Respiratory distress with pamidronate treatment in infants with severe osteogenesis imperfecta

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Abstract

This report aims to describe the adverse respiratory events associated with the first pamidronate cycle in four infants with severe osteogenesis imperfecta (OI) who were less than 2 years of age. Fifty-nine infants with severe OI were commenced on cyclical intravenous pamidronate therapy in an observation trial. Routine observations were measured during each infusion cycle.

During the first treatment cycle, four infants (7%) with preexisting respiratory compromise developed respiratory distress. The respiratory distress was successfully managed with bronchodilator therapy. Two of the infants required intensive care admission. There was no recurrence of respiratory distress with subsequent pamidronate infusion cycles.

In infants with severe OI and preexisting respiratory compromise, the first pamidronate infusion cycle may be associated with an acute deterioration of respiratory function. The etiology is unclear but may involve cytokine release and/or hemodynamic compromise from fluid administration during the first infusion cycle. Close monitoring throughout the first treatment cycle is of paramount importance.

Introduction

Severe osteogenesis imperfecta (OI) is a debilitating disease characterized by bone fragility, short stature, limb and spinal deformity, and a reduced life span [4,14]. Pamidronate therapy of children with OI improves muscle force, as well as vertebral bone mass and size, reduces bone pain and fracture rate, and allows for straight long bone growth [1,5,8,12,16,17]. Children who begin therapy under 3 years of age appear to benefit most from pamidronate [10]. However, in such patients, extreme bone fragility frequently results in concomitant respiratory compromise, small stature, and developmental delay [2,3,10]. These comorbidities may also place this patient group at a higher risk of complications from medical intervention.

Frequently reported side effects in children treated with pamidronate include an acute phase “flu-like” reaction, with fever, myalgia, bone pain and vomiting, and hypocalcemia following the first dose [4,10,11]. The “flu-like” symptoms can usually be managed with antipyretic medication such as paracetamol or acetaminophen.

Since we have reported our initial results with pamidronate therapy in infants with OI [10], we have started intravenous pamidronate therapy in another 50 severely affected OI patients below 2 years of age. OI patients were eligible for pamidronate therapy if they had long bone deformities, had sustained three or more fractures per year of life, or had radiological evidence of vertebral compression fractures. Pamidronate was administered intravenously on 3 consecutive days, every 8 weeks.

In this patient group, we have noted adverse respiratory events that are probably treatment-related. This report describes four infant boys with OI type III who developed significant respiratory insufficiency during the initial pamidronate treatment cycle.
Case presentations

Case 1 was born at 37 weeks gestation via spontaneous vaginal delivery. He had numerous congenital long bone and rib fractures, which necessitated intubation and ventilation for the first 48 h of life. At 8 months of age, he was hospitalized with viral pneumonia and was oxygen-dependent for the subsequent 2 months. The first cycle of pamidronate was administered at 11 months of age. At that time, his weight was 4090 g (−5.4 standard deviation score (SDS)) [7], and length was 49.9 cm (−9.3 SDS) [7]. He was very weak with delayed motor development. Before the first infusion, he was afebrile, his heart rate was 120/min, and respiratory rate was 46/min with nasal flare, subcostal recession, and pectus carinatum. His chest was clear on auscultation, and he had no heart murmurs. Oxygen saturation (SaO₂) in room air was 99%. He had microcytic anemia with a hemoglobin of 87 g/l (reference range: 105−140) and a mean corpuscular volume of 68.6 fl (reference range 70.0−86.0). Before pamidronate therapy, his serum ionized calcium (Ca²⁺), PTH, and 25-hydroxyvitamin D (25-OHD) concentrations were within reference ranges [11]. The dose of pamidronate was 0.125 mg/kg on Day 1 and 0.25 mg/kg on Day 2. He did not receive a third dose. Pamidronate was diluted in 50 ml of normal saline and administered over 4 h. Following the second pamidronate infusion, his body temperature rose to 38.2°C, and he developed increased respiratory distress with a respiratory rate of 64/min, a heart rate of 160/min, and SaO₂ of 86% while breathing room air. Chest X-ray demonstrated numerous rib fractures of differing ages and a diffuse increase in lung markings, most notably at the left perihilar region and in the right lower lobe (Fig. 1). The respiratory distress settled over the next 48 h following treatment with nasal oxygen and bronchodilators. Serum ionized calcium concentrations were normal throughout this episode. Subsequent pamidronate therapy cycles were uneventful.

