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Prolonged, Symptomatic Hypocalcemia with Pamidronate Administration and Subclinical Hypoparathyroidism

Alita Mishra,[1] Lisa Wong,[2] and Jacqueline Jonklaas[2]

[1]*Medical College of Wisconsin, Milwaukee,*
and [2]*Division of Endocrinology, Georgetown University Medical Center, Washington, DC*

A 62-yr-old woman with thyroid carcinoma metastatic to bone, and a history of subclinical hypoparathyroidism was admitted to the hospital in hypocalcemic crisis 5 wk after receiving iv pamidronate. The patient had tetany and laryngospasm. An electrocardiogram showed junctional rhythm with QT segment prolongation. The patient had previously maintained a low-normal serum calcium on 500–750 mg of calcium carbonate and 600 IU of vitamin D daily. One week after pamidronate administration the patient's calcium and vitamin D supplementation were inadvertently discontinued. She continued to take daily intranasal calcitonin. At the time of her hospitalization for hypocalcemia, the patient's serum calcium was 4.3 mg/dL. The patient received aggressive calcium and vitamin D supplementation. However, her serum calcium remained below 6 mg/dL for a 2-wk period, and took another week to return to the normal range. In this article, we discuss the counterregulatory responses necessary to maintain calcium homeostasis following osteoclast inhibition by bisphosphonates. We also review the risk factors for hypocalcemia following bisphosphonate administration. Pamidronate and other bisphosphonates are becoming an integral part of the management of normocalcemic patients with malignant bone disease. Therefore, awareness of risk factors for hypocalcemia and familiarity with avenues available for protection from potentially catastrophic hypocalcemia are both crucial.

Key Words: Hypocalcemia; bisphosphonates; pamidronate; malignant bone disease.

Introduction

This article describes a case of symptomatic and persistent hypocalcemia following pamidronate treatment for bony metastases in a patient with hypoparathyroidism. Following a single dose of pamidronate, the patient developed severe hypocalcemia resulting in hospitalization for cardiac arrhythmia and respiratory distress. Despite aggressive treatment, the patient's hypocalcemia persisted for a further 3 wk. This case report highlights the need to assess calcium homeostasis and risk factors for hypocalcemia, on an individual patient basis, before administration of pamidronate.

Recently, pamidronate has been demonstrated to provide marked relief of bone pain, reduce biochemical markers of bone turnover, and decrease skeletal morbidity in normocalcemic patients with advanced breast cancer *(1)* and stage III multiple myeloma *(2)*. A potential role of bisphosphonates in prevention of bony metastases *(3–5)* or retardation of tumor progression *(1)* has also been suggested. In fact, a recent consensus conference has recommended that bisphosphonate treatment be given for all multiple myeloma patients with osteolytic lesions and also be considered for some patients with breast cancer *(5)*. Pamidronate is already well established as an agent for treatment of hypercalcemia *(6)*. Intravenous pamidronate rapidly reduces the degree of hypercalcemia with relatively few side effects. The response is often sustained for up to 4 wk with an average maintenance of normocalcemia of 15 d. In some cases, serum calcium may remain normal for as long as 2 mo *(7)*.

These therapeutic uses of bisphosphonates arise directly from their potent inhibition of osteoclast activity. They reduce the production of protons, lysosomal enzymes, and prostaglandins necessary for osteoclast-mediated bone resorption *(8)*. They also appear to shorten the life span of osteoclasts by inducing apoptosis *(9)*. Tumor-induced osteoclast activity is similarly reduced by bisphosphonates. Bisphosphonates also have an additional indirect antiresorptive effect via an action on osteoblasts. This is achieved by stimulation of osteoclast inhibitory factors *(10)* and inhibition of osteoclast-stimulating factors *(11)*. These actions are in opposition to the action of parathyroid hormone (PTH). PTH-directed calcium release from bone is achieved through an action on osteoblasts, which then leads to osteoclast activation *(12)*. Thus, the osteoclast, which is subject to control by ambient PTH levels, plays a pivotal role in maintenance of normocalcemia.

