

Hypocalcemia Secondary to Zoledronate Therapy in a Patient With Low Vitamin D Level

Narendranath Epperla, MD; Ram Pathak, MD, FACE, FACP

ABSTRACT

Zoledronate (ZDA) is a bisphosphonate used to treat hypercalcemia that commonly occurs with malignancy, multiple myeloma, and bone metastases from solid tumors. It acts primarily by decreasing osteoclastic activity, thereby slowing the release of skeletal calcium. However, a potential adverse effect of ZDA is hypocalcemia that can be symptomatic, especially in patients with risk factors such as hypomagnesemia, hypoparathyroidism, renal failure, and vitamin D deficiency. We report the case of a patient with extensive stage small cell lung cancer with multiple osseous and visceral metastases who developed symptomatic hypocalcemia following ZDA administration. Significant clinical improvement occurred following administration of calcium and vitamin D, and his calcium levels returned to normal within a few days. Due to the high incidence of vitamin D deficiency and the low accuracy of clinical risk factors to predict vitamin D deficiency, screening for vitamin D deficiency before administration of ZDA may be appropriate.

INTRODUCTION

Zoledronic acid, also known as zoledronate (ZDA), is a bisphosphonate that decreases skeletal calcium release by inhibiting osteoclastic activity. It has been used for several clinical indications, including hypercalcemia of malignancy, multiple myeloma, and bone metastases from solid tumors, as well as treatment of osteoporosis and Paget's disease.¹⁻⁷ Common side effects include bone pain, arthralgias, myalgias, and flu-like symptoms (eg, fever,

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Author Affiliations: Department of Hematology and Oncology, Medical College of Wisconsin, Milwaukee (Epperla); Department of Endocrinology, Marshfield Clinic, Marshfield (Pathak)

Corresponding Author: Narendranath Epperla, MD, Medical College of Wisconsin, Department of Hematology and Oncology, 9200 W Wisconsin Ave, Milwaukee, WI 53226; phone 414.805.4600; e-mail nepperla@mcw.edu.

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nausea). Dose-dependent nephrotoxicity, osteonecrosis of the jaw, and hypocalcemia are observed less frequently.⁸⁻¹⁰ The incidence of symptomatic hypocalcemia requiring treatment is low (based on the data from clinical trials);¹¹⁻¹³ however, in certain clinical settings, the incidence has been shown to be higher (up to ~35%). This is especially true in patients with additional risk factors like pre-existing hypoparathyroidism, vitamin D deficiency, renal failure, or hypomagnesemia.^{14,15}

Herein we report a case in which the patient developed symptomatic hypocalcemia following administration of ZDA. He made significant clinical improvement following administration of calcium and vitamin D, with his calcium levels returning to normal within a few days of therapy.

CASE PRESENTATION

A 54-year-old man with a history of extensive stage small cell lung cancer with multiple osseous and visceral metastases was started on chemotherapy 4 months prior to the presentation. Eight days before presentation, he completed cycle 5 of multiagent chemotherapy (cisplatin and irinotecan). He received intravenous (IV) ZDA (4 mg infused over 15 to 20 minutes) the next day to treat skeletal metastases. He was advised to take calcium and vitamin D (600 mg + 400 IU) supplements. However, the patient forgot to take the advised supplements, and 7 days later presented with complaints of nausea, vomiting, paraesthesias, lightheadedness, and weakness. His total serum calcium (Ca^{2+}) of 10.3 mg/dL before ZDA therapy had decreased to 7.7 mg/dL (normal range 8.5-9.8 mg/dL). The ionized Ca^{2+} was 3.9 mg/dL (normal range 4.5-5.3 mg/dL), while creatinine was at his baseline of 1.1 mg/dL (normal range 0.8-1.2 mg/dL). The 25-hydroxy vitamin D (25-OH vitamin D) was low at 24 ng/mL (normal range 30-60 ng/mL), while parathyroid hormone (PTH) was elevated at 104 pg/dL (normal range 12-72 pg/dl). He received IV calcitriol (0.25 mcg) and IV calcium gluconate, and the next day his ionized Ca^{2+} was