Case 2 was born at 39 weeks gestation via lower segment cesarean section for breech presentation. He had multiple congenital long bone and rib fractures necessitating ventilation for the first 2 weeks for life. At the age of 4 months, he was ventilated for 2 weeks following respiratory syncytial virus-induced bronchiolitis. This resulted in ongoing oxygen-dependency and regular bronchodilator administration. At 1.4 years of age, pamidronate therapy was commenced. Examination demonstrated a length of 60.3 cm (−7.3 SDS), a weight of 6300 g (−4.5 SDS), and global developmental delay. He had significant respiratory compromise with a respiratory rate of 50/min, grunting respirations, nasal flaring, and quiet breath sounds. SaO₂ was 70% in room air and 100% on 1.5 l/min of oxygen via nasal prongs. He was afebrile. Chest X-ray demonstrated new and old rib fractures, hyperinflation, left lower lobe consolidation, and cardiomegaly. He had a mild normocytic anemia, with hemoglobin at 105 g/l (reference range: 115−135). His serum Ca²⁺, PTH, and 25-OHD concentrations were within reference ranges [11]. He received pamidronate 0.25 mg/kg per day for 3 consecutive days. Pamidronate was diluted in 60 ml of normal saline and administered over 4 h. Following the third dose, he developed a fever of 39.2°C, his respiratory rate decreased to 30/min, and he had episodes of bradycardia. Arterial blood gas analysis demonstrated a pCO₂ of 79 mm Hg. He was transferred to a pediatric intensive care unit where he was ventilated and treated with antibiotics, glucocorticoids, and bronchodilators. His serum calcium concentration was normal throughout this admission. Subsequent pamidronate infusion cycles were uneventful.

Case 3 was born by cesarean section at term with multiple congenital rib and long bone fractures. Respiratory compromise necessitated admission to a neonatal intensive care unit for his first week of life. His first cycle of pamidronate was administered at 4 months of age. At this time, he weighed 2660 g (−4.3 SDS) and had a length of 38.5 cm (less than −8.8 SDS). He had respiratory difficulties with tachypnea, poor chest excursion, and paradoxical movements of the chest and abdomen. He was anemic with a hemoglobin of 81 g/l (reference range: 105−140). The dose of pamidronate on Day 1 was 0.23 mg/kg and on Day 2 was 0.45 mg/kg, diluted in 50 ml of normal saline and administered over 4 h. He did not receive a third dose. Following the second dose of pamidronate, he developed increased respiratory distress, with increased tachypnea, audible wheeze, and SaO₂ of 70% in room air. A chest radiograph showed multiple rib fractures of various ages and clear lung fields. Nebulized salbutamol alleviated the respiratory distress. Serum calcium was normal throughout this episode. Subsequent cycles of pamidronate have been uneventful. At 10 months of age, 6 weeks following his fourth pamidronate infusion cycle, Case 3 died of respiratory failure secondary to respiratory syncytial virus infection.
Case 4 was born at term via cesarean section with multiple congenital rib and long bone fractures. He had respiratory distress at birth and had four episodes of pneumonia requiring hospitalization in his first year of life. The first pamidronate infusion cycle was administered at 1.2 years of age. At this time, his weight was 6100 g (−4.3 SDS) and his length was 60 cm (−6.8 SDS). He had respiratory compromise with tachypnea and subcostal recession and was afebrile. His serum Ca²⁺, PTH, and 25-OHD concentrations were within reference ranges [11]. The dose of pamidronate was 0.5 mg/kg on Day 1 and 1 mg/kg on Day 2. He did not receive a third dose. Pamidronate was diluted in 120 ml of normal saline and administered over 4 h. Following the second infusion, he developed fever of 39.0°C and increased respiratory distress with a respiratory rate of 50/min, heart rate of 170/min, and SaO₂ of 70% in room air. His chest was clear on auscultation. A chest X-ray demonstrated multiple rib fractures of various stages of healing but no focal lung pathology. He was admitted to a pediatric intensive care unit for 3 days and treated with oxygen and bronchodilators. His serum calcium concentration was normal throughout this admission. The second cycle of pamidronate was administered 4 months later without complications. One month after his second pamidronate infusion cycle, the boy died of an unknown cause aged 1.7 years.

