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# Disodium pamidronate for treating severe hypercalcemia in a hemodialysis patient

**Hernán Trimarchi*, Fernando Lombi, Mariano Forrester, Cristina Elizondo, Deirdre Sawinski, Horacio Pereyra and Emilio Freixas**


## SUMMARY

**Background** A 48-year-old man with a recent diagnosis of multiple myeloma and rapidly progressive oliguric end-stage renal disease requiring hemodialysis, presented with a serum calcium concentration of 3.4 mmol/l (13.6 mg/dl).

**Investigations** Serum laboratory analysis, electroencephalogram, MRI of the brain and bone marrow, and kidney biopsies.

**Diagnosis** Hypercalcemia secondary to multiple myeloma.

**Management** Short-term intravenous disodium pamidronate therapy (30 mg daily) and daily monitoring of serum calcium concentration.


**KEYWORDS bisphosphonates, hemodialysis, hypercalcemia, multiple myeloma, pamidronate**

**CME**

*H Trimarchi is a nephrologist, Chief of the Renal Section and Renal Transplant Unit and Associate Director of the Renal-Pancreas Transplant Unit, Department of Medicine, Hospital Británico de Buenos Aires, Argentina, and also a Fellow of the American College of Physicians. F Lombi is a nephrology fellow, M Forrester and H Pereyra are specialists in Internal Medicine and nephrologists in the Division of Nephrology, C Elizondo is a resident of the Internal Medicine Service, and E Freixas is Chief of the Internal Medicine Service and a nephrologist, all at the Hospital Británico de Buenos Aires, Argentina. D Sawinski is a resident of Internal Medicine, Columbia University Medical Center, New York, NY, USA.*

**Correspondence**
*Hospital Británico de Buenos Aires, Perdriel 74 (1280), Buenos Aires, Argentina
htrimarchi@hotmail.com

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## THE CASE

A 48-year-old man with a history of hypertension, hyperlipidemia, and tobacco use presented with generalized fatigue, diffuse bone pain, oliguria and a serum creatinine level of 2,033.2 μmol/l (23 mg/dl). Urinalysis detected Bence–Jones proteinuria with kappa light chains. Two serum electrophoretic proteinograms did not show M components. A bone marrow biopsy was consistent with multiple myeloma and a renal specimen revealed myeloma involvement. Hemodialysis and chemotherapy (vincristine sulphate, doxorubicin hydrochloride [previously known as adriamycin®, Pharmacia & Upjohn, Milan, Italy] and dexamethasone) were started. A surveillance bone marrow biopsy showed that the tumor mass had regressed to 15–20% of its original size. The chemotherapeutic regimen was discontinued after 3 months because of seizures secondary to reversible multi-focal leukoencephalopathy.

Six months later, the patient developed confusion, anorexia, weight loss and fatigue. He had a serum calcium level of 3.4 mmol/l (13.6 mg/dl), corrected to 3.6 mmol/l (14.4 mg/dl) for a serum albumin level of 30 g/l (normal serum calcium: 2.05–2.55 mmol/l [8.2–10.2 mg/dl]). The patient had no history of hypercalcemia; previous calcium levels in the patient ranged from 2.10 mmol/l to 2.40 mmol/l (8.4–9.6 mg/dl). At presentation, he had a serum phosphorus concentration of 2.2 mmol/l (normal: 0.74–1.52 mmol/l), serum parathyroid hormone (PTH) level of 24 ng/l (normal: 10–50 ng/l]) and a hematocrit of 0.42 (normal: 0.41–0.50). The patient was on 1,200 mg sevelamer daily, 10 mg folic acid daily and 20 mg omeprazole daily. An electroencephalogram was consistent with metabolic disarray, but a brain MRI was unrevealing.

On three consecutive days, 30 mg of disodium pamidronate diluted in 300 ml of normal saline



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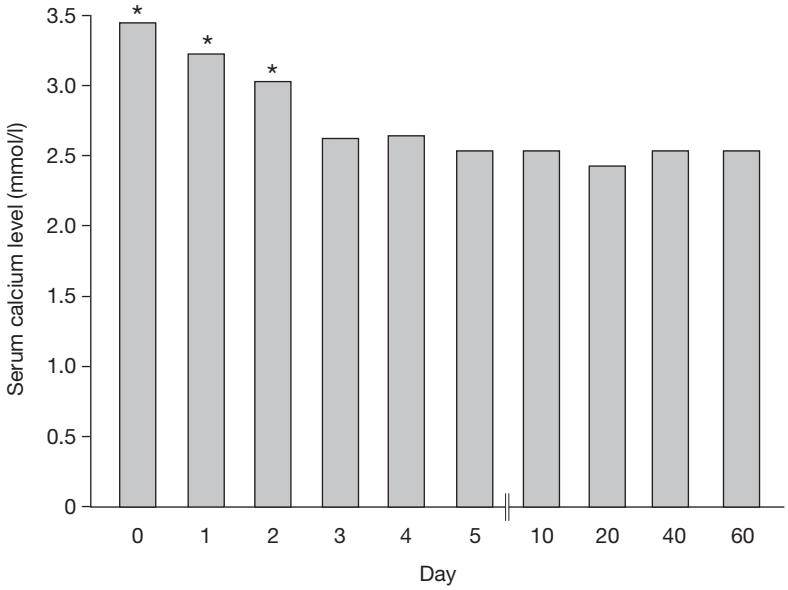


