

ADVERSE DRUG REACTION

Hypoparathyroidism unmasked by alendronate

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Abstract

The case of an elderly woman is reported in whom alendronate, given for osteoporosis, led to severe hypocalcaemia a few days after starting the drug treatment. This was caused by the unmasking of previously unrecognised hypoparathyroidism.

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Alendronate is widely used in the prevention and treatment of osteoporosis. It is a bisphosphonate, which acts by inhibiting osteoclast mediated bone resorption. Gastrointestinal symptoms, oesophagitis, and oesophageal ulceration are the prominent side effects.¹

Case report

A 68 year old woman had undergone a total thyroidectomy for multinodular toxic goitre at the age of 32 years. She was on regular thyroid replacement therapy with L-thyroxine 150 µg daily. She was referred to the endocrine outpatient department in December 1998 when she complained of diffuse thoracolumbar pain aggravated by standing and on sudden movements of two months' duration. She had attained the menopause at 51 years of age. Clinically she had tenderness over the lower thoracic spine, and dorsal kyphosis. The rest of the examination was normal. Her blood count, erythrocyte sedimentation rate, serum calcium, phosphate, albumin, alkaline phosphatase, hepatic transaminase enzymes, serum protein immune electrophoresis, and 24 hour urinary calcium concentrations were normal. A thoracolumbar spine radiograph revealed osteoporotic "codfish" vertebral bodies with diffuse decrease in mineral density, an increase in the prominence of vertical striations, and prominence of the end plates. There were no vertebral fractures. The patient could not afford bone mineral density measurement. Her serum thyroid stimulating hormone, and 25-hydroxy vitamin D concentrations were normal. The patient was advised, but refused, to take hormone replacement therapy. Therefore, she was advised to take alendronate 5 mg/day, elemental calcium 1500 mg/day, and vitamin D 800 IU/day for osteoporosis. Ten days after starting alendronate she developed breathlessness, palpitations, hoarseness of voice, and spontaneous laryngeal, hand, and tongue spasms. She also had circumoral tingling, and feeling of apprehension.

Clinically she had positive Schultze, Chvostek, and Trousseau signs. Her serum ionised calcium concentration was 0.8 mmol/l (normal 1.1-1.4) and inorganic serum phosphorus 2.0 mmol/l (normal 1.0-1.4); results of thyroid function tests were normal. An electrocardiogram revealed a QTc interval of 0.54 seconds. Her serum intact parathyroid hormone concentration was 14 pg/ml (normal 10-65); this was inappropriately low for her serum calcium concentrations. The patient was managed with intravenous calcium chloride infusion for hypocalcaemia. Alendronate was discontinued. Clinical symptoms and signs of hypocalcaemia and cardiac failure resolved when serum calcium concentrations reached 1.0 mmol/l. She was discharged on calcium carbonate 3 g/day and calcitriol 0.75 µg/day.

Box 1: Learning point

Alendronate (and other bisphosphonates) may lead to symptomatic hypocalcaemia in patients with pre-existing subclinical hypoparathyroidism.

Box 2: Drugs causing hypocalcaemia*Complexing anions*

- Phosphate: oral, rectal, intravenous
- Citrate: blood transfusions, radiographic contrast
- Edetate: radiographic contrast
- Bicarbonate
- Foscarnet
- Fluoride

Inhibition of bone resorption

- Oestrogen
- Calcitonin
- Bisphosphonates
- Plicamycin
- Parathyroid related disorders
- Hypomagnesaemia: aminoglycosides, pentamidine, loop diuretics, cisplatin, amphotericin B
- Drugs: aluminium, asparaginase, doxorubicin, cytosine arabinoside, cimetidine

Vitamin D related disorders

- Vitamin D deficiency: lack of absorption cholestyramine
- Accelerated loss: phenytoin, phenobarbital
- Impaired 25-hydroxylation: isoniazid
- Target organ resistance: phenytoin

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Discussion

Prolonged or permanent hypocalcaemia may result from removal of all four parathyroid glands or from disruption of the vascular supply to the remaining tissue. Hypocalcaemia after extensive thyroid surgery may be transient or permanent.² Permanent hypoparathyroidism after total thyroidectomy is reported in 2%–13% of cases.³ Progressive dysfunction of the parathyroid gland may result in late manifestation of hypoparathyroidism.⁴

In this patient the most likely explanation of hypocalcaemia is the unmasking of pre-existing subclinical hypocalcaemia caused by hypoparathyroidism, by alendronate therapy. The duration of hypoparathyroidism is difficult to date in this patient.