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Author to whom all correspondence and reprint requests should be addressed: Jacqueline Jonklaas, Division of Endocrinology, Building D, Suite 232, 4000 Reservoir Road, NW, Washington, DC 20007. E-mail: jj@bc.georgetown.edu

An acknowledged potential side effect of bisphosphonates, including pamidronate, is hypocalcemia. As iv pamidronate becomes more widely used in normocalcemic cancer patients, the incidence of symptomatic hypocalcemia will probably increase. Risk factors for development of hypocalcemia following pamidronate treatment in normocalcemic patients include hypoparathyroidism (present in our patient), vitamin D deficiency, concurrent use of other osteoclast inhibitors, and renal calcium wasting. In this article, we discuss the pathogenesis of prolonged hypocalcemia in the presence of these risk factors. We also explore possible prevention and treatment strategies.

Case Report

A 62-yr-old woman with a history of metastatic thyroid cancer and postsurgical hypoparathyroidism was readmitted to the hospital for a hypocalcemic crisis. She had tetany and laryngospasm and her electrocardiogram revealed a junctional rhythm. Her serum calcium was 4.3 mg/dL. The patient had been diagnosed 20 yr previously with a mixed follicular-papillary thyroid cancer with Hurthle cell features, for which she had undergone a thyroidectomy and left-neck dissection. She did not receive radioiodine treatment at that time. Twelve years later she developed a mediastinal recurrence and underwent a mediastinotomy and neck reexploration. She later received radioactive iodine treatment for residual disease. She was also given radiation therapy to the chest for a second mediastinal recurrence and for metastases involving both the tibia and humerus bilaterally.

The patient had developed transient hypocalcemia following her second neck surgery but had subsequently maintained a low-normal serum calcium on 500–750 mg of elemental calcium and 600 IU of vitamin D daily. In addition to her known mediastinal mass and bony metastases leading to pathologic fractures, the patient had documented pulmonary metastases. Her medications included calcitonin, which she took for bony pain. Five weeks prior to this current admission for hypocalcemia, the patient had been given 90 mg of pamidronate intravenously by her oncologist. One week after pamidronate administration she had been admitted to the same hospital for left hip replacement following a pathologic fracture of the left femur. Her serum calcium at this time was 8.2 mg/dL, and oral calcium supplementation was not continued. She developed symptomatic hypocalcemia with a serum calcium of 4.1 mg/dL (ionized calcium 1.68 mg/dL). She was given iv and oral calcium replacement and was discharged from the hospital with a serum calcium of 6.1 mg/dL (albumin not checked; ionized calcium 3.27 mg/dL).

At the time of the patient's readmission to the hospital because of tetany, an endocrine consultation was obtained. The patient complained of muscle cramps, eye twitching, hand spasm, and difficulty breathing. In the emergency department she was noted to have stridor and an electrocardiogram showed a junctional rhythm with a prolonged QT interval. Her serum calcium was 4.3 mg/dL, serum phosphorus was 4.4 mg/dL, magnesium level was 1.5 mg/dL, albumin was 2.1 g/dL, and ionized calcium was 1.79 mg/dL. The patient received an iv bolus of 186 mg of elemental calcium, followed by an infusion of 1116 mg of elemental calcium. She was also started on 3 g of elemental calcium and 0.5 μg of calcitriol daily. Magnesium replacement was also given both intravenously and orally. Her serum calcium remained in the range of 4.5–5.6 mg/dL. A serum PTH level at the time of a serum calcium of 4.8 mg/dL was 17 pg/mL. However, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were both normal (*see* Table 1 for laboratory evaluation).

