Clinical Pediatric Endocrinology

Vol.33 / No.2
April 2024
pp 76–81

Case Report

Fatality owing to pulmonary hemorrhage following pamidronate disodium administration in a neonate with osteogenesis imperfecta type 2: A case report

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Highlights

- A newborn with OI type 2 died of pulmonary hemorrhage after PA administration.
- Pamidronate disodium for OI may be related to pulmonary hemorrhage.
- Bisphosphonates use in neonates require appropriate systemic management.

Abstract. We report the case of a patient with osteogenesis imperfecta (OI) who developed pulmonary hemorrhage 4 d after pamidronate disodium (PA) administration, despite a relatively stable respiratory status. Bisphosphonates are introduced to reduce osteoclast activity and are now widely used in patients with OI. Bisphosphonates are typically well-tolerated in children, and the standard of care involves cyclic intravenous administration of PA. However, in practice, there is limited experience with the use of PA for severe OI during the neonatal period, and its safety remains uncertain. This report aimed to describe the respiratory events potentially associated with PA in a neonatal patient with OI type 2, suggesting that serious life-threatening complications of pulmonary hemorrhage may occur after PA administration. Further studies are required to assess the relationship between pulmonary hemorrhage and PA administration, aiming to enhance prophylaxis measures.

Key words: pamidronate disodium, bisphosphonates, osteogenesis imperfecta, pulmonary hemorrhage

Received: October 3, 2023 Accepted: January 17, 2024 Advanced Epub: February 9, 2024

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Introduction

Osteogenesis imperfecta (OI) is a rare inherited disease characterized by systemic bone fragility and progressive bone deformation. OI is caused by qualitative or quantitative defects in type I collagen. A deficiency of type I collagen affects multiple organs, including bones, joints, ears, eyes, skin, and other tissues composed of type I collagen. OI presents with varying degrees of connective tissue manifestations and is characterized by macrocephaly, blue sclera, dental dysplasia, deafness, hyperextensible skin, and abnormal heart valves. Respiratory dysfunction due to bone fractures and spinal deformities and heart failure caused by valvular diseases can significantly affect prognosis and outcome. Approximately 90% of OI cases are caused by variants in the *COL1A1/2* gene encoding the alpha-1/2 chains of type I collagen (1).

The prevalence of OI ranges from approximately 1:10,000 to 1:20,000 births. OI is classified as type 1 (classic non-deforming OI with blue sclerae), type 2 (perinatally lethal OI), type 3 (progressively deforming OI), type 4 (common variable OI), and type 5 (OI with calcification in the interosseous membranes and hyperplastic callus), in addition to other types. This classification depends on clinical features, causative gene mutations, inheritance mode, and radiographic findings (Sillence classification) (1, 2).

OI type 2 is the most severe type of fetal skeletal defect and can be diagnosed using early prenatal ultrasonography. About one-fifth are stillborn, and approximately 90% die within 4 weeks of birth. The bone is very weak, resulting in multiple fractures during the fetal period and at birth. Death is often caused by intracranial hemorrhage or respiratory failure due to thoracic hypoplasia (1).

The goals of OI treatment are fracture prevention, symptom control, and bone mass gain. Treatment includes both nonsurgical and surgical procedures. The drugs commonly used to treat OI in children include bisphosphonates, anti-RANKL monoclonal antibodies, synthetic parathyroid hormones, and growth hormones. Bisphosphonates, designed to reduce osteoclast activity, have been introduced as a treatment for OI to increase bone mineral density and prevent fractures and bone pain. Therefore, they have been the most commonly used drugs in many patients with OIs in recent years. Cyclic therapy with intravenous bisphosphonates has become the standard of care for children with moderate to severe OI (3). Bisphosphonates are generally well tolerated by children (4, 5). Nevertheless, we encountered an atypical case of OI type 2 that resulted in pulmonary hemorrhage and respiratory failure-induced fatality, unrelated to thoracic and pulmonary hypoplasia. We report this rare and critical case, with a description of the course of the disease and a discussion of its possible causes. The patient's guardians provided written informed consent for this report.

Case Report

A female infant was born at 38 wk and 0 d of gestation via cesarean section to nonconsanguineous healthy parents. Her weight, height, and head circumference at birth were 1904 g (–2.6 SD), 34.0 cm (–5.2 SD), and 33.0 cm (0.0 SD), respectively. The parents had no family history of congenital skeletal disorders. A prenatal ultrasound examination at 22 wk of gestation revealed short and incurved limbs and a narrow chest resulting from hypomineralization and multiple fractures of the ribs and long bones on fetal ultrasonography and a fetal CT scan.