Figure 1. The Patient's Total Serum Calcium (Ca^{2+}) Levels

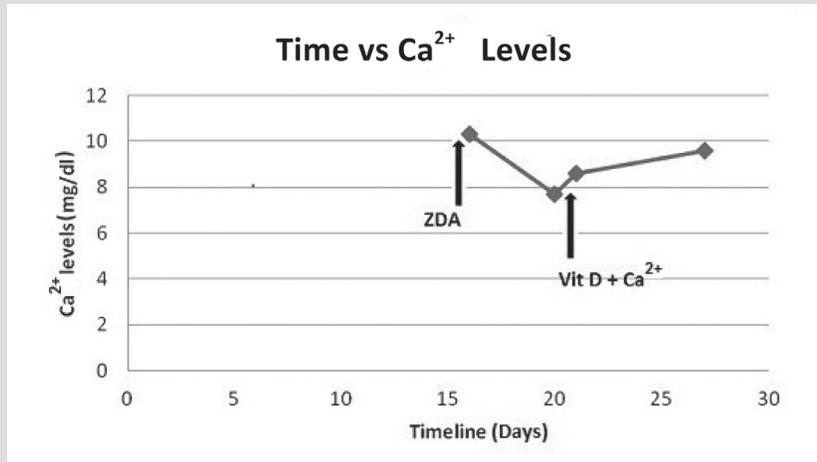
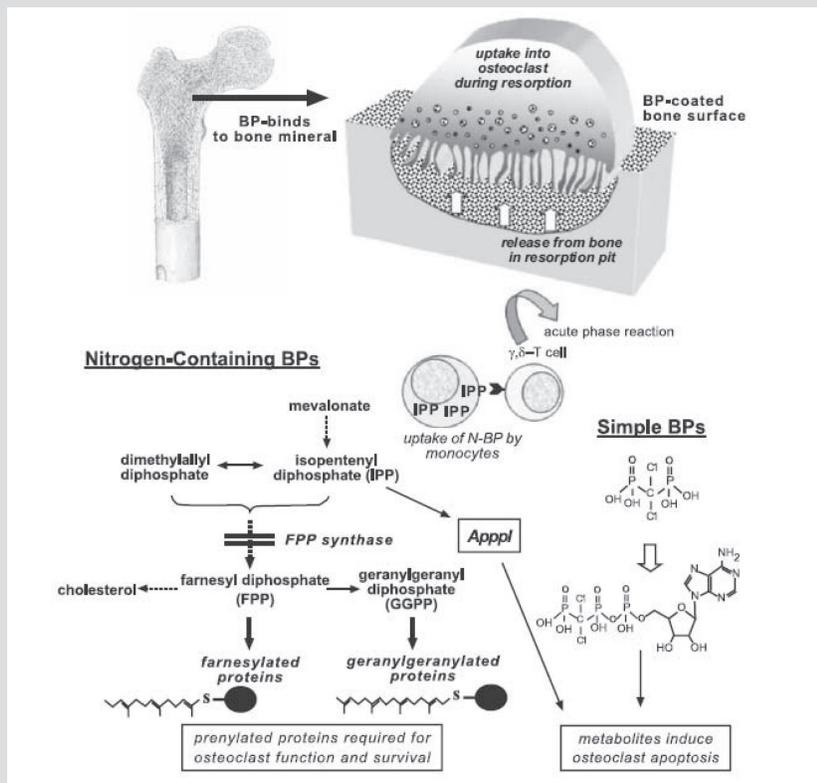


Figure 2. Mechanism of Action of Bisphosphonates on Osteoclasts



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4.6 mg/dL (total calcium 8.3 mg/dl). He was advised to continue calcitriol and take calcium (1200 mg) and vitamin D (800 U) orally twice daily.