The patient again developed hypocalcemic symptoms (including laryngospasm and a prolonged QT interval) at a serum calcium of 4.3 mg/dL. An iv bolus of 186 mg of calcium was again given. A second infusion containing 1395 mg of calcium was administered. The patient was advised to switch her oral calcium preparation from calcium carbonate to calcium citrate, but she refused. The patient's oral calcium carbonate was increased to 4.5 g daily and calcitriol was increased to 1.0 μg daily. The patient's serum calcium remained in the 5.0–5.4 mg/dL range, with some mild symptoms of hypocalcemia. A third calcium infusion containing 930 mg of calcium was given for a serum calcium of 4.7 mg/dL, accompanied by a return of hypocalcemic symptoms. The patient was then maintained on a daily dose of 372 mg of iv calcium for 7 d, in addition to her oral calcium replacement. A 24-h urine calcium collection was obtained and 25 mg of hydrochlorothiazide daily was begun after the collection was complete. However, this was discontinued after two doses, when the patient's urine calcium was found to be 42 mg/24 h (urine creatinine 600 mg/24 h). Intravenous calcium was discontinued when the patient's calcium stabilized at 6 mg/dL. The patient's calcium supplementation was finally changed from calcium carbonate to 1800 mg of calcium citrate daily. Oral magnesium supplementation was also continued. The patient's serum calcium slowly rose to 7–7.2 mg/dL and remained at that level at the time of her discharge 9 d later. Five months after her discharge, the patient suffered an additional pathologic fracture of the left humerus. However, she has had no further hypocalcemia over a 7-mo period of follow-up. Her serum calcium levels have ranged between 8.4 and 9.0 mg/dL on 1800 mg of calcium citrate and 0.5 μg of calcitriol daily.

Discussion

Malignant bone disease is mediated by humoral and paracrine factors, which cause a pathologic stimulation of osteoclasts. Humoral factors, such as PTH-related protein, are produced by tumor cells and act to increase osteoclast activity. In addition, invasion of bone by tumor cells is

Table 1
Serum Calcium Levels during Patient's Hospitalization, with Patient's Symptoms and Treatment Noted[a]

Hospital day	Calcium (mg/dL)	Magnesium (mg/dL)	Phosphorus (mg/dL)	Albumin (g/dL)	Other	Oral calcium and vitamin D	Intravenous calcium (elemental)
1	4.3	1.5	4.4	2.1	Patient with severe sxs, Ca^{++} 1.79	1 g $CaCO_3$ TID and 0.25 μg calcitriol BID	186 mg bolus, 1116 mg infusion
2	5.5	1.9	4.3			1 g $CaCO_3$ TID and 0.25 μg calcitriol BID	
3	5.2	1.8	4.9	2.2		1 g $CaCO_3$ TID and 0.25 μg calcitriol BID	
4	4.8	1.7	4.9		PTH 17, 25vitD 36, 1,25vitD 51	1 g $CaCO_3$ TID and 0.25 μg calcitriol BID	
5	4.7	1.7	5.4	2.4	Ca^{++} 2.60	1 g $CaCO_3$ TID and 0.25 μg calcitriol BID	
6	4.3	1.6	5.9		Patient with severe sxs	1.5 g $CaCO_3$ TID and 0.5 μg calcitriol BID	186 mg bolus, 1395 mg infusion
7	5.9	1.8	5.7	2.4		1.5 g $CaCO_3$ TID and 0.5 μg calcitriol BID	
8	4.7	1.7	5.5		Patient with mild sxs	1.5 g $CaCO_3$ TID and 0.5 μg calcitriol BID	930 mg infusion
9	5.2	1.6	5.0			1.5 g $CaCO_3$ TID and 0.5 μg calcitriol BID	372 mg infusion
10	5.9	1.7	4.8	2.3		1.5 g $CaCO_3$ TID and 0.5 μg calcitriol BID	372 mg infusion
11	5.6	1.8	4.7		Urine Ca, 42 mg/24 h	1.5 g $CaCO_3$ TID and 0.5 μg calcitriol BID	372 mg infusion
12	4.9	1.8	5.1	2.4		1.5 g $CaCO_3$ TID and 0.5 μg calcitriol BID	372 mg infusion
13	6.0	1.8	5.2			1.5 g $CaCO_3$ TID and 0.5 μg calcitriol BID	372 mg infusion
14	6.0					1.5 g $CaCO_3$ TID and 0.5 μg calcitriol BID	372 mg infusion
15	5.8					1.5 g $CaCO_3$ TID and 0.5 μg calcitriol BID	372 mg infusion
16	6.1	2.0				600 mg Ca citrate TID and 0.5 μg calcitriol BID	
17	5.9	2.0				600 mg Ca citrate TID and 0.5 μg calcitriol BID	
18	6.6	2.2	4.9			600 mg Ca citrate TID and 0.5 μg calcitriol BID	
19	6.8	2.2	5.0	2.4		600 mg Ca citrate TID and 0.5 μg calcitriol BID	
20	7.2	2.1	4.9			600 mg Ca citrate TID and 0.5 μg calcitriol BID	
21	7.0	2.0	4.6			600 mg Ca citrate TID and 0.5 μg calcitriol BID	
22	7.7	2.0	4.8			600 mg Ca citrate TID and 0.5 μg calcitriol BID	
23	7.7	2.0	4.8			600 mg Ca citrate TID and 0.5 μg calcitriol BID	
24	7.9	2.0	5.0			600 mg Ca citrate TID and 0.5 μg calcitriol BID	
25					d/c	600 mg Ca citrate TID and 0.5 μg calcitriol BID	

