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Hypocalcemia in Children with Osteogenesis Imperfecta Treated with Intravenous Zoledronic Acid

Bassam Bin-Abbas[1*], Asmaa Al Zahrani[1], Fahad Bin-Abbas[1], Rafah Ghazi[1], Afaf Al Sagheir[1], Faisal Al Shareef[2], Abdullah Al Fares[2]

[1]Section of Pediatric Endocrinology, Department of Pediatrics, King Faisal Specialist Hospital and Research Center, MBC 58, Riyadh 11211, Saudi Arabia
[2]Security Forces Hopsital, Riyadh, Saudi Arabia

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***Corresponding author:** Bassam Bin-Abbas
Section of Pediatric Endocrinology, Department of Pediatrics, King Faisal Specialist Hospital and Research Center, MBC 58, Riyadh 11211, Saudi Arabia

Abstract **Original Research Article**

Background: Bisphosphonates (Pamidronate and Zoledronic acid) mainly used for the treatment of childhood osteoporosis such as osteogenesis imperfecta have been associated with adverse effects ranging from acute phase response, hypocalcemia, musculoskeletal pain and up to serious side effects such as osteonecrosis of the jaw. In this report, we describe the prevalence of hypocalcemia among Saudi children treated with Zoledronic acid. ***Method:*** The biochemical profile of 13 Saudi children with osteogenesis imperfecta treated with Zoledronic acid was reviewed. The bone profile including calcium and phosphorus levels were monitored before and 4-24 hours after Zoledronic acid administration. The annual total Zoledronic acid dose was 0.1 mg/kg/year. ***Results:*** Post therapy, 46% of the treated children had mild hypocalcemia and 15% had mild hypophosphatemia. None of the children had hypocalcemic or hypophosphatemic signs or symptoms. No reports of seizure or tetany or muscle spasm. ***Conclusion:*** Hypocalcemia associated with Zoledronic acid administration is common, however mild. Close monitoring and calcium supplementation might be needed.

Keywords: Zoledronic acid, hypocalcemia, hypophosphatemia, osteogenesis imperfect.

INTRODUCTION

Zoledronic acid is a high potency heterocyclic imidazole bisphosphonate. It inhibits bone resorption efficiently by reducing the activity and inducing apoptosis of osteoclasts [1]. Due to its high potency, Zoledronic acid is indicated and widely used for the treatment of bone metabolic diseases, including osteoporosis and osteogenesis imperfecta [2]. Zoledronic acid is generally well-tolerated, with a flu-like reaction being the most common immediate side effect [2]. Other side effects include gastrointestinal symptoms, transient low-grade fever, arthralgia, and bone pain [2]. Hypocalcemia has been reported in patients treated with intravenous intravenous Zoledronic acid, ranging from mild asymptomatic to severe life-threatening hypocalcemia involving cardiac arrhythmias and neurologic adverse events such as seizures and tetany [2]. The United States Food and Drug Administration agency instructs that hypocalcemia must be corrected before initiating Zoledronic acid, by adequately supplementing patients with calcium and vitamin D [2]. Seizures after the administration of bisphosphates have been reported in few cases in the medical literature [3-5], mostly in patients with other precipitating factors, such as hypoglycemia, acute infection, or predisposition to post-bisphosphonate hypocalcemia [6]. The incidence of hypocalcemia is not well studied in children with osteogenesis imperfecta treated with Zoledronic acid. Here, we report our experience with Zoledronic acid in a group of patients who are vitamin D sufficient to determine their needs of calcium supplementation during Zoledronic acid administration.

METHODS

We retrospectively reviewed the biochemical profile of 13 children (6 males, 7 females) treated with Zoledronic acid intravenously at 6 months intervals at the Pediatric Endocrinology Day Medical Unit, King Faisal Specialist Hospital, and Security Forces Hospital, Riyadh, Saudi Arabia for 2 years (Jan 2020-Jan 2022). The age of these children ranged from 1-14 years.

The bone profile including calcium and phosphorus levels were monitored before and 4-24 hours after Zoledronic acid administration. Baseline parathyroid hormone (PTH), 25 hydroxyvitamin D and alkaline phosphatase were obtained. These children were not supplemented with vitamin D or calcium due to their normal baseline levels. The annual total Zoledronic acid dose was 0.1 mg/kg/year. The study was approved by King Faisal Specialist Hospital Research Ethic Committee (RAC# 2231223).

RESULTS

The bone profile of these 13 children is listed in table No. 1. All children had normal baseline PTH (mean 52ng/L) and acceptable 25 vitamin D level (>45nmol/l). The mean baseline calcium and phosphorus levels were 2.3mmol/l and 1.8mmol/l respectively. The mean calcium and phosphorus levels post Zoledronic acid first infusion were 2.0mmol/l and 1.6mmol/l respectively. Post therapy, 46% and 15% of treated children had calcium level and phosphorus level respectively below the lower limit of normal. None of the children had symptomatic hypocalcemia or hypophosphatemia. No reports of seizure or tetany or muscle spasm. None of the children had severe hypocalcemia below 1.8mml/l.

