

LIFE-THREATENING HYPOCALCAEMIA FOLLOWING FIRST ZOLEDRONIC ACID TREATMENT FOR OSTEOPOROSIS

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Description of Case

A 91- year old woman was found by staff at her nursing home with reduced level of consciousness. On arrival of paramedics, she was recorded with a systolic blood pressure of 70mmHg, a heart rate of 25/minute and Glasgow Coma Score of 3. She regained adequate sinus rhythm and blood pressure shortly after arrival in the Emergency Department, following fluid resuscitation and chronotropic support. The initial 12-lead ECG demonstrated prolonged QT interval. The first serum corrected calcium was 1.7mmol/L.

Her cognitive function was slow to recover. Her voice was hoarse suggestive of laryngospasm. Chvostek's and Trousseau's signs were negative.

3 weeks earlier, she had been admitted with fractures of her right pubic rami following a fall at home. During that admission she was treated with a first dose of intravenous zoledronic acid (Zometa, 4mg) and subsequently discharged to a nursing home. Serum corrected calcium at the time was normal. No recent 25(OH) vitamin D or parathyroid hormone (PTH) levels had been assessed.

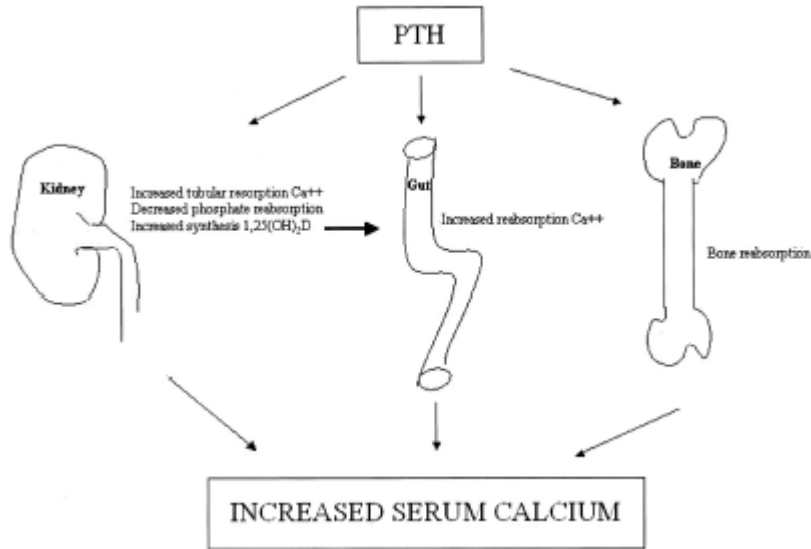
Other notable initial serum biochemistry showed a phosphate level of 1.87mmol/L, creatinine 155µmol/L, ALP 151 U/L and PTH 12.6pmol/L. She was significantly vitamin D depleted with a 25(OH) vitamin D level of 27nmol/L. Initial serum magnesium was 1.07mmol/L but fell to a nadir of 0.55 on day 5. Urinary calcium excretion was undetectable.

The presumptive diagnosis of bisphosphonate-induced hypocalcaemia was made. She was initially treated with intravenous (IV) calcium chloride (2 ampoules). On day 2, she required a further dose of IV calcium chloride and was commenced on high dose oral calcium carbonate and calcitriol (up to 0.5 µg bd). She also received magnesium replacement. She had been on long-term diltiazem which was ceased.

On discharge 10 days later, serum corrected calcium stabilized at borderline level of 2.06, serum phosphate 1.09, serum magnesium 0.82, plasma PTH 7.7 and serum creatinine 72. When she was reviewed in clinic 3 weeks later, serum corrected calcium was 2.19. She was weaned off calcitriol and remained on maintenance treatment with ergocalciferol 2000 IU/d and calcium carbonate 600 mg bd.

This case highlights an uncommon, and perhaps under-recognized side-effect of what is otherwise a highly effective treatment for osteoporosis. It raises a number of issues for discussion:

1. What are the mechanisms of bisphosphonate-induced hypocalcaemia?
2. What is the incidence of hypocalcaemia associated with zoledronic acid treatment for osteoporosis and the possible risk factors of severe hypocalcaemia in this setting?
3. What measures may be instituted to minimize the risk of severe hypocalcaemia associated with IV bisphosphonates?



The major action of the bisphosphonates is to suppress the formation and function of the osteoclast and therefore bone resorption. Most patients treated with bisphosphonates do not become hypocalcaemic because of compensatory mechanisms as demonstrated above, the most important of which is the feed-back increase in PTH secretion (1,2). Vitamin D deficiency is highly prevalent in elderly osteoporotic patients (3). In addition, hypomagnesaemia which may be associated with bisphosphonate use can interfere with PTH secretion and action (4). These factors have been linked to severe hypocalcaemia following bisphosphonate treatment (2,4).

Recent major published studies of zoledronic acid in postmenopausal osteoporosis indicate that the incidence of hypocalcaemia in this setting is less than 1.3% (5). The data for severe hypocalcaemia is limited to case reports in cancer patients with bone involvement or malignant hypercalcaemia (2,4). To our knowledge, severe hypocalcaemia following zoledronic acid treatment for postmenopausal osteoporosis has not previously been described.

The routine use of calcium and vitamin D replacement in large interventional trials of zoledronic acid in osteoporosis may explain the low rate of hypocalcaemia. Several case reports of severe hypocalcaemia further highlight the need to assess the calcium, vitamin D and PTH status of the patient and appropriately replace vitamin D and calcium as required prior to commencing bisphosphonate therapy.

References

1. Ariyan CE, Sosa JA. Assessment and management of patients with abnormal calcium. *Critical Care Medicine* 2004; 32(Suppl.): S146-S154.
2. Peter R, Mishra V, Fraser WD. Severe hypocalcaemia after being given intravenous bisphosphonate. *BMJ* 2004; 328: 335-6
3. Nowson CA, Margerison C. Vitamin D intake and vitamin D status of Australians. *MJA* 2002; 177: 149-152
4. Henley D, Kaye J, Walsh J, Cull G. Symptomatic hypocalcaemia and renal impairment associated with bisphosphonate treatment in patients with multiple myeloma. *Intern Med J* 2005; 35: 726-8
5. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *NEJM* 2007; 356: 1809-22