[a]Ca, calcium; Ca^{++}, ionized calcium; PTH, parathyroid hormone; 25vitD, 25-hydroxyvitamin D; 1,25vitD, 1,25-dihydroxyvitamin D; urine Ca, 24-h urinary calcium excretion; sxs, symptoms; d/c, discharge from hospital. Normal ranges: calcium, 8.4–10.2 mg/dL; magnesium, 1.6–2.6 mg/dL; phosphorus, 2.7–4.5 mg/dL; albumin, 3.5–5.0 mg/dL; ionized calcium, 4.44–5.24 mg/dL; PTH, 12–72 pg/mL; 25-hydroxyvitamin D, 8.9–46.7 ng/mL; 1,25-dihydroxyvitamin D, 6–62 pg/mL; 24-h urinary calcium, 100–300 mg/24 h.

associated with production of cytokines or other factors that activate osteoclasts *(3,5,6)*. The net result of these forces is often hypercalcemia of malignancy. There is a similar impairment of the balance between bone resorption and bone formation, even in normocalcemic malignant bone disease. Osteolysis is predominant even if areas of new bone formation can be identified histologically. This complex balance of hormonal and paracrine factors affects the milieu of the osteoclast. In the setting of malignancy, this balance is such that bone resorption is favored.

Pamidronate has been well established as a therapeutic agent for patients with malignant hypercalcemia, but its use is now becoming part of the care of normocalcemic cancer patients because of the bone-preserving benefits of osteoclast inhibition. In such patients, it has been used for the purpose of reducing pain and other skeletal complications owing to bone metastases. Pamidronate inhibits abnormal bone resorption by its inhibitory effect on osteoclasts *(8)*. Accelerated osteolysis and an inflammatory response also contribute to the development of bone pain. Bisphosphonates seem to reduce bone pain by inhibiting the osteoclastic process and exerting an antiinflammatory effect *(3)*.

Hypocalcemia is a recognized adverse effect of pamidronate, particularly in the setting of normocalcemia. In a multinational trial of pamidronate to delay the progression of bone metastases in breast cancer patients, the reported rate of asymptomatic hypocalcemia was 16% *(4)*. However, given that calcium levels are not routinely monitored or reported in some trials, the true rate of asymptomatic hypocalcemia is hard to establish. Symptomatic hypocalcemia, on the other hand, appears to occur less frequently. Clinical trials of pamidronate for reduction of osteolytic bone destruction in patients with breast cancer and multiple myeloma report rates of symptomatic hypocalcemia varying from 0 to 0.5% *(2,4)*. An oncology unit that administered 181 doses of pamidronate over a 12-mo period reported an incidence of symptomatic hypocalcemia of 1.7% *(13)*.