**Figure 1** Decrease in the patient's serum calcium levels after disodium pamidronate administration. *, disodium pamidronate infusion.

were administered intravenously over a period of 30 min. Low dialysate fluid calcium concentrations (1.5 mEq/l [0.75 mmol/l]) were used in hemodialysis. Serum calcium levels were closely monitored. An immediate, steady and sustained decrease in serum calcium level was observed after the pamidronate infusion was started (Figure 1). After 3 days of treatment the patient's serum calcium concentration was 2.65 mmol/l (10.6 mg/dl). Dialysis sessions were rescheduled to occur every other day with a dialysate calcium concentration of 1.5 mEq/l (0.75 mmol/l). The patient improved symptomatically. After 2 months of follow-up, calcium, phosphate and PTH levels were within normal limits. Sevelamer 1,200 mg/day was administered as a phosphate binder. Chemotherapy could not be restarted because of hepatotoxicity; methylprednisone remained the main treatment for the myeloma.

## DISCUSSION OF DIAGNOSIS

Hypercalcemia is diagnosed if the serum calcium concentration exceeds 2.63 mmol/l (10.5 mg/dl) or the ionized calcium concentration is greater than 1.2 mmol/l (4.8 mg/dl). Hypercalcemia must be distinguished from pseudohypercalcemia.[1] Pseudohypercalcemia occurs when the serum calcium level is elevated because of an increased concentration of albumin or paraproteins, but ionized calcium level is unaffected. Pseudohypercalcemia is rare and can occur when paraproteins bind calcium with high affinity. This might lead to a marked increase in total plasma calcium concentration. A lack of associated symptoms indicate that the ionized fraction is normal and is a major diagnostic criterion for pseudohypercalcemia. Therapy is unnecessary in this setting.[2]

The principal causes of hypercalcemia, the most frequent of which are primary hyperparathyroidism and cancer, are summarized in Box 1. Malignancies most commonly associated with hypercalcemia are breast cancer, squamous cell carcinoma of the lung, and multiple myeloma.[1] There are three main mechanisms by which malignancies cause hypercalcemia: production of parathyroid hormone-related peptide (PTH-rP), osteolytic metastasis, and calcitriol synthesis.

The most common mechanism of hypercalcemia in patients with non-metastatic solid tumors, and in some patients with non-Hodgkin's lymphoma, is secretion of PTH-rP. This is also known as humoral hypercalcemia of malignancy.[3] PTH levels are typically low in this setting. PTH-rP is expressed in many different non-neoplastic tissues, with multiple physiological roles.[4] PTH-rP and PTH bind to the same receptor; they both increase bone resorption, distal tubular calcium reabsorption and phosphaturia, but PTH-rP is unlikely to stimulate calcitriol production. Increased tubular calcium reabsorption is thought to have a more important role in the genesis of hypercalcemia.

In multiple myeloma, hypercalcemia is mainly caused by interleukin-6 and tumor necrosis factor α. These cytokines cause a dysregulation in bone remodeling. Myeloma cells activate genes that both stimulate bone resorption via osteoclast activation and prevent new bone creation by inhibiting osteoblasts.[5] A particularly important mechanism of regulation involves the receptor activator of nuclear factor kappa B ligand (RANKL). When RANKL binds to receptors on osteoclasts, it activates differentiation in these cells. Serum levels of RANKL are increased in multiple myeloma and this leads to the formation of lytic lesions. Myeloma cells secrete not only RANKL, but also Dickkopf homolog 1 (DKK1), a molecule that inhibits bone formation.[6] Serum creatinine levels are elevated in approximately 50% of myeloma patients but hypercalcemia is diagnosed in 25% of myeloma cases.[5]



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In Hodgkin's disease, and in approximately one-third of cases of non-Hodgkin's lymphomas, hypercalcemia might occur as a result of vitamin D secretion or because of a bone-resorbing factor produced by the neoplastic lymphoid cells, and usually responds to glucocorticoid therapy.[7] The frequency of hypercalcemia in patients with hematologic malignancies, mainly Hodgkin's and non-Hodgkin's lymphomas, is approximately 14%.[5]

