Lesson of the week

Severe hypocalcaemia after being given intravenous bisphosphonate

Rajesh Peter, Vinita Mishra, William D Fraser

Bisphosphonates are increasingly used to treat metabolic bone disease and as prophylaxis against metastatic bone cancer.[1 2] Zoledronic acid is a new intravenous bisphosphonate licensed to treat hypercalcaemia of malignancy, but it has been used off licence as prophylaxis for metastatic cancer, bone pain, treatment of osteoporosis, and Paget's disease of the bone. Zoledronic acid is 100 to 1000 times more potent than disodium pamidronate or oral alendronic acid, risedronate sodium, sodium clodronate, or disodium etidronate. A randomised controlled trial found that zoledronic acid is more effective than disodium pamidronate in treating hypercalcaemia of malignancy.[3] Zoledronic acid does not cause the gastrointestinal side effects associated with oral bisphosphonates, but increased potency carries a higher risk of hypocalcaemia. We have recent experience of patients becoming hypocalcaemic after doctors gave intravenous bisphosphonates.

Case reports

Case 1

A 49 year old man with transitional cell carcinoma of the bladder received chemotherapy with cisplatin, methotrexate, and vinblastine after resection of a tumour. His prechemotherapy adjusted calcium was normal. Despite four cycles of chemotherapy every two weeks he had bone pain due to metastases. Doctors gave him 4 mg of zoledronic acid and intravenous diamorphine after diclofenac sodium and co-proxamol failed to relieve his symptoms. His adjusted calcium six days before being given zoledronic acid was low (table).

Three days after being given intravenous zoledronic acid, he had tetanic spasms and paraesthesia. Trousseau's sign was positive and an electrocardiogram showed a long QT interval—474 ms (RR < 440 ms). His adjusted calcium was low and decreased further despite doctors giving him 50 ml of 10% calcium gluconate intravenously over six hours. His parathyroid hormone was increased, and he had low serum vitamin D. Doctors gave him 80 ml of 10% calcium gluconate over the next 24 hours and started oral chewable ergocalciferol tablets twice a day and 250 ng α calcidol once a day. After 10 days, his calcium returned within the reference range.

Case 2

A 59 year old man with carcinoma of the lung was unwell for three weeks. He had nausea, vomiting, decreased appetite, and profuse diarrhoea. At an outpatients' clinic, investigations found hypercalcaemia and low parathyroid hormone (table). Admitting doctors started him on 0.9% sodium chloride. Magnesium on admission was low. Doctors gave 4 mg of zoledronic acid, and his adjusted calcium decreased to within the reference range in five days. Two days later, he developed peri-oral paraesthesia and numbness and tingling in his extremities. Despite giving him calcium gluconate, his adjusted calcium and magnesium remained low. Doctors gave 40 mmol of magnesium sulphate over 48 hours in addition to calcium gluconate; his adjusted calcium increased into the reference range in seven days.

Case 3

A 50 year old woman was admitted with an abdominal mass. Computed tomography showing widespread lymphadenopathy indicated a non-Hodgkin's lymphoma. On admission, her adjusted calcium after chemotherapy was high, and her magnesium was within the reference range. Admitting doctors gave her 0.9% sodium chloride and frusemide for three days, but her calcium concentrations remained high until she received 60 mg of disodium pamidronate, cyclophosphamide, vincristine, and dexamethasone. Five days later she developed tetany and hypocalcaemia. Low vitamin D concentrations were detected. Doctors gave 10 ml of 10% calcium gluconate, started calcium infusions, and oral chewable ergocalciferol tablets twice a day. She received 40 ml of calcium gluconate over two days. After 15 days her calcium increased to within the reference range (table).