Immediately after birth, the newborn presented with bradycardia and respiratory distress and required bag-mask ventilation. She was admitted to the NICU with nasal continuous positive airway pressure (N-CPAP). Her Apgar scores were 3 at 1 min and 8 at 5 min.

Physical examination revealed a disproportionately large head, soft skull with widely opened sutures, blue sclera, small chest, and very short, curved, and distorted limbs. A bone X-ray showed the following findings: hypomineralization, narrow thorax, multiple fractures of ribs and limb bones, marked ossification defects of the cranial crown, and cartilaginous ossification of the cranial base (**Fig. 1A**). Based on these findings, the patient was clinically diagnosed with OI type 2. In addition, whole-exome sequencing of a panel of genes involved in OI revealed a de novo *COL1A2* heterozygous variant (NM_000089:c.2891G>A (p.Gly964Asp)). Although there have been no reports of the detailed clinical information of this variant, it is registered as a pathogenic germline variant in the public archive (ClinVar) (6). Based on the ACMG guidelines, it is also interpreted as pathogenic (PS2, PM1, PM2, PP3, PP4, and PP5) (7, 8). The patient had persistent agitation and crying episodes from the second day of life. Given that this appeared to stem from pain due to bone fractures, she was treated with daily acetaminophen (40 mg/kg/d) and temporary opioid analgesia (0.3 μg/kg/dose of intravenously administered fentanyl or 20 μg/kg/dose of oral morphine hydrochloride) during procedures such as repositioning. Opioids were initially administered 1-2 times per day before day 13 but were no longer required thereafter. Her breathing gradually stabilized, and respiratory support was switched to high-flow nasal cannula (HFNC) therapy (F_IO_2 0.25, flow rate 8 L/min) on day 5. Feeding via a gastric tube and oral feeding were initiated on days 1 and 7, respectively.

As a treatment for bone fragility, 0.25 mg/kg of pamidronate disodium (PA) was administered intravenously for 4 hours on day 14. The following tests were performed prior to administration: radiography confirmed no new fractures; echocardiography showed no signs of heart failure, including significant valvular regurgitation, atrial or ventricular enlargement, or poor ventricular contraction (end-diastolic left ventricle diameter, 19.1 mm, left ventricular ejection fraction, 64%). Blood tests revealed no electrolyte abnormalities,