Table 1: Biochemical Profile of Osteogenesis Imperfecta Children before and After First Dose of Zoledronic Acid

PATIENTS	PTH (15-65ng/L)	VITAMIN D (>50nmol/L)	PRE-ZA CA (2.1-2.6mmol/l)	Post-ZA CA (2.1-2.6mmol/l)	PRE-ZA PO4 (1.4-2.3mmo/l)	POST-ZA PO4 (1.4-2.3mmol/l)
1	43	49	2.3	2.1	2	1.8
2	59	52	2.2	1.9	1.8	1.6
3	62	50	2.1	2	1.5	1.4
4	66	45	2.4	2	1.4	1.3
5	34	55	2.2	2.1	1.6	1.6
6	32	63	2.6	2.5	2.1	1.9
7	47	65	2.5	2.3	2.2	2
8	41	53	2.4	2.1	2.3	2
9	65	48	2.2	1.9	1.4	1.4
10	55	47	2.4	2.1	1.7	1.8
11	52	71	2.3	2.2	1.9	1.5
12	68	58	2.1	1.9	1.3	1.2
13	48	55	2	2	2.3	1.8

DISCUSSION

Intravenous Zoledronic acid has been used to treat children with osteogenesis imperfecta for many years. Favorable side effect profile and improvements in bone mineral density have been demonstrated. We aimed from this study to determine the prevalence of mild and severe hypocalcemic episodes in patients with sufficient calcium and normal vitamin D stores to find out if these children are in need of calcium supplementation.

Limited number of studies discussed the prevalence of hypocalcemic episodes among children treated with Zoledronic acid. A 7-year retrospective chart review of 123 pediatric patients with osteoporosis. Hypocalcemia following intravenous Zoledronic acid infusions occurred in 7%. Severity of hypocalcemia was generally mild, requiring intravenous calcium in 3% of infusions. Hypophosphatemia occurred frequently, however rarely required intravenous supplementation. There were no reports of osteonecrosis of the jaw nor atypical femoral fracture [7]. In our series, almost half of the treated osteogenesis imperfecta children developed hypocalcemia. All episodes were mild and did not require intravenous calcium infusion.

The short and long-term side effects of zoledronate were also evaluated in 26 children with osteogenesis imperfecta. 3% had symptomatic hypocalcemia 15 days after the infusion. 11% had acute phase reactions and one had long-term side effects, including osteonecrosis of the jaw [8]. In our group of children, the calcium level was monitored immediately post Zoledronic acid infusion and up to 24 hours post. The effect of Zoledronic acid may last several days post infusion and it might be necessary to check calcium and phosphorus levels several weeks after.

Another study aimed to characterize the short-term safety profile of Zoledronic acid in children with osteoporosis and osteogenesis imperfecta. The median Zoledronic acid dose was 0.025 mg/kg. Adverse effects were mild and more common after the first Zoledronic acid infusion. Hypophosphatemia was reported in 25% of infusions, acute phase reactions in 19%, and hypocalcemia in 6.4%. Symptomatic hypocalcemia requiring intravenous calcium occurred after two infusions. It was concluded that acute adverse reactions related to Zoledronic acid infusion in youths are common, occur principally after the first Zoledronic acid infusion in bisphosphonate-naive patients, and are

typically mild and easily managed [9]. Based on this report and others, we felt that gradual start of Zoledronic acid is recommended to avoid severe hypocalcemia. In our practice, we usually start with 0.025mg/kg/dose and gradually increase it to 0.05mg/kg/dose as needed. We rarely use 0.1mg/kg/dose.

A study that included 17 patients with type I osteogenesis imperfecta. The infusions were associated with a transient decrease in serum calcium and phosphate and a significant increase in serum PTH. Two patients developed symptomatic hypocalcemia [10]. A descriptive study evaluated the efficacy and safety of zoledronic acid in children with osteogenesis imperfecta. The patients were kept for 24 hours after dose administration to monitor any short-term side effects. 13.4% had fever and 2.4% had flu-like illness. No other side effects were observed [11]. We do not recommend keeping children in the hospital post Zoledronic acid infusion since hypocalcemic events are mild and self-limiting. Calcium levels can be monitored regularly post infusion and parents can be educated about symptoms of hypocalcemia.

CONCLUSION

Adverse effects due to Zoledronic acid administration including hypocalcemia and hypophosphatemia are common, however mild. Children with osteogenesis imperfecta who have normal baseline calcium/phosphate levels might not need calcium or phosphorus supplementation before or during therapy. Close monitoring of these metabolites is necessary. We recommend initiating calcium supplementation and correction if baseline calcium levels are subnormal. Further long-term studies might be needed to determine the long-term effects of Zoledronic acid on calcium level and the right time of post infusion monitoring.

Author Contributions:

All the authors were equally involved in the curation and development of this manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest: No conflict of interest

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