There are a handful of case reports in the literature describing symptomatic hypocalcemia following pamidronate administration *(13–18)*. A review of these case reports illustrates the time course and duration of pamidronate-induced hypocalcemia. Most cases of symptomatic hypocalcemia appear to occur about 1 wk after pamidronate administration, although cases as early as 4 d *(15)* and as late as 24 d have been seen *(14)*. This corresponds with the nadir observed at 6 d with pamidronate treatment of hypercalcemia *(19)*. The duration of normocalcemia after treatment of hypercalcemia ranges from 2 wk to 3 mo *(20,21)*. This again corresponds to the duration of hypocalcemia that has been reported, which varies from several weeks *(13,15)* to 3 mo *(14)*. Our patient's hypocalcemia began about a week after pamidronate was given and continued for approximately 8 wk, despite aggressive calcium replacement.

These previously mentioned case reports also highlight risk factors for developing hypocalcemia. When the use of a bisphosphonate results in a decline in calcium level, calcium homeostasis appears to be maintained by two counterregulatory hormones: PTH and 1,25-hydroxyvitamin D *(22,23)*. The serum levels of these hormones increase following bisphosphonate treatment. Individuals with chronic renal failure are known to be susceptible to hypocalcemia following pamidronate administration *(7)*. This is probably because of a combination of delayed renal clearance of pamidronate and a blunted 1,25-dihydroxyvitamin D response to hypocalcemia. The response of PTH levels to pamidronate-induced alterations in calcium homeostasis is illustrated by one case report *(24)*. The patient described was initially hypercalcemic with a subnormal PTH level. He developed hypocalcemia associated with a PTH level increasing to within the normal range. His PTH level subsequently decreased to a low-normal range as his serum calcium returned to the upper limits of normal.

Thus, it appears that adequate parathyroid function is one means of protection from hypocalcemia after bisphosphonate therapy. Our patient had a history of hypoparathyroidism. PTH levels prior to pamidronate administration are not available, but she had maintained a low-normal calcium level with modest calcium and vitamin D supplementation. At a time when her serum calcium was clearly low (4.8 mg/dL), she had an inappropriately normal PTH level of 17 pg/mL. Similarly, Sims et al. *(14)* have reported a case of prolonged symptomatic hypocalcemia with pamidronate in a patient with subclinical hypoparathyroidism. This patient experienced symptomatic hypocalcemia for about 60 d *(14)*, despite being hypercalcemic prior to pamidronate administration. The importance of PTH in preventing hypocalcemia in such patients is also demonstrated by another case report in which a patient with breast carcinoma, with bone metastases and subclinical hypoparathyroidism, developed symptomatic hypocalcemia following administration of pamidronate. Comlekci et al. *(15)* postulate that in this patient, hypocalcemia, owing to latent hypoparathyroidism, was compensated by extensive osteolysis because of bone metastasis, and administration of pamidronate impeded this process, leading to symptomatic hypocalcemia *(15)*. All these cases illustrate the importance of having a normal parathyroid reserve to augment PTH levels and thereby maintain normal calcium levels upon administration of pamidronate.

In addition to awareness of possible hypoparathyroidism and vitamin D deficiency, other precautions might provide protection from hypocalcemia with the use of pamidronate. One of the reported cases of hypocalcemia occurred in an individual whose initial serum calcium level was below the normal range *(15)*. Data are not available as to whether patients developing symptomatic hypocalcemia, while enrolled in clinical trials of pamidronate, had low or low-normal baseline calcium levels *(2,4)*. We suspect that our patient had a low-normal serum calcium level at the time she received pamidronate. Adequate calcium and vita-

min D supplementation, especially in individuals with low-normal calcium levels, might prevent symptomatic hypocalcemia. Unfortunately, our patient's calcium and vitamin D supplementation had been inadvertently omitted after she was given pamidronate. Hypomagnesemia is thought to inhibit the peripheral actions of PTH *(12)*, therefore, a magnesium deficiency at the time of pamidronate administration might also exacerbate hypocalcemia. Baseline measurement and periodic monitoring of calcium and magnesium levels would, therefore, appear to be indicated.

