SYMPTOMATIC HYPOCALCAEMIA FOLLOWING INTRAVENOUS ADMINISTRATION OF ZOLEDRONIC ACID IN A FEMALE PATIENT WITH OSTEOPOROSIS

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ABSTRACT

Bisphosphonates (BPs) are widely used in the treatment of postmenopausal osteoporosis. Zoledronic acid has the highest affinity with the bone as well as alters mineral surface properties, allowing greater adsorption. A 58-year-old woman presented with osteoporosis, was treated with a once-a-year IV of 5 mg of Zoledronic Acid. Before this once-a-year treatment, her serum calcium levels were normal although after the treatment, she was hospitalized with nausea, perioral and acral paresthesias and tingling. Biochemical analysis recorded Calcium levels as 5.94 mg/dl and low levels of vitamin D Serum. The Hypocalcaemia was initially treated with IV Calcium Gluconate solution followed by oral calcium and vitamin D supplements.

***Key words**: Zoledronic Acid, Osteoporosis, Hypocalcaemia.*

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Introduction

Osteoporosis is a considerate health problem for both men and women and its prevalence is increasing with the age. Osteoporosis develops in one out of two women and in one out of four males respectively after the age of 50[(1)]. According to The World Health Organization data (WHO) in Europe, USA and Japan, 75 million of people suffers from osteoporosis[(1)]. As the elderly population increases, osteoporosis and related fractures are becoming a considerate health problem[(2,3)]. The osteoporosis related fractures are associated with decrease quality life and increase mortality rate and health care expenses[(2,3)].

Bisphosphonates (BPs), which are potent inhibitors of bone reabsorbtion, are gold standard for the treatment of osteoporosis[(4,5)]. Zoledronic acid can be administer intravenously (IV) in long dose intervals that improve patient's compliance. The Food and Drug Administration (FDA) approved zoledronic for osteoporosis treatment[(6)].

Some rare side effects caused by the use of BPs such as hypocalcaemia are frequently observed. Hypocalcaemia is an adverse effect that patients with vitamin D deficiency primarily develop, thus can be prevented with calcium and vitamin D supplements.

Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial have shown that hypocalcaemia (defined as calcium <8.3 mg/dl [2.075 mmol/l]) is frequently more developed than placebo (1.3% vs 0.002%) while administrating IV zoledronic acid (7). Hypocalcaemia was observed 9-11 days after the IV administration and was reported as transient and asymptomatic. However, it could be severe and prolonged in patients with vitamin D deficiency[(8, 9)].

In this case, we present a patient who has had developed hypocalcaemia - a rare side effect- after been administrated with IV zoledronic acid for the treatment of osteoporosis.

Case Presentation

A 58-year-old woman was admitted to the emergency department of our hospital complaining of nausea, vomiting, fatigue, pruritus, irritability, numbness and tingling in the perioral area as well as fingers and toes, muscle cramps particularly on the back and lower extremities and carpopedal spasms. In her medical history, she has had hypertension for seven years and has been treated with Lisinopril 20 mg/day, and diabetes mellitus for six years that has been treated with metformin 850 mg two times a day and gliclazide 80 mg two times a day.

Upon admitted, she has had expiratory wheezes, bradycardia (58 bpm) and excoriations on her extremities. Biochemical analysis showed as follow: Haemoglobin (Hgb) 12.5 g/dL, white blood cells (WBC) 4140/mL (normal differential); platelets 162000/mL blood glucose 93 mg/dL (70-110), Alanine aminotransferase (ALT) 15 U/L (0-40), Aspartate aminotransferase (AST) 14 U/L (0-40), Alkaline phosphatase (ALP) 65 U/L (35-104), Gamma glutamyl transferase (GGT) 18 U/L (5-61), Lactate dehydrogenase (LDH) 293 U/L (240-480), Creatine kinase (CK) 69 U/L (26-308), Urea 23 mg/dL (10-50), Creatinine (Cr) 0.8 gr/dL (<1.3), Total Protein 6.2 g/dl (6.6-8.7), Albumin 3.4 g/dl (3.4-4.8), Total Bilirubin 0.6 mg/dL (0-1.2), Direct Bilirubin 0.2 mg/dL (0-0.3), Amylase 73 U/L (28-100), Calcium (Ca) 5.94 mg/dL (8.6-10.2). Repeated serum Ca was measured as 5.92 mg/dL[8.6-10.2].

An abdominal ultrasound (USG) revealed two simple cortical cysts in the right kidney (3 mm and 4 mm) and one simple cortical cyst in left one (3 mm). The patient was diagnosed with Hypocalcaemia and was admitted in the Internal Medicine service Area.

When her detailed medical history was inquired, we observed that she was treated with 5 mg/100 mL of IV zoledronic acid (Aclasta) for the osteoporosis diagnosis previously reported by the department of Physical Medicine and Rehabilitation (FTR) two weeks before. Before the administration of zoledronic acid, a Dual energy x-ray Absorptiometry (DEXA) test results showed a Total Femoral T score of -2.2, and a Total Lomber T score of -2.3, L1 -1.9, L2 -1.8, L3 -2.3, L4 -3.2.