Chronic renal insufficiency is often characterized by hypocalcemia. Hypocalcemia starts to develop as phosphate levels increase, vitamin D synthesis decreases and PTH levels rise, causing secondary hyperparathyroidism. In certain circumstances, however, hypercalcemia can occur in patients with renal failure (Box 2). With the current use of calcium-containing phosphate binders and of vitamin D therapy in chronic dialysis patients, the prevalence of hypercalcemia in patients with chronic renal impairment is increasing, with estimates ranging from 10% to 35%. In addition, the hypercalcemia caused by diseases such as sarcoidosis, multiple myeloma, immobilization, and milk–alkali syndrome, usually causes renal failure.

We believe that in the patient presented here, the hypercalcemia was secondary to multiple myeloma progression, as the patient was not receiving calcium-containing phosphate binders or vitamin $D_3$. Symptoms ascribed to hypercalcemia are non-specific and do not correlate directly with increasing serum calcium levels. They do usually occur, however, when serum calcium levels exceed 3 mmol/l (12 mg/dl). Fatigue, depression, altered mental status, anorexia, nausea, vomiting, constipation, polyuria, and cardiac arrhythmias have all been observed.[8]

**Box 1** Causes of hypercalcemia.

**1) Increased intestinal calcium absorption**

Increased calcium ingestion with decreased excretion
- Chronic renal insufficiency
- Milk–alkali syndrome

Hypervitaminosis D
- Ingestion of vitamin D derivatives
- Granulomatous diseases
- Lymphoma

**2) Increased bone resorption**

Primary hyperparathyroidism
Secondary hyperparathyroidism
Malignancy
Immobilization
Hypervitaminosis A

**3) Miscellaneous**

Ingestion of pharmacologic agents (e.g. lithium, thiazides, theophylline, aluminum)
Acute renal insufficiency due to rhabdomyolysis
Adrenal insufficiency
Pheochromocytoma
Familial hypocalciuric hypercalcemia

**Box 2** Circumstances in which hypercalcemia can occur in patients with chronic renal failure.

- High doses of calcium salts are given as phosphate binders
- Vitamin D therapy is given to decrease PTH levels
- Calcium is released from bone due to PTH-rP (malignant hypercalcemia)
- Autonomous PTH secretion (primary or tertiary hyperparathyroidism)
- Autocrine cytokine secretions (multiple myeloma)

Abbreviations: PTH, parathyroid hormone; PTH-rP, parathyroid hormone-related peptide.

## DISCUSSION OF MANAGEMENT

The aim of initial treatment for hypercalcemia is to restore intravascular volume depletion and to promote hypercalciuria. In patients with adequate cardiovascular and renal function this is usually accomplished with 0.9% normal saline infusions at 300–500 ml/h until fluid deficit is restored. Loop diuretics, such as furosemide or torasemide, are concomitantly used to keep balance with fluid administration and to increase urinary calcium excretion. Steroids, such as prednisolone and methylprednisolone, are useful only in certain hypercalcemic conditions, such as granulomatous diseases in which vitamin D has a main role. Administration of calcitonin is of limited use, particularly for prolonged periods of time, because of tachyphylaxis.

In patients with renal failure, treatment options are reduced. Hemodialysis is the mainstay treatment for decreasing serum calcium levels in these patients, and in those with heart failure or those who are resistant to all other standard treatments. As in the case presented here, dialysis might not be sufficient to rapidly



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correct hypercalcemia, even though low dialysate calcium concentrations (1.5 mEq/l [0.75 mmol/l]) were used. Unless patients are treated with daily dialysis sessions, the beneficial effects might not be long-lasting. In this setting, the bisphosphonate disodium pamidronate might be given alone or as a complement to other treatments. Because there was a lack of response to hemodialysis, and because there was an immediate decrease in serum calcium levels after pamidronate infusion, we believe pamidronate was the cause of the hypercalcemia correction in the case presented here.

Bisphosphonates attach to bony surfaces, exerting physicochemical effects very similar to those of polyphosphates. Bisphosphonates bind to the surface of calcium phosphate crystals and inhibit osteoclast formation, aggregation and dissolution. They impair the capacity of osteoclasts to form the ruffled border, to adhere to the bone surface and to produce the protons necessary for bone resorption, and they reduce osteoclast survival by promoting apoptosis.[9] Bisphosphonates are excreted unchanged by glomerular filtration and by active tubular secretion.[10] Disodium pamidronate administration has been associated with proteinuria and renal insufficiency resulting from collapsing focal segmental glomerulosclerosis.[11] Physicians should be aware of these complications when considering long-term treatment with bisphosphonates in hemodialysis patients.