doi: 10.1297/cpe.33.2023-0061

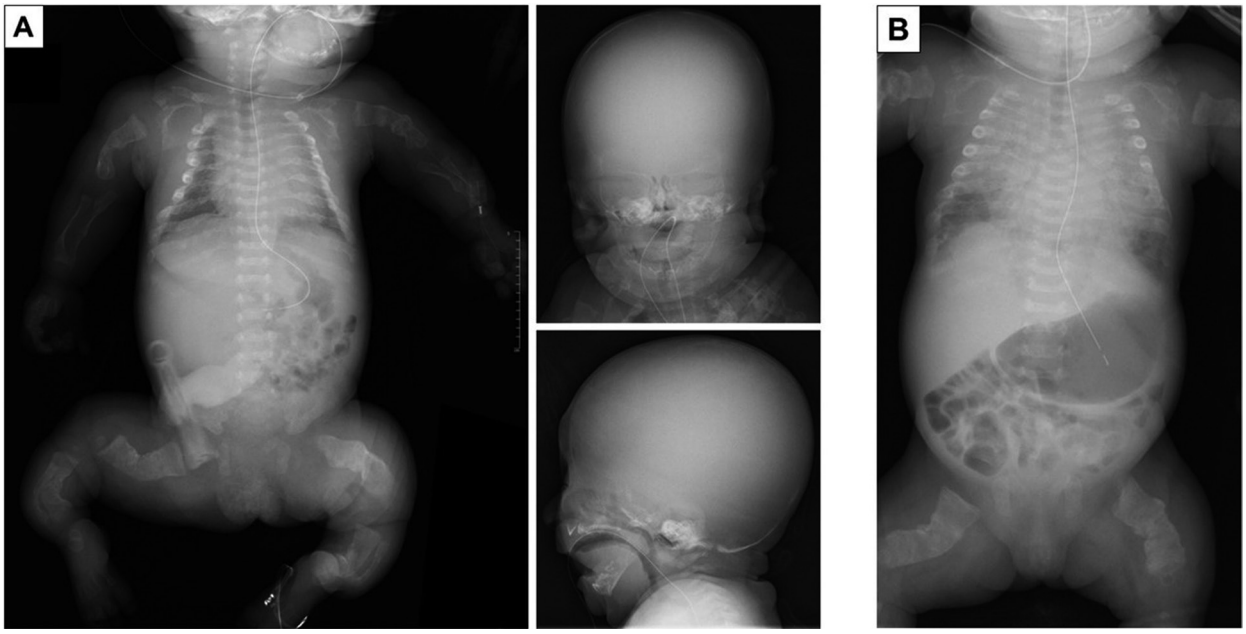

Fig. 1. Imaging study of the study patient. (A) Bone X-ray on admission: hypomineralization, narrow thorax, multiple fractures of ribs and long bones, marked ossification defects of the cranial crown, and cartilaginous ossification of the cranial base. (B) Chest X-ray at the time of exacerbation (day 18): diffuse infiltrative shadows visible in both lungs.

including calcium (Ca) and phosphorus (P). On the same day, oral administration of alfacalcidol (0.1 μg/kg/d) and calcium gluconate (150 mg/kg/d) was initiated. Blood ionized Ca, serum P, and urinary electrolytes were measured daily and were within appropriate ranges. No known adverse reactions to PA, including anaphylaxis, flu-like symptoms, interstitial pneumonia, or jaw osteonecrosis, were observed. From day 15, the patient was mostly in a good temper with enteral feeds alone and was in a relatively stable condition.

However, on day 18, the patient suddenly developed bradycardia and hypoxia after crying for approximately 1.5 h. Pale hemorrhagic secretions were found in the oral cavity, and chest radiography showed decreased translucency in both lung fields, consistent with pulmonary hemorrhage (**Fig. 1B**). Although tracheal intubation and mechanical ventilation were indicated for respiratory failure, the family refused further aggressive treatment because of the severity of her basal disease. Following in-depth discussions between the medical staff and her family, a collective decision was made to refrain from administering further treatment. Consequently, she died of respiratory failure two hours after the onset of the event. Coagulopathy or electrolyte abnormalities were not observed. Platelet counts and sizes were normal in a complete blood count test performed under a microscope.

Post-mortem examination included a CT scan taken one hour after death, which showed no intracranial bleeding. In addition, there was decreased air content in both lung fields and fluid in the airway, which was consistent with pulmonary hemorrhage. No abnormal findings were observed to indicate potential causes of death. An autopsy was not performed because of the lack of consent from the family.

Discussion

We reported the case of a patient with OI type 2 who developed pulmonary hemorrhage four days after initiating PA despite having been in a relatively stable condition (**Fig. 2**).

Pulmonary hemorrhage frequently results in severe respiratory failure. It can be caused by extensive damage to the alveolar capillaries, causing blood to pool in the alveoli, and gas exchange is disrupted when numerous alveoli are injured. Common causes of pulmonary hemorrhage include severe lung disease, abnormal blood flow around the blood vessels in the lungs, coagulopathy, infections, and toxins. This patient was born at term and did not require surfactant treatment after birth. Although thoracic hypoplasia was observed, intubation and ventilation were not required. No cardiac complications were evident, and the ductus arteriosus was nearly closed by day 3. In addition, no drugs that have been reported as obvious causative agents of pulmonary hemorrhage were administered. In general, respiratory insufficiency in OI type 2 is due to pulmonary hypoplasia and skeletal deformities; however, pulmonary hemorrhage is uncommon. The present case of OI type 2 had an unusual course, with patient fatality due to pulmonary hemorrhage, despite a relatively stable respiratory status after birth. The possible causes in this case are discussed below, including complications of OI such as pulmonary hypoplasia or vascular anomalies, and the effects of PA or acetaminophen.

