significantly more potent than pamidronate. Its advantages include a shorter infusion time and reduced frequency of dosing as compared to pamidronate. It was investigated in 34 children with various bone disorders at the doses of 0.02–0.025 and 0.05 mg/kg. First-time administration in these children was associated with hypocalcemia, hypophosphatemia, and flu-like illness within the first 72 h (2004) [18]. In 2007, a report of 63 children with a variety of bone disorders treated with an initial dose of 0.0125 mg/kg zoledronic acid (comparable to what our patient received) suggested a lower intensity of hypocalcemia, but no difference in the incidence of flu-like symptoms [19]. A trial was conducted in healthy, adult individuals to investigate the sterile acute inflammatory response in the absence of confounding factors like cancer and infection, which revealed both peripheral $\gamma\delta$ T cells and monocytes become rapidly activated after treatment with zoledronic acid. This study also underscored a key role of IFN-γ and demonstrated pretreatment levels and responsiveness of monocytes and central/memory Vγ9/Vδ2 T cells as predictive risk factors for the occurrence of symptoms [20]. However, none of these patients developed NISIRS, as did our patient.

Conclusion

Although experience regarding safety and efficacy of intravenous BPs in children with a variety of low bone mass disorders is generally favorable, some will develop significant side effects. Our case highlights the importance of careful monitoring of children following zoledronic acid therapy. We recommend inpatient observation after an initial infusion of zoledronic acid in medically complex children. Children and their parents should be thoroughly counseled on the potential risks of bisphosphonate treatment, which can sometimes be severe and life threatening.

Compliance with ethical standards

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Conflicts of interest None.

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