The standard daily infusion dose of disodium pamidronate for the treatment of hypercalcemia in patients with normal renal function is 60–90 mg over 2–4 h. Little is known about the effect of bisphosphonates in patients with renal failure, and these drugs should be used with caution in this population until more data are available. We, therefore, advise using lower doses of disodium pamidronate (30 mg/day) in dialysis patients until more is known about their effects in patients with renal failure. Disodium pamidronate appears to reduce calcium levels for prolonged periods of time, and hypocalcemia, which would increase PTH levels, might be an adverse complication. Although one study revealed that intravenous disodium pamidronate aggravated secondary hyperparathyroidism,[12] Torregrosa *et al.* showed that, for short periods of time, disodium pamidronate is a safe and effective treatment for the correction of hypercalcemia due to secondary hyperparathyroidism in chronic dialysis patients.[13] In patients with renal failure, the effects of pamidronate seem to be rapid but longer-lasting than in the general population; this might be because the drug is excreted through the kidney. Zoledronic acid (4 mg intravenously over 15 min) is superior to disodium pamidronate for the treatment of cancer-related hypercalcemia, but the former drug has not yet been tested in dialysis patients.[14]

Bisphosphonates are also used in the treatment and prophylaxis of Paget's disease, tumor bone disease, and osteoporosis.[9,10] Bisphosphonates should not only be considered for the treatment of hypercalcemia in renal failure patients, but should also be assessed in randomized clinical trials to improve bone density in dialysis patients, a population in which bone fractures are more common than in the general population.[15]

## CONCLUSION

Intravenous disodium pamidronate might be safe, rapid and effective for treating hypercalcemia in hemodialysis patients, as described in the present case; calcium levels decreased after infusions of disodium pamidronate and remained within normal limits, and the patient's hypercalcemia-related symptoms resolved. Nevertheless, the effects of disodium pamidronate are long-lasting and this bisphosphonate might cause serious complications in patients with renal failure; until more data are available, it should be used with caution in this population.

### References

1 Barri YM *et al.* (1996) Hypercalcemia and electrolyte disturbances in malignancy. *Hematol Oncol Clin North Am* **10:** 775–790
2 Pearce CJ *et al.* (1991) Hypercalcemia due to calcium binding by a polymeric IgA Kappa paraprotein. *Ann Clin Biochem* **28:** 229–234
3 Ratcliffe WA *et al.* (1992) Role of assays for parathyroid-hormone-related protein in the investigation of hypercalcaemia. *Lancet* **339:** 164–167
4 Strewler GJ (2000) The physiology of parathyroid hormone-related protein. *N Engl J Med* **342:** 177–185
5 Rajkumar V and Kyle R (2005) Multiple myeloma: diagnosis and treatment. *Mayo Clinic Proc* **80:** 1371–1382
6 Glass DA *et al.* (2003) A new insight into the formation of osteolytic lesions in multiple myeloma. *N Engl J Med* **349:** 2479–2480
7 Scheinman SJ *et al.* (1991) Hypercalcemia with excess serum 1,25 dihydroxyvitamin D in lymphomatoid granulomatosis/angiocentric lymphoma. *Am J Med Sci* **301:** 178–181
8 Popovtzer M *et al.* (1992) Disorders of calcium, phosphorus, vitamin D, and parathyroid hormone activity. In *Renal and Electrolyte Disorders*, edn 4, 287–369 (Ed. Schrier R) Boston: Little, Brown and Company



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9 Rodan GA and Fleisch HA (1996) Bisphosphonates: mechanisms of action. *J Clin Invest* **97:** 2692–2696
10 Fleisch HA (1998) Bisphosphonates: mechanism of action. *Endoc Rev* **19:** 80–100
11 Markowitz G *et al.* (2001) Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. *J Am Soc Nephrol* **12:** 1164–1172
12 Lu KC *et al.* (2003) Acute effect of pamidronate on PTH secretion in postmenopausal hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* **42:** 1221–1227
13 Torregrosa JV *et al.* (2003) Usefulness of pamidronate in severe secondary hyperparathyroidism in patients undergoing hemodialysis. *Kidney Int* **63 (Suppl):** S88–S90
14 Major PP and Cook R (2002) Efficacy of bisphosphonates in the management of skeletal complications of bone metastasis and selection of clinical endpoints. *Am J Clin Oncol* **25 (Suppl 1):** S10–S18
15 Lindberg J and Moe S (1999) Osteoporosis in end-state renal disease. *Semin Nephrol* **19:** 115–122

**Competing interests**
The authors declared they have no competing interests.



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