doi: 10.1297/cpe.33.2023-0061

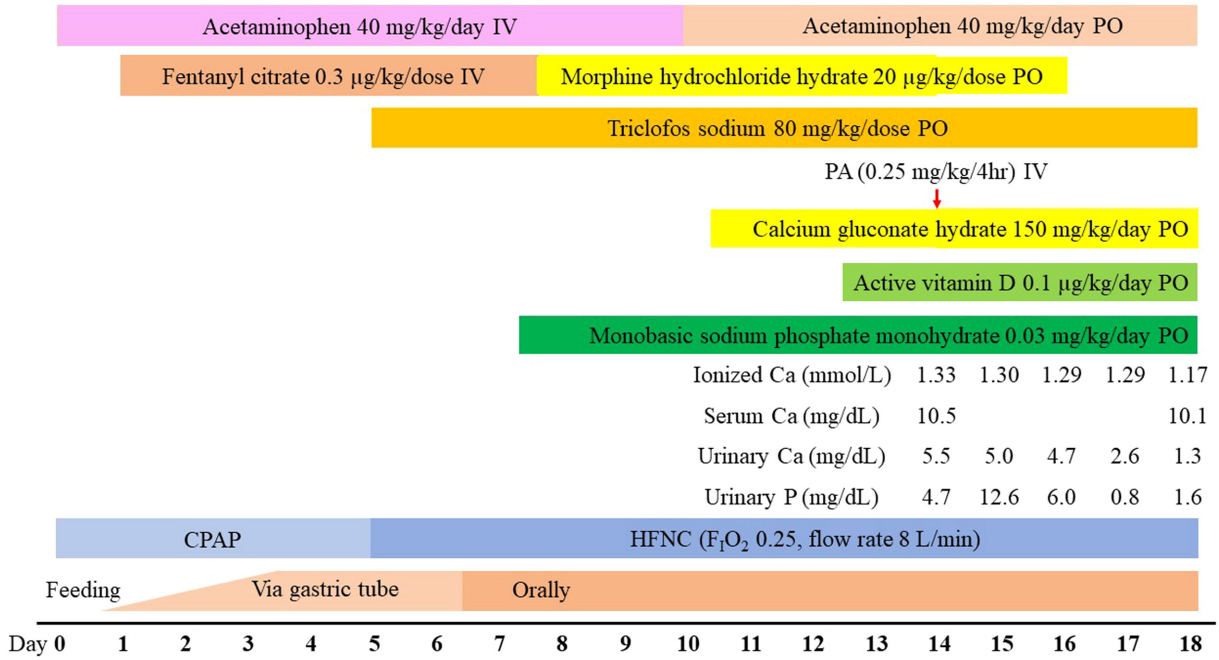

Fig. 2. Clinical course. CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula. Serum albumin concentration was used to correct calcium levels.

Pulmonary hemorrhage as a possible complication of OI

In addition to major skeletal and extra-skeletal signs, OI may be associated with bleeding due to impaired platelet aggregation. Hemorrhage-related complications of OI include epistaxis, melena, hematoma, subconjunctival hemorrhage, preretinal hemorrhage, and intracranial hemorrhage (9). Qualitative platelet abnormalities, such as impaired clot retraction, reduced ristocetin cofactor, abnormal platelet morphology (large platelets), and impaired aggregation capacity, have been reported. Several studies have reported that patients with OI show increased capillary fragility, reduced factor VIII-related antigens, prolonged thromboplastin time, and extended bleeding time on hemostatic testing (10, 11). Patients with OI may also have an underlying early diastolic cardiac dysfunction that requires special attention (12).

Although the patient in this report had no abnormal findings on general blood tests or ultrasound scans before sudden deterioration, we cannot rule out that she had mild cardiac dysfunction or abnormal platelet function that could not be detected in the preceding examinations. In this context, intense and prolonged crying may have caused a turbulent rise and drop in intrathoracic pressure and a drastic fluctuation in venous return, leading to pulmonary hemorrhage through an increase in pulmonary hydrostatic pressure and vascular permeability. The agitation she displayed might have been triggered by bone pain and symptoms of opioid withdrawal. Furthermore, the positive pressure exerted on the airways and lungs by HFNC may also have contributed to the aggravation of pulmonary hemorrhage via damage to the airway mucosa; however, there have been no reports of pulmonary hemorrhage attributable to HFNC.

Effect of pamidronate disodium (PA)

Pulmonary hemorrhage with PA has not been reported, and there is no evidence that drug interactions contribute to hemorrhage or increased respiratory compromise. The adverse effects of bisphosphonates include acute phase reactions (fever, flu-like symptoms, and musculoskeletal pain), hypocalcemia, hypophosphatemia, thrombocytopenia, platelet dysfunction, gastrointestinal irritation, osteonecrosis of the jaw, and upper gastrointestinal bleeding (13). Acute phase reactions usually occur 1-3 d after drug administration and resolve within a few days. Most cases are transient; however, severe symptoms can occasionally occur. Particularly, in infants with severe OI and pre-existing respiratory distress, the first infusion cycle of bisphosphonates may be associated with an acute exacerbation of the respiratory status. Munns *et al.* reported that four of 59 infants (7%) with severe OI developed significant respiratory distress characterized by pulmonary edema, dyspnea, and fever during the initial PA infusion (14). The acute phase may require treatment with bronchodilators, diuretics, and corticosteroids (15). Although the etiology has not yet been identified, the inflammatory properties of bisphosphonate preparations have been considered. Bisphosphonate administration could induce pro-inflammatory cytokines IL-6, INF-g, and TNF-a produced by gd T-cells. Pretreatment with non-steroidal anti-inflammatory drugs, acetaminophen, or statins before each bisphosphonate infusion may

doi: 10.1297/cpe.33.2023-0061

reduce symptoms, although its efficacy is not clear (16).