Seven days later, his symptoms had improved, and his PTH levels had normalized to 36 pg/mL. Calcitriol was discontinued, but the calcium and vitamin D were continued. Two weeks later,

he was asymptomatic, and his total serum Ca^{2+} was within normal limits (9.4 mg/dL) (Figure 1). Transient hypocalcemia and secondary hyperparathyroidism after ZDA infusion in this patient with inadequate vitamin D levels was successfully treated with vitamin D and calcium supplements with no recurrence of symptoms during subsequent follow-up visits.

DISCUSSION

Total calcium level lower than 8.5 mg/dL (2.12 mmol/L) in the serum is defined as hypocalcemia. Calcium in the body is mostly present in the bones (99%), with only 1% distributed in the serum. This serum calcium exists in 3 forms:

- Free or ionized calcium (50%)—physiologically active form.
- Calcium bound to plasma proteins (40%)—albumin is the plasma protein to which serum calcium is predominantly bound (approximately 80%).
- Calcium complexed to anions (10%)—the anions include citrate, phosphate, bicarbonate, and lactate.

Thus, serum calcium can be affected by serum albumin, especially when the serum albumin level is high or low. Therefore, it is important to measure serum albumin concentration first and correct serum calcium based on the albumin levels. Alternatively, one can directly measure ionized calcium, which is a true estimate of the individual's calcium level in the body.

ZDA is a third generation amino-bisphosphonate that inhibits farnesyl pyrophosphate synthase, a key enzyme in the mevalonate pathway. This has a few important ramifications: (1) it leads to decreased production of sterols that are required for osteoclast function and survival; (2) it leads to accumulation of an alternative metabolite that induces osteoclast apoptosis.^{4,9,16} Thus, ZDA prevents osteoclastic resorption of the bone by decreasing osteoclastic activity and promoting programmed cell death^{4,9,16} (Figure 2). ZDA has a high

affinity for bone tissue without any evidence of biotransformation and exhibits rapid elimination from the circulation. Plasma protein binding is low (~22%), indicative of lower likelihood of displacement of other drugs that are highly plasma protein bound. Thus ZDA has a favorable pharmacodynamic and pharmacokinetic profile. It is, in fact, preferred over other bisphos-

phonates available for the treatment of bony metastases, since it is more potent, has a short infusion time (15 minutes), and has the advantage of a shorter length of stay in the ambulatory setting.^{5,11-13,17}

ZDA lowers serum calcium in both normocalcemic and hypocalcemic individuals by its effect on osteoclast activity (as detailed above). In most instances, the hypocalcemia that arises is asymptomatic and mild, with normal levels restored rapidly provided the factors involved in calcium homeostasis are intact. However, patients who have additional risk factors like vitamin D deficiency, renal insufficiency, or hypomagnesemia are less likely to counteract the hypocalcemic stimuli when treated with ZDA.

Calcium levels in the blood are maintained within the normal range by vitamin D and PTH. Vitamin D deficient patients have elevated PTH levels, which try to keep calcium within normal limits through osteoclast-mediated bone resorption. However, when ZDA is started in patients with vitamin D deficiency, this defense mechanism is blocked (ie, osteoclast-mediated bone resorption), and the patient is predisposed to developing hypocalcemia. We believe this to be the cause of hypocalcemia in our patient.

