Case Study

Zoledronic Acid-induced transient elevated liver enzymes in a neonate with osteogenesis imperfecta: A case report

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Background: Zoledronic acid, a bisphosphonate, is currently used to treat osteogenesis imperfecta (OI). Elevated liver enzymes or hepatotoxicity induced by zoledronic acid infusion have been rarely reported, especially in a neonate with OI.

Aims: This report aims to describe the case of a neonate with OI who developed transiently elevated liver enzymes accompanied by a fever after zoledronic acid treatment.

Clinical Descriptions: A one-month-old neonate diagnosed with OI in utero was scheduled for the first treatment of zoledronic acid. Before zoledronic acid was administered, liver enzymes were normal. Eighteen hours following the zoledronic acid infusion (0.025 mg/kg intravenously for 30 minutes slow infusion), the patient developed a fever. At 48 hours after treatment, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels increased by 2.8 and 3.7 times, respectively, without jaundice. On day 5, the AST level decreased to 1.7 times from baseline, but not the ALT level (4.0 times from baseline). Paracetamol was administered only when the baby had a fever.

Conclusion: Potential liver injury as an adverse effect following zoledronic acid treatment in a neonate with OI should not be overlooked.

Keywords: adverse effect, bisphosphonate, liver enzyme, osteogenesis imperfecta, zoledronic acid

INTRODUCTION

Osteogenesis imperfecta (OI), or brittle bone disease, is a connective tissue disorder with a wide range of clinical manifestations ranging from lethal in the perinatal period to a mild clinical form. OI has a triad of clinical symptoms: fragile bones, blue sclerae, and early deafness. The reported incidence of OI varies across studies. It is estimated to be between 6 and 7 in 100,000 live births, without significant differences between different races. About 80–90% of OI patients are known to have COL1A1 or COL1A2 mutations that disrupt polypeptide chains pro alpha 1 and pro alpha 2 of type I collagen synthesis, as they play a significant role as structural proteins in the human body.[1,2]

Currently, no medical or surgical treatment can cure OI. Supportive treatment should be carried out to minimize the risk of fracture and disability. In addition to orthopedic management, bisphosphonates, a class of drugs used to treat osteoporosis, have been used to treat OI. This class of drug may reduce osteoclast activity while extending the life of osteoblasts.[1,2] These drugs have been reported to be safe. Bisphosphonate treatment in children and adolescents has been described with satisfactory outcomes.[3] Cases of mild zoledronate-induced

hepatotoxicity have been previously reported in adults with Paget's disease and glucocorticoid-induced osteoporosis,[4,5] but not in a neonate with OI. This case report aims to describe a transient hepatic injury as a possible adverse effect following zoledronic acid administration.

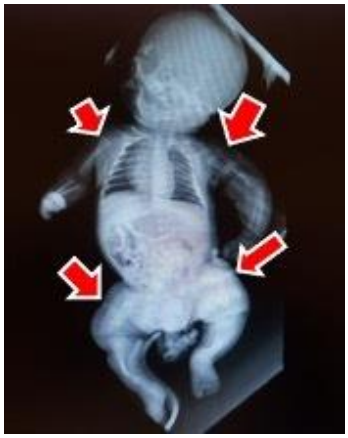
METHODOLOGY

This is a case report and the authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given their consent for clinical information to be reported in this study. The patients' parents understand that name and initials will not be published. Based on the hospital policy, neither institutional ethical approval nor specific permission is not required for reporting case reports or series.

CLINICAL DESCRIPTION

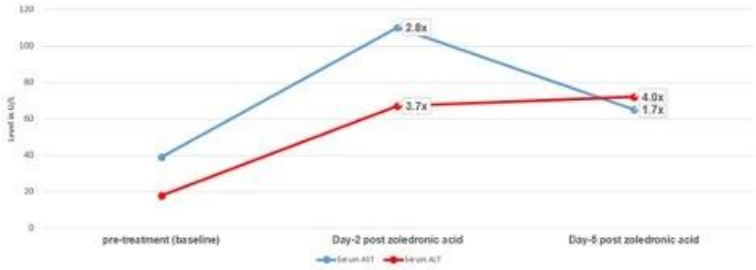
A baby boy was born by cesarean section at 38 weeks of gestation due to premature rupture of membranes and breech presentation. The mother was a healthy 35-year-old woman, and the father was 37 years old; there was no history of consanguinity. Routine antenatal care was performed. At 23 weeks of gestation, fetal ultrasonography revealed that the fetus's femur length was shorter than normal; thus, a feto-maternal obstetrician was consulted. Fetal ultrasonography at 25 weeks of gestation found multiple fractures on both femurs, which suggested OI. Upon delivery, both lower extremities were noticeably bowed and short, with "frog-like" positions. The baby is the second child of the family; none of the family members have the same symptoms.