Discussion

Pamidronate therapy is the most significant recent development in the medical treatment of children with OI [1,5,10,16]. As described in this report, however, significant respiratory distress and fever may accompany the initial pamidronate infusion cycle in infants with severe OI and preexisting respiratory compromise. Although no direct causal relationship can be drawn from this report, the temporal association between the initial pamidronate infusion and the onset of the respiratory distress suggests that the two events are linked. We have not observed this complication in 158 OI patients over 2 years of age who started pamidronate treatment during the observation interval of the present study.

The etiology of these adverse events is not clear at present, although the severity of the respiratory disease in these patients predisposed them to further deterioration from even minor stressors. In adults, the acute “flu like” illness after the first dose of pamidronate has been associated with elevated tumor necrosis factor alpha concentrations [9,15]. This may have played a role in our patients, but it is likely that no single factor was solely responsible for the development of respiratory distress. The fact that all infants were treated successfully with bronchodilator therapy may indicate that bronchospasm was part of the problem. Bronchospasm following bisphosphonate therapy has also been reported in adult patients who received pamidronate [13]. It is also possible that the fluid load associated with pamidronate administration, albeit small (between 10 and 19 ml/kg of normal saline over 4 h), was sufficient to further compromise the respiratory status. The respiratory deterioration may also have resulted from the added metabolic demands imposed by fever.

The natural history of respiratory distress in infants with OI type III has not been described in detail. However, it is clear from our observations that at least a few of these severely affected children will continue to have some degree of respiratory compromise. This is exemplified by Case 3 and possibly Case 4 from this report who died from respiratory failure. Pamidronate treatment is presently the only form of medical therapy that promises to improve the severe bone fragility of such patients. It is, therefore, important to search for ways to limit the adverse events described here by limiting the acute phase response and minimizing the fluid load these infants receive. We have adopted the following approach.

1. Where possible, avoid the use of pamidronate in infants with acute respiratory distress.
2. After our initial experience with pamidronate therapy in children less than 3 years of age [10], we have been treating infants below 2 years of age according to a standard protocol (Table 1). However, when there is a history of respiratory distress, we now reduce the dose of pamidronate during the initial infusion cycle by half (e.g., 0.125 mg/kg is given instead of 0.25 mg/kg on Day 1 and 0.25 mg/kg instead of 0.5 mg/kg is given on Days 2 and 3 of the first treatment cycle).
3. When respiratory distress is present at the time of starting pamidronate treatment, one dose of pamidronate (0.125 mg/kg) is given as the first treatment cycle. At the second treatment cycle, a half dose is given as described above, and for subsequent treatment cycles, a full treatment course is given as outlined in Table 1.
4. Antipyretic medication is used to limit fever.
5. In children with respiratory distress, the infusion rates given in Table 1 are halved, so as to minimize the effect of the fluid load.

<table>
<thead>
<tr>
<th>Treatment cycle number</th>
<th>Day</th>
<th>Pamidronate dosea (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.5</td>
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<tr>
<td></td>
<td>3</td>
<td>0.5</td>
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<tr>
<td>All subsequent</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Treatment cycles are repeated every 8 weeks.

a If the pamidronate dose is 0.1 to 5 mg, the drug is diluted in 50 ml of normal saline and administered at 15 ml/h. If the pamidronate dose is 5.1 to 10 mg, it is diluted in 100 ml of normal saline and administered at 30 ml/h.
Although the adult data do not suggest that a reduction in the initial pamidronate dose limits the acute phase reaction [6], no significant respiratory distress has been noted in the 10 infants who started pamidronate since this approach was adopted. Until a greater number of infants with moderate to severe OI are treated with this regime, it is obviously premature to claim that such events can be avoided altogether. Increased vigilance and close monitoring of the young child receiving the first dose of pamidronate remain mandatory.

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References