Symptomatic Hypocalcemia in a Patient with Latent Hypoparathyroidism and Breast Carcinoma with Bone Metastasis Following Administration of Pamidronate

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Pamidronate is an effective drug used not only in patients with tumor-associated hypercalcemia, but also in normocalcemic patients with metastatic bone disease to relieve pains. We describe a 39-year-old normocalcemic patient with subclinical hypoparathyroidism and bone metastasis due to breast carcinoma. Following parenteral administration of 60 mg pamidronate, the corrected serum level of calcium decreased from 2.12 mmol/l (=8.9 mg/dl) to 1.42 mmol/l (5.7 mg/dl), accompanied with carpal pedal spasm. The present case indicates that the hypocalcemia due to latent hypoparathyroidism was compensated by extensive osteolysis due to bone metastasis, and that overt hypocalcemia may develop after intravenous administration of pamidronate in such a patient.

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Key words: bisphosphonate, malignancy

Introduction

Bone metastases are a common cause of morbidity in patients with malignancy. Bisphosphonates are being used to treat not only patients with tumor-associated hypercalcemia, but also normocalcemic patients with metastatic bone disease to relieve pain. Here, we describe a 39-year-old female patient with symptomatic hypocalcemia after pamidronate administration.

Case Report

A 39-year-old female patient was admitted to hospital because of spontaneous carpal pedal spasm, and muscle cramps. She had advanced breast carcinoma with extensive bone metastases, for which she underwent chemotherapy in six sessions. She had received palliative radiotherapy at the right femur, acetabulum, and cervical vertebra. As she had been suffering from severe bone pain, 60 mg pamidronate (Aredia®) was administrated intravenously for alleviating bone pain when she was on radiotherapy. Laboratory studies before the administration of pamidronate were as follows: serum calcium: 2.12 mmol/l (normal range (NR): 2.30–2.80) (8.5 mg/dl), phosphate: 2.22 mmol/l (NR: 1.0–1.4), alkaline phosphatase: 437 U/l (NR: 41–133), serum albumin: 36 g/l (NR: 35–55), blood urea nitrogen (BUN): 5.3 mmol/l (NR: 3.6–7.1), creatinine: 97.2 μmol/l (NR: <133). All of these biochemical tests were assayed simultaneously in serum samples using a DACOS autoanalyzer with commercial reagents supplied by Biomerieux Diagnostics. On the first day after the administration of pamidronate she had perioral and fingertip paresthesia and on the fourth day she was admitted to the hospital because of spontaneous carpal pedal spasm. Her blood pressure was 90/60 mmHg, and pulse rate, 88/min. Except for the spontaneous carpal pedal spasm, the remainder of the physical examination was unremarkable. Laboratory data on admission were as follows: serum calcium: 1.32 mmol/l (5.3 mg/dl), serum phosphate: 1.96 mmol/l, albumin: 32 g/l, magnesium: 0.9 mmol/l (NR: 0.8–1.2), serum alkaline phosphatase: 430 U/l, serum parathyroid hormone: 13 pg/ml (NR: 9–55). All of these laboratory parameters were measured in simultaneously obtained serum samples. A coated-tube immunoradiometric assay kit was used for quantitative measurement of intact parathyroid hormone (Diagnostic Systems Laboratories Inc., Frankfurt, Germany).

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Calcium gluconate (40 mmol) was infused over four hours and the signs and symptoms were improved. When the previous laboratory studies were examined carefully, it was noticed that the patient had mild hypocalcemia and hyperphosphatemia consistent with hypoparathyroidism before pamidronate treatment. She was treated with calcitriol 1 μg/day and calcium 3 gm/day and on the seventh day of therapy serum calcium, phosphate, and alkaline phosphatase (ALP) were 2.43 mmol/*l*, 2.22 mmol/*l*, and 438 U/*l* respectively. After then she was advised to take calcitriol 0.5 μg/day and 1 gm calcium/day.

Discussion

Patients with advanced breast cancer can not be cured and nowadays treatment aims primarily at palliation of the symptoms. Approximately 70% of the patients develop symptomatic bone metastases. These are a major cause of pain, pathologic fractures, hypercalcemia, and neurologic complications, which require frequent treatment (1, 2). Bisphosphonates are being used not only in patients with tumor-associated hypercalcemia, but also in normocalcemic patients with metastatic bone disease to relieve pain and skeletal morbidity (2). Pamidronate is one of the drugs which has been most extensively studied. In recent reports it has been shown to be effective in reducing bone pain and skeletal morbidity (1–3).

Bisphosphonates are non-biodegradable synthetic analogues of pyrophosphate which inhibit bone resorption (4, 5). Bisphosphonates not only impair the maturation of osteoclast precursors to mature osteoclasts (4, 6), but also have direct toxic effects on osteoclasts (4, 7). They decrease the osteoclast activity by decreasing acid production, lysosomal and other enzymes, prostaglandin formation and membrane permeability (4). Bisphosphonates also decrease the number of osteoclasts by decreasing recruitment and increasing apoptosis (4). The potency and the side effects of bisphosphonates varies widely with different compounds. It is reported that newer generation bisphosphonates have minor side effects on mineralization (4, 5).

While serum calcium levels frequently fall to the lower limit of normality following administration of high doses of oral (1,200 mg) and intravenous (30–90 mg) pamidronate to patients with Paget's disease or hypercalcemia of malignancy, symptomatic hypocalcemia has only been rarely reported (3, 8, 9). In general in patients who do not have significantly disturbed bone metabolism, preservative mechanisms sustain calcium levels near the normal range (10, 11). However, patients with disturbed bone metabolism such as chronic renal failure and hypoparathyroidism, have the risk of developing symptomatic hypocalcemia as they have disturbed parathyroid hormone and 1,25-(OH)2D response to hypocalcemia when bone resorption is inhibited with bisphosphonates. It seems that our patient had primarily subclinical hypoparathyroidism, as she had no history of operation in the neck region or irradiation to the neck and no sign of metastasis to the cervical region. Probably, the hypocalcemia was partially balanced by increased osteolysis from metastatic bones in this patient. Following inhibition of bone resorption with pamidronate, severe symptomatic hypocalcemia developed since she had a disturbed parathyroid hormone and 1,25-(OH)2D response to hypocalcemia.

It is important not to overlook or neglect the important information obtained from the routine clinical tests. Despite the fact that bisphosphonate-associated symptomatic hypocalcemia is rare, all patients with non-hypercalcemic bone disease should be carefully examined before bisphosphonate treatment due to the possibility of preexisting subclinically disturbed calcium metabolism.

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