At one day old, a full-body x-ray was performed that revealed bilateral distal femur fractures. Thus, an orthopedic doctor was consulted, and bilateral long casts were fitted for two weeks. At 25 days old, right arm movement suddenly decreased, and the baby looked to be in pain when he was handled. A second full-body x-ray revealed bilateral humeral fractures, a right femur refracture, and a left tibial fracture (Figure 1). Subsequent management consisted of bilateral upper and lower extremity casts for two weeks. Zoledronic acid treatment was scheduled.



At one month of age, zoledronic acid was administered. Before zoledronic acid was administered, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are normal (ALT: 18 U/L, AST: 39 U/L). Eighteen hours following zoledronic acid infusion (0.025 mg/kg intravenously for 30 minutes slow infusion),

the patient developed a fever. Forty-eight hours after treatment, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels increased by 3.7 and 2.8 times (ALT : 67 U/L, AST:110 U/L), respectively, without jaundice. Paracetamol was given only when there was a fever. Calcium and vitamin D supplementations were also administered.



On day 5 after zoledronic acid treatment, the AST level decreased to 1.7 times from baseline, but not the ALT level (4.0 times from baseline; Figure 2). The baby was then discharged from the hospital with a plan to undergo a second zoledronic acid treatment the following month.

DISCUSSION

We reported a neonate diagnosed with OI who had transient liver injury after zoledronic acid infusion. To the best of our knowledge, this is the first report of hepatotoxicity following zoledronic acid treatment in a neonate with OI. Previously, only three cases of elevated liver enzymes induced by zoledronic acid infusion have been reported. All of them were adult patients presenting with Paget's disease,[4] primary osteoporosis,[6] or glucocorticoid-induced osteoporosis.[5] In all cases, the serum AST and ALT levels returned to normal after one to two weeks.

The mechanism by which bisphosphonates induce hepatic injury has not been clearly elucidated. The acute-phase response with a febrile reaction following bisphosphonate treatment has been described, but with an unknown mechanism. This phenomenon cannot be explained pharmacokinetically because half of the zoledronate will be excreted in the urine within a few hours of administration.[7] Based on an *in vivo* study, IL-1, IL-6, and TNF-α might be responsible for this reaction. After administration of a bisphosphonate, serum IL-1 and IL-6 may be increased.[8,9] Furthermore TNF-α can stimulate macrophages to produce more IL-1 and IL-6. While IL-1 induces pyrexia, liver damage is possibly correlated with the level of TNF-α.[10] We postulated that this transient dysregulation of cytokines contributed to the increased liver enzyme activity in our case. It is also worth noting that the Asian population tends to have a higher incidence of acute-phase response following zoledronic acid treatment.[11]

Early administration of bisphosphonates for neonates with OI has been evaluated previously. Antoniazzi et al. found that neonates with OI who were treated with a bisphosphonate at one month of age grew significantly better in terms of weight and height compared to those started after the age of six months. The incidence of fractures was also lower among those who started bisphosphonates early. An acute-phase response with fever was common (9 out of 10 patients), but not elevated liver enzymes.[12] Intravenous bisphosphonate use is currently recommended in children with severe OI.[13]

Our case highlights the possibility of liver injury, expressed by transiently increased liver enzymes, following zoledronic acid treatment. Serum AST and ALT levels should be monitored in cases with an acute-phase response. Although the elevated liver enzymes tend to be transient and asymptomatic, other drugs (e.g., antibiotics) should be administered cautiously following zoledronic acid infusion due to the risk of liver damage that can be further aggravated. Hepatoprotective agents may be needed if the liver damage persists.

CONCLUSION

Although hepatotoxicity is reported to be rare, our report describes a possible adverse effect of zoledronic acid infusion, which may be encountered in neonates treated early with bisphosphonates. Pediatricians should pay attention to patients with concomitant liver or systemic diseases. Baseline and subsequent liver enzyme tests should be carried out to monitor the liver damage.

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