Alendronate therapy leads to short term transient asymptomatic reductions in serum calcium concentrations, which is restored towards normal by parathyroid hormone release.⁵ Patients who are unable to mount a compensatory response because of pre-existing parathyroid dysfunction may present with symptomatic hypocalcaemia. Other bisphosphonates are also likely to produce similar

complication since the underlying mechanism of action is the same. Extensive literature search revealed only one other subsequent report of a similar patient.⁶

Follow up

There has been no recurrence of hypocalcaemia over a follow up period of four months. The patient continues to be on regular L-thyroxine, calcium carbonate, and calcitriol.

A learning point and a list of drugs causing hypocalcaemia are shown in boxes 1 and 2.

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- 4 Bellamy RJ, Kendall P. Unrecognized hypocalcaemia diagnosed 36 years after thyroidectomy. *J R Soc Med* 1995;**88**:690–1.
- 5 Chestnut CH III, Harris ST. Short term effect of alendronate on bone mass and bone remodeling in postmenopausal osteoporosis. *Osteoporos Int* 1993;**3**(suppl 3):S17–9.
- 6 Schussheim AH, Jacobs TP, Silverberg SJ. Hypocalcaemia associated with alendronate. *Ann Intern Med* 1999;**130**:329.

Commentary—bisphosphonates and calcium homoeostasis

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Bisphosphonates are synthetic analogues of pyrophosphate (antiscaling agents), and are mainly used in the treatment of hypercalcaemia, Paget's disease of bone, and osteoporosis. The latter is by far their most important indication with latest figures indicating that one in three women and one in 12 men over the age of 50 years will have an osteoporotic fracture.¹

Bisphosphonates decrease bone resorption by inhibiting osteoclastic activity. This is accompanied by an increase in calcium balance and in the mineral content of bone. The consequent increase in bone mass is the basis by which these compounds prevent osteoporosis in man. In hypercalcaemia of malignancy, their ability to inhibit bone resorption makes them most effective when osteolytic, rather than humoral, mechanisms are involved.² Indeed, normalisation of the calcium concentrations is often followed by transient hypocalcaemia; however, this is rarely clinically significant.

What effect do bisphosphonates have on serum calcium concentrations in normocalcaemic conditions such as osteoporosis and Paget's disease? In the case described by Kashyap and Kashyap, a 68 year old woman with osteoporosis developed clinically symptomatic hypocalcaemia after taking alendronate (5 mg/day) for 10 days. Intuitively, given the mode of action of bisphosphonates, this would not be considered to be an unexpected observation. Indeed, the serum calcium con-

centration is well known to decrease on initiating therapy with bisphosphonates, particularly when they are used intravenously. However, this is short lasting and usually clinically asymptomatic. It is rapidly followed by restoration of serum calcium to normal.³ The mechanism by which this occurs is through a negative feed-back loop which increases parathyroid hormone (PTH) secretion within minutes. PTH in turn increases serum calcium concentrations by increasing bone resorption, intestinal calcium absorption, and renal tubular reabsorption of calcium. It is important to note that the parathyroid response to a hypocalcaemic challenge is not affected by long term bisphosphonate therapy.⁴ This is a reassuring observation given that in conditions such as osteoporosis, these drugs will have to be used for many years. Thus, clinically significant hypocalcaemia is only likely to occur in patients with deficient parathyroid hormone secretion, as observed in the patient reported in this issue and in other recent case reports with alendronate⁵ and pamidronate.^{6,7}

In summary, although bisphosphonates lead to a decrease in serum calcium, in most patients rapidly acting homoeostatic mechanisms involving an increase in PTH secretion lead to a restoration in calcium concentrations. In patients with known or suspected hypoparathyroidism, for example after thyroid or parathyroid surgery, these compensatory

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