Severe hypocalcaemia after giving bisphosphonates may be caused by pathology interfering with parathyroid function

Department of Clinical Chemistry, Royal Liverpool University Hospital, Liverpool L69 3GA
Rajesh Peter *senior house officer*
Vinita Mishra *specialist registrar*
William D Fraser *professor*
Correspondence to: W D Fraser
w.d.fraser@liv.ac.uk

BMJ 2004;328:335–6

Serum analyte concentrations in patents given bisphosphonates

	Adjusted calcium (mmol/l)	Magnesium (mmol/l)	Parathyroid hormone (pmol/l)	Vitamin D_2 (ng/ml)	Vitamin D_3 (ng/ml)
Reference range	2.20-2.60	0.75-1.00	1.1-6.8	<10	>15
Case 1					
Before starting bisphosphonate	2.36				
6 days before starting (after chemotherapy)	2.09		21.9		
3 days after	1.17	0.70	22.4		
4 days after	1.11		35.4	<4.0	8.0
14 days after	2.36				
Case 2					
Before starting bisphosphonate	3.21	0.33	<0.7		
5 days after	2.58		<0.7		
7 days after	2.14		<0.7		
9 days after	1.48	0.38	<0.7		
11 days after	2.07	0.82	23.2		
Case 3					
Before starting bisphosphonate	2.96	0.89	<0.7		
5 days after	1.79	0.67	14.1	<4.0	5.0
15 days after	2.22	1.03	12.6		
Case 4					
Before starting bisphosphonate	4.12		<0.7		
5 days after	2.34	0.83	<0.7	<4.0	32.0
9 days after	1.66	0.92	<0.7		
19 days after	2.28	1.02	<0.7		

Case 4

A 35 year old woman with medullary carcinoma of the thyroid treated by thyroidectomy, radical neck dissection, and radioactive iodine presented acutely unwell. She was confused with headache, nausea, vomiting, fatigue, weakness, polydipsia, and polyuria. Before admission she had experienced symptoms of hypocalcaemia and had bought calcium supplements, which she had taken alongside her prescribed oral chewable ergocalciferol tablets, vitamin D, and thyroxine. She was dehydrated with prerenal uraemia (urea 20.6 mmol/l, creatinine 180 µmol/l) and had hypercalcaemia. Doctors diagnosed hypercalcaemia of malignancy and gave her 0.9% sodium chloride with 90 mg pamidronate. A day later her adjusted calcium decreased marginally, and doctors gave her another 60 mg pamidronate. Her adjusted calcium normalised within five days but continued to decrease, and her profound hypocalcaemia was associated with numbness, tingling, paraesthesia, and tetany (table). Taking 1000 ml of 10% calcium gluconate over 10 days and oral supplements of calcium and vitamin D plus α calcidol returned her calcium concentrations within the reference range.

Discussion

Several reports note patients have become hypocalcaemic after receiving bisphosphonates.[4–7] Most patients do not become hypocalcaemic because of compensatory mechanisms, the most important of which is increased secretion of parathyroid hormone.[1] The ability of the parathyroid gland to start a parathormone response and the degree of increase in parathyroid hormone prevents hypocalcaemia, due to renal reabsorption of calcium, increased vitamin D production, and stimulation of osteoclasts to resorb bone. For patients taking bisphosphonates, the effect of parathyroid hormone on resorption by osteoclasts is blocked, to an extent, depending on the potency of the bisphosphonate.

Each patient showed a different reason for the lack of a parathyroid hormone response to hypocalcaemia. We saw surgical hypoparathyroidism, hypomagnesaemic hypoparathyroidism, and pre-existing secondary hyperparathyroidism; each pathology interfered with the expected physiological response to hypocalcaemia. Lack of increase in parathyroid hormone results in reduced compensatory mechanisms. In addition, low vitamin D in two patients (cases 1 and 3) may have also contributed to hypocalcaemia and decreased synthesis of 1,25-dihydroxy vitamin D. Bone lining cells are present on the surface of bone and retract to expose the bone for osteoclasts. Parathyroid hormone or cytokines may stimulate retraction. Although little evidence shows inhibition of the activity of lining cells by bisphosphonates, such action may affect the normal calcaemic response.