The need to evaluate changes in serum Ca levels, particularly for 4–10 d after bisphosphate infusion, has been emphasized. Transient hypocalcemia occurs more often in children. This can be avoided or attenuated by pretreatment with calcium and active vitamin D. However, symptomatic hypocalcemia has been reported despite the administration of these drugs (17). In this case, although the serum and urinary Ca levels tended to decrease, the concentration of ionized Ca immediately after sudden deterioration was 1.17 mmol/L, within the normal range.

The frequency and severity of bisphosphonate-associated adverse events, including acute phase response, osteonecrosis of the jaw, and ocular adverse events, are dose- and potency-dependent (intravenous bisphosphonates such as zoledronic pamidronate are more potent than oral bisphosphonates) (18). In this case, although the blood level of PA could not be determined owing to insufficient sample volume, the concentration of PA should not have been abnormally high because only one dose of 0.25 mg/kg was administered slowly over 4 h, which is not as high a dose as previously reported for children under 2 yr of age (19, 20). However, the patient's Ca level decreased, albeit within the normal range, indicating that PA had reached the blood level at which it could have been active. Considering that the pulmonary hemorrhage occurred on the fourth day after the administration of PA, a period when adverse reactions may occur, it could be inferred that PA had an effect on inflammation and Ca regulation in our patient, which led to pulmonary hemorrhage, possibly influenced by circulatory changes induced by crying. Munns *et al*. recommended that PA should be avoided as much as possible in infants with respiratory distress based on their experience with four OI type 3 patients with respiratory deterioration after PA administration at less than 2 yr of age. They also stated that, if administered, the dose should be reduced to 0.125 mg/kg to prevent acute-phase reactions (14). Although the appropriate dosage of PA for infants with respiratory distress is still under discussion, we could not exclude PA as a potential cause of the pulmonary hemorrhage, given the patient's respiratory compromise and the administration of a dose exceeding the recommended amount.

Effect of acetaminophen

Concerns have been raised regarding the adverse effects of high doses of acetaminophen, including the risk of gastrointestinal hemorrhage and blood disorders. Long-term prescriptions of 3000 mg/day or more to the older individuals increase the risks of peptic ulcer and renal failure (21). However, in the present case, the dose of acetaminophen was not high (40 mg/kg/d in three divided doses) and was less than one-tenth of the established toxic dose in children (150 mg/kg/dose) (22). In addition, blood tests showed no hepatic dysfunction, even at the time of sudden deterioration. Thus, acetaminophen is highly unlikely to be solely responsible for the pulmonary hemorrhage in this case. However, the inflammatory situation associated with OI itself and PA administration may enhance the susceptibility to platelet dysfunction resulting from acetaminophen at the usual dose.

Conclusions

We encountered a patient with OI type 2 experiencing sudden and unexplained pulmonary hemorrhage. We speculated that the pulmonary hemorrhage might be attributable to circulatory changes caused by prolonged crying based on pulmonary hypoplasia and vascular abnormalities due to OI, the effects of PA, or both. However, there was no clear evidence, including serum concentration of PA and post-mortem examination, and no definite conclusion was reached.

Nevertheless, the possibility of their individual or combined impacts on deterioration cannot be completely ruled out. As experience with the use of bisphosphonates for OI type 2 during the early neonatal period is still limited, patients in similar situations should be closely monitored, particularly in the early stages of PA treatment. Furthermore, it is essential to accumulate experience to elucidate the pathophysiology and natural course of neonates with OI type 2 treated with bisphosphonates, aiming for improved outcomes.

Conflict of interests: The authors declare no conflicts of interest.

Acknowledgments

We would like to express our respect for the participating patient and thank the parents for their cooperation. Additionally, we are deeply grateful to Dr. Kosuke Taniguchi and Dr. Kenichiro Hata, both of whom are affiliated with the Department of Human Molecular Genetics, Gunma University Graduate School of Medicine, and the Department of Maternal-Fetal Biology, National Research Institute for Child Health and Development, for their efforts in the genetic testing and interpretation of our patient. We also thank the Center for Postgraduate Education and Training at the National Center for Child Health and Development for their English language reviews.

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doi: 10.1297/cpe.33.2023-0061