From the medical records obtained from our hospital database, the serum Ca levels were 8.9 mg/dL before the administration of zoledronic acid, although her serum vitamin D levels before the zoledronic acid administration were nonexistent.

After the hospitalization of the patient, further analysis showed low serum vitamin D levels (3,7 ng/ml, reference range 10-50 ng/ml) and normal serum Parathyroid hormone levels (36,51 pg/ml). Hypocalcaemia was initially treated with IV Calcium Gluconate infusion followed by oral Calcium and Vitamin D therapy. Her symptoms responded and were eliminated after the initial IV calcium gluconate therapy. Further analysis performed showed that a twenty-four hour urinary calcium sample collected in two separate occasions were normal, so urinary calcium loss was excluded. Serum calcium levels returned to normal (8.57 mg/dL) after 14 day of therapy and the blood test follow-up results showed normocalcemia.

Discussion

Osteoporosis is characterised with low bone mineral density and weak bone quality that results in decreased strength of the bone and increase of fracture risk[10].

Osteoporosis diagnosis is established according to the WHO criteria by measuring the bone density with DEXA and the results are compared with the T scores references of young adult populations. T scores >-2.5 and T scores between -1 and -2.5 are named osteoporosis and osteopenia, respectively[11].

Osteoporosis is a major health problem increasing with age. Over 50 years old of age, it develops approximately in 1 out of 2 women and in 1 out of 4 men and it is associated with fracture risk in their remaining life[12].

The medical treatment agents, developed to prevent osteoporosis such as Estrogen, Raloxifen and Bisphosphonates (Alendronat, Risedronat, and Ibandronat) which inhibit Osteoclastic activity are called antiresorptive agents. The antiresorptive agents developed to treat osteoporosis are Alendronat, Risedronat, Ibandronat, Zoledronic Acid, Salmon Calcitonin and the anabolic agent Teriparatid (Parathyroid Hormone I-34)[13].

The most frequent agents used for the treatment of osteoporosis and prevention of the fractures are BPs. Since oral bioavailability of BP is low, the ingestion must be done at least 30 minutes before meals followed by patients not lying down for the next 30 minutes in order to prevent esophageal irritation[14]. Because of these specifications, the compliance of the patients to the drug could decrease

resulting in suboptimal treatments[15, 16]. In addition to weekly and monthly IV or oral BPs administration treatments, a once-a-year dose of IV zoledronic acid treatment was recently supplemented in order to increase the tolerability and compliance of the treatment.

Zoledronic acid is a BP that includes nitrogen. The main composition consists of Phosphorus-Carbon-Phosphorus nucleus and a Hydroxyl group composition, which was added at R1 position. The Heterocyclic Imidazole group which was added at R2 position discriminates zoledronic acid from other BPs[17].

Zoledronic acid is a potent inhibitor of bone reabsorbtion. It inhibits reabsorbtion of osteoclasts and induces apoptotic cell death of it. The high affinity of zoledronic acid to the mineralised bone tissue, especially to the areas of high bone turnover, is the reason of its effectiveness[17].

In a three year randomized double-blind placebo controlled study, it was shown that 5 mg doses of once-a-year zoledronic acid decreased the vertebral, hip and other fractures in postmenopausal women. In this study, zoledronic acid was generally well tolerated and was associated with a good safety profile[18].

The reported adverse effects related to zoledronic acid are acute phase reactions (such as low grade fever, fatigue, bone pain, arthralgia), pains in muscle and skeletal systems, arrhythmias such as atrial fibrillation, nephrotoxicity, atypical femur diaphysis fractures, osteonecrosis of jaw, ocular inflammation, uveitis, scleritis, hypocalcaemia and secondary hyperparathyroidism and upper gastrointestinal side effects[19]. After the BP treatment, hypocalcaemia is reported several times as a side effect[20,21]. Hypocalcaemia does not develop in many patients due to compensatory mechanisms such as secondary hyperparathyroidism[22]. The deficiency in response of parathyroid hormones to hypocalcaemia can be seen in different mechanisms, such as surgical hypoparathyroidism, previously existing hyperparathyroidism and hypomagnesemic hypoparathyroidism. Furthermore, hypocalcaemia can be developed with low levels of vitamin D[19].

In this case, symptomatic hypocalcaemia was developed after IV zoledronic acid administration. After detailed laboratory analysis, we detected vitamin D deficiency in our patient. The patient's symptoms and the laboratory analysis showed response to the treatments and hypocalcaemia was treated.

Conclusion

Recently, zoledronic acid increases its use as an IV BP and it decreases osteoclast formation and it functions better than other BPs[13, 21]. Before the potent and long acting BP such as zoledronic acid is administrated to the patient, the patient must be clinically analysed and laboratory tests should be run, and serum levels of Calcium, Parathormone and Vitamin D must be measured.

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