At the time of presentation, our patient's vitamin D level was 24 ng/mL. His calcium was kept within normal limits before initiating ZDA therapy by the compensatory increase in PTH. In anticipation of hypocalcemia, he was advised to take calcium and vitamin D supplements once ZDA was initiated. Due to the high incidence (~60%) of vitamin D deficiency in elderly and hospitalized patients,^{9,18,19} it would be prudent to screen for 25(OH) D concentration prior to initiating ZDA. It has been stated "to prevent fatal hypocalcemic episodes, administer adequate vitamin D and calcium supplements in patients who have normal to low calcium levels when commencing treatment with bisphosphonates."²⁰

Other conditions that predispose to the development of symptomatic hypocalcemia in patients using ZDA are pre-existing hypomagnesemia, renal insufficiency, and hypoparathyroidism. Magnesium is a key element required for the release and action of PTH; hence, patients with low magnesium levels have inappropriately low PTH levels in the presence of hypocalcemia.²¹ Some authors have strongly suggested the routine monitoring of magnesium in patients at risk, such as those using diuretics, and to consider prophylactic supplementation in selected cases.¹⁴

ZDA, like other bisphosphonates, is cleared renally, and if the dose is not adjusted in patients with impaired creatinine clearance, there is a high likelihood of ZDA toxicity. Current guidelines advocate against the use of ZDA in patients with creatinine clearance of less than 30ml/min, and a graded dose reduction is recommended for patients with creatinine clearance of 30ml–60ml/min.^{10,22} Therefore, it is considered prudent by many clini-

cians to monitor renal function prior to every dose of ZDA.⁸

Patients with pre-existing hypoparathyroidism are extremely susceptible to symptomatic hypocalcemia when started on bisphosphonates. This is because in addition to losing osteoclast-mediated calcium release from bone resorption, they also typically have renal calcium wasting. Therefore, it is important to screen routinely for hypoparathyroidism in all patients with non-hypercalcemic bone disease before starting bisphosphonates.²³ In a patient with low parathyroid reserve, it is strongly recommended that bisphosphonates be used cautiously and in lower doses, and that one should be prepared to give large doses of calcitriol and calcium to avoid tetany.²⁴

Receptor activator of nuclear factor- κ B ligand (RANKL) binds to and activates its receptor RANK, a transmembrane protein receptor on the surface of osteoclast precursors and through downstream signals activates nuclear factor κ B and mitogen-activated protein (MAP) kinases. This leads to the differentiation, activation, and increased survival of osteoclasts, leading to enhanced bone resorption.²⁵ Osteoprotegerin is a natural inhibitor of RANKL, preventing RANKL from binding to its osteoclast receptor. Although other hormones and cytokines participate in osteoclast differentiation and activation, RANKL appears to be an essential factor and the final common regulator of osteoclastogenesis.²⁶ Denosumab (AMG 162) is a human monoclonal IgG2 antibody that has high affinity for human RANKL and blocks the binding of RANKL to RANK, thereby inhibiting osteoclast differentiation and survival. It is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors, osteoporosis, and hypercalcemia of malignancy. Though denosumab is an acceptable alternative to ZDA, it also can cause severe hypocalcemia (similar to ZDA), and caution must be exercised to correct pre-existing hypocalcemia prior to initiating therapy.²⁷⁻²⁹

CONCLUSION

With more patients being treated with IV bisphosphonates for varying conditions, such as osteoporosis, skeletal metastases, and hypercalcemia of malignancy, the incidence of symptomatic hypocalcemia will probably increase, particularly in patients with undiagnosed calcium and bone metabolism disorders.³⁰ We advocate routine screening of 25 (OH)D levels for vitamin D deficiency in patients who are being started on ZDA for multiple reasons—high incidence of vitamin D deficiency among the elderly and inpatient population, increasing long-term use of proton pump inhibitors (that limit the absorption of dietary calcium), and the low accuracy of clinical risk factors to predict vitamin D deficiency. We also strongly recommend administration of adequate calcium and vitamin D supplements in patients who have normal to low calcium levels when initiating treatment with bisphosphonates. It might be prudent to incorporate routine

screening for hypoparathyroidism in all patients with non-hypercalcemic bone disease before starting bisphosphonates. These recommendations, along with regular monitoring of calcium, magnesium, and renal function before administration of every dose, could be effective in decreasing the incidence of symptomatic hypocalcemia in patients taking ZDA.

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