

Hypomagnesemia and vitamin D deficiency complicating bisphosphonate induced hypocalcaemia

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Abstract

Zoledronic acid is a potent bisphosphonate that is used to treat patients with metastatic cancer by reducing bone pain and preventing skeletal complications of bone metastasis.

We reported the case of a lady suffering from metastatic breast cancer who developed seizures secondary to severe hypocalcaemia after being treated with Zoledronic acid. Hypocalcaemia was unresponsive to treatment until vitamin D and magnesium deficiencies were corrected. This case highlights the importance of taking serum magnesium and vitamin D levels in patients presenting with resistant hypocalcaemia following bisphosphonate administration, especially in those with underlying bone malignancy.

Keywords

Hypocalcaemia, bisphosphonate, vitamin D deficiency, hypomagnesemia

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Case report

A 70 year old Caucasian woman was referred to Karen Grech Rehabilitation Hospital for rehabilitation after sustaining a pathological fracture in the left femur in January 2010. She was diagnosed with breast carcinoma in 2005 and was treated with surgery and radiotherapy. She developed a pathological fracture of the lumbar vertebrae in January 2009 which was treated by surgical fixation followed by radiotherapy. She was later started on regular disodium Pamidronate 90mg every 6 weeks. She then spent 12 months in overall good health at home but presented with a pathological fracture of her left femur. This was managed by surgical fixation. A bone scan taken at the time showed multiple bone metastasis. According to current recommendations, disodium Pamidronate was changed to Zoledronic acid which was given at the standard dose of 4mg diluted in 100ml sterile 0.9% sodium chloride intravenously over one hour. Prior to commencing Zoledronic acid the patient's serum creatinine was 68umol/l (reference range 45-84) and the corrected serum calcium was 2.34 mmol/l(reference range 2.15-2.55). She was also on the recommended doses of calcium (600mg) and vitamin D (400IU) daily.

Her condition deteriorated after being given the second dose of Zoledronic acid. She complained of perioral tingling, parasthesia, developed tetany with a positive Trousseau's sign and Chvostek's sign and then sustained generalised tonic clonic seizures. Her serology revealed hypocalcaemia with corrected calcium level of 1.35 mmol/l(reference range 2.15-2.55). Serum 25 (OH) vitamin D level was also taken and was later found to be low (<7 ng/ml; reference range 20 -70). Multiple doses of 10cc of 10% intravenous calcium gluconate were initially administered, followed by concurrent administration of oral calcium carbonate tablets (3g daily) and alfacalcidol (0.25 microgram daily). Hypocalcaemia was resistant to treatment even though treatment was

given for several days and the seizures worsened in frequency and severity.

Further investigations revealed a concomitant hypomagnesaemia with magnesium level of 0.25 mmol/l (reference range 0.65-1.05). This was corrected with several bolus of 4g intravenous magnesium sulphate (16g over 8 days). Upon treating the hypocalcaemia and hypomagnesaemia, the tetany and seizures subsided and the patient's condition improved.

Discussion

Zoledronic acid is an intravenous bisphosphonate that suppresses the formation and function of osteoclasts.¹ The majority of patients receiving bisphosphonates do not suffer from hypocalcaemia because of the compensatory mechanism of parathyroid hormone which induces renal reabsorption of calcium, increases vitamin D production and stimulates osteoclasts to resorb bone. In this case report hypocalcaemia was not corrected by the parathyroid hormone response because of the lack of vitamin D.

This case and similar cases in literature highlight the need for avoiding bisphosphonate-induced hypocalcaemia by routine checking of renal function, calcium levels and vitamin D levels and adequate replacement prior to starting therapy.¹⁻⁶

In the setting of hypocalcaemia, hypomagnesaemia must not be overlooked. The homeostasis of magnesium depends upon gastrointestinal absorption and renal excretion. Most of the absorption of magnesium occurs in the ileum by two processes. The principal route is across the transient receptor potential melastatin (TRPM6) channel.⁷⁻¹⁰ This channel is a bifunctional protein that combines both calcium and magnesium and actively transport them across the membrane.^{7,9,10} The second route through which magnesium is absorbed in the ileum is the paracellular route and this occurs passively.⁸ Magnesium is mostly reabsorbed by the thick ascending loop of Henle (TAL) (60-70%) and only some magnesium is absorbed in the proximal and distal convoluted tubule. In the TAL, magnesium is passively absorbed with calcium via paracellular tight junctions known as paracellin-1. The driving force behind this passive reabsorption is the positive electrochemical gradient caused by reabsorption of sodium chloride. Also in the basolateral membrane of the TAL there are Ca^+/Mg^+ -sensing receptors. These receptors sense both calcium and

magnesium and when there is excess of either of these ions, they decrease magnesium absorption.⁸ In the distal convoluted tubule, magnesium is actively absorbed via the TRPM6 channel.^{9,10} Apart from the above, patients who have hypomagnesaemia have inappropriately low serum levels of parathyroid hormone (PTH) and bone is resistant to the effect of PTH.^{7,8} The reason for this is still unknown but this low PTH level would further lower calcium levels.

The above discussion highlights how the calcium, vitamin D and magnesium homeostatic mechanisms are closely interlinked and in the case presented hypocalcaemia was refractory to treatment until the concomitant hypomagnesaemia and vitamin D deficiency were corrected.

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