Awareness of other medications that may contribute to the development of hypocalcemia might also be helpful. For instance, our patient was taking salmon calcitonin, which is known to be a potent inhibitor of osteoclast action *(9)*, and is, in fact, used to treat hypercalcemia. Another class of agents may also be associated with increased risk of hypocalcemia after bisphosphonate administration. There are at least two case reports of symptomatic hypocalcemia following combined use of bisphosphonates and aminoglycosides *(25,26)*; one of these cases had a fatal outcome *(25)*. Aminoglycosides are known to increase renal tubular loss of calcium and magnesium. Presumably the renal calcium wasting antagonizes the counterregulatory effect of PTH to increase renal calcium reabsorption, thereby removing one of the avenues by which PTH acts to maintain normocalcemia.

Although our patient was an ideal candidate for pamidronate, based on her malignant bone disease, the importance of risk factors for hypocalcemia are clearly illustrated in her case. There were several possible reasons for her prolonged and persistent hypocalcemic response to pamidronate. She obviously had diminished parathyroid function as a result of presumed parathyroid damage following her neck surgeries. In addition, the effect of calcitonin and bisphosphonates to inhibit osteoclast-mediated calcium mobilization was likely combined. Initially, vitamin D deficiency, and the resultant compromised absorption of dietary calcium, was suspected in this hypoparathyroid, malnourished, bed-bound patient. However, vitamin D deficiency was not confirmed; our patient, in fact, had normal vitamin D levels (*see* Table 1). This patient was not known to have achlorhydria or any other condition known to decrease gastrointestinal absorption of calcium. However, in the face of persistently low calcium levels, attempts were made to potentially improve absorption by using calcium citrate as the patient's calcium supplementation. The patient initially refused this change. When calcium citrate was finally initiated the patient's calcium levels did begin to stabilize. However, this occurred 7 wk after the patient's pamidronate dose and could also be attributed to a waning of pamidronate's effect. Reducing urinary calcium losses by using a diuretic was also not an avenue available to help maintain normocalcemia in our patient. Pamidronate is known to be associated with a decrease in the fractional excretion of calcium *(24)*. Hypoparathyroidism can be associated with renal calcium wasting. Despite her hypoparathyroidism, our patient's urinary calcium losses were not significant enough that hydrochlorothiazide would likely have improved calcium balance.

Hypocalcemia is a potentially serious and life-threatening condition. Along with paresthesias, carpopedal spasms, laryngeal spasms, and convulsions, prolongation of the QT interval leading to fatal arrythmias is possible. Given our case and the others we have discussed, and given the increasing use of pamidronate in normocalcemic patients, potential ways of protecting patients from hypocalcemia may need to be considered. Baseline calcium and magnesium measurements would be prudent. Calcium supplementation could be considered in individuals with low-normal serum calcium levels. Awareness of hypoparathyroidism, vitamin D deficiency, or renal insufficiency would also be important. Other medications that might potentially exacerbate hypocalcemic events, such as aminoglycosides or calcitonin, could be discontinued. Finally, patient education regarding the symptoms of hypocalcemia and routine monitoring of serum electrolytes would be invaluable for preventing potentially catastrophic situations. Bisphosphonates should be used cautiously for metastatic bone disease in patients with hypoparathyroidism or other risk factors for development of hypocalcemia.

Methods

PTH was measured by a double-antibody immunometric assay using a chemiluminescent substrate. The assay is highly specific for the intact PTH molecule. Both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were measured by radioimmunoassay. Frozen serum samples were submitted for all assays. All assays were performed by American Medical Laboratories.

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