Zoledronic acid is a new potent bisphosphonate with increased effectiveness, and it suppresses the formation and function of osteoclasts more than recommended doses of older bisphosphonates.[3 8] Care is needed in patients who are normocalcaemic or hypocalcaemic, with low urinary calcium filtration and excretion, because the normal effect of calcium reabsorption promoted by parathyroid hormone at the renal tubules may not be present to protect against hypocalcaemia. Also, in patients with established renal impairment, care is needed because the kidneys predominantly excrete bisphosphonates.[9]

Patients given zoledronic acid adjuvantly or for prophylactic treatment for cancer, should also be prescribed a supplement of calcium and vitamin D. This would help prevent hypocalcaemia and secondary hyperparathyroidism. Patients with pre-existing gastrointestinal disease may also experience problems as a result of malabsorption of calcium or magnesium or gastrointestinal loss of these cations and may benefit from dietary supplementation.

The effectiveness of bisphosphonates at treating hypercalcaemia has resulted in their increased use, regardless of cause. Before starting treatment with bisphosphonates or repeating prescriptions, doctors should consider the cause of hypercalcaemia and the calcium and parathyroid status of the patient. Hypercalcaemia is not usually life threatening; immediate rehydration with sodium chloride often lowers serum calcium.[10] Rehydration with sodium chloride also improves the effectiveness of bisphosphonates.[11] We recommend careful clinical and biochemical evaluation before giving the more potent and longer acting bisphosphonates, such as zoledronic acid.

Contributors: RP and VM collected information and data on the patients. RP, VM, and WDF were involved in managing the patients and wrote the article. WDF had the idea and is guarantor.

Funding: None.

Competing interests: WDF has given lectures and received funding from Boehringer Ingelheim, MSD, Novartis, Procter & Gamble, Roche, and Sanofi. WDF has acted in a consulting capacity for Boehringer Ingelheim, MSD, and Novartis.

1 Fraser WD, Logue FC, Gallacher SJ, O'Reilly DS, Beastall GH, Ralston SH, et al. Direct and indirect assessment of the parathyroid hormone response to pamidronate therapy in Paget's disease of bone and hypercalcemia of malignancy. *Bone Miner* 1991;12:113-21.
2 Vinholes J, Guo CY, Purohit OP, Eastell R, Coleman RE. Metabolic effects of pamidronate in patients with metastatic bone disease. *Br J Cancer* 1996;73:1089-95.
3 Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey JA, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double blind comparative trial. *Cancer J* 2001;7:377-87.
4 Mishra A, Wong L, Jonklaas J. Prolonged symptomatic hypocalcaemia with pamidronate administration and subclinical hypoparathyroidism. *Endocrine* 2001;14:159-64.
5 Sims EC, Rogers PB, Besser GM, Plowman PN. Severe prolonged hypocalcaemia following pamidronate for malignant hypercalcaemia. *Clin Oncol (R Coll Radiol)* 1998;10:407-9.
6 Comlekci A, Biberoglu S, Hekimsoy Z, Okan I, Piskin O, Sekeroglu B, et al. Symptomatic hypocalcaemia in a patient with latent hypoparathyroidism and breast carcinoma with bone metastasis following administration of pamidronate. *Intern Med* 1998;37:396-7.
7 McIntyre E, Bruera E. Symptomatic hypocalcaemia after intravenous pamidronate. *J Palliat Care* 1996;12:46-7.
8 Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcaemia: a pooled analysis of two randomised, controlled clinical trials. *J Clin Oncol* 2001;19:558-67.
9 Machado CE, Flombaum CD. Safety of pamidronate in patients with renal failure and hypercalcemia. *Clin Nephrol* 1996;45:175-9.
10 Hosking DJ, Cowley A, Bucknall CA. Rehydration in the treatment of severe hypercalcaemia. *Q J Med* 1981;50:473-81.
11 Harinck HI, Bijvoet OL, Plantingh AS, Body JJ, Elte JW, Sleeboom HP, et al. Role of bone and kidney in tumour-induced hypercalcaemia and its treatment with bisphosphonate and sodium chloride. *Am J Med* 1987;82:1133-42.

(Accepted 4 July 2003)