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Profound and Protracted Hypophosphatemia after A Single Dose of Zoledronic Acid Infusion for Osteoporosis Associated with Normocalcemic Primary Hyperparathyroidism

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Abstract

Bisphosphonates are widely used in the treatment of osteoporosis. The Intravenous bisphosphonate, Zoledronic acid (ZA) does not cause the gastrointestinal side effects associated with oral bisphosphonates and can be given as a once yearly infusion. ZA has the rare potential to cause hypophosphatemia. However, when reported, the hypophosphatemia following ZA infusion has been in the setting of treatment of oncological conditions such as hypercalcemia of malignancy and bone metastases. We present a case of severe and prolonged hypophosphatemia in a patient with post-menopausal osteoporosis and mild normocalcemic primary hyperparathyroidism who received a single dose of 5 mg of intravenous ZA. The severe hypophosphatemia manifested itself almost 2 months after the administration of the medication. The patient required very high doses of both oral and intravenous phosphate throughout the duration of her prolonged stay in hospital with failure to normalize the serum phosphate levels even after 13 days.

Keywords: Zoledronic acid; Hypophosphatemia; Osteoporosis; Normocalcemic primary hyperparathyroidism; Vitamin D; Bisphosphonate

Introduction

Bisphosphonates form the mainstay for the prevention and treatment of osteoporosis. They bind to bone surfaces, particularly sites of active bone remodeling to reduce osteoclastic bone resorption. Zoledronic acid (ZA) is a third-generation nitrogen containing bisphosphonate and the most potent bisphosphonate available. It's use has been associated with electrolyte disturbances including profound hypophosphatemia but this has been observed only when it has been used in the setting of hypercalcemia of malignancy (HCM) and prevention of skeletal events in malignancies and that too very infrequently. We describe a case of delayed onset, profound and protracted hypophosphatemia in a patient treated with a single dose of ZA for post-menopausal osteoporosis that was associated with normocalcemic primary hyperparathyroidism.

Case Presentation

A 65-year old Chinese lady was admitted to our hospital for non-specific abdominal pain and generalized body ache. Her background medical history includes severe osteoporosis, gastritis, and iron deficiency anemia. She had been referred to her endocrinologist 56 days prior to the current admission with a history of multiple thoracic (T7, T9, T10 and T12) and lumbar (L1) spine fractures on minimal trauma. For this, the patient had received a single dose of 5 mg IV ZA then. 7 months prior to the endocrinology referral, she had been noted to have an elevated serum iPTH level of 7.9 pmol/l (reference range 0.9-6.2 pmol/l) with a serum calcium (corrected for albumin) that was normal at 2.20 mmol/l (reference range 2.09-2.46 mmol/l). Her renal function had always been normal. Her 25 hydroxyvitamin D level was 20.1 ng/ml a month prior to the Zoledronic acid infusion and though this was not considered to be deficient, she was aggressively replaced with Vitamin D2 (Ergocalciferol) 50,000 IU weekly along with Vitamin D3 (Colecalciferol) 1000 U daily. Her serum 25 D level was 35.6 ng/ml at the current admission. At the time of receiving the Zoledronic acid, her serum iPTH level was 8.1 pmol/l with a serum calcium (corrected for albumin) level of 2.22 mmol/l and a serum phosphate level of 1.15 mmol/l (reference range 0.94-1.50 mmol/l).

On examination at the current admission, her blood pressure was 123/71 mmHg, heart rate was 82 bpm and saturations 97% on room air. Her physical examination was normal apart from reduced power in the proximal muscles of the upper and lower limbs (Medical Research Council Scale 4). Chvostek's and Trousseau's signs were negative. Her electrocardiogram did not reveal any abnormalities.

Laboratory investigations revealed a profound hypophosphatemia, with a serum phosphate level of 0.28

mmol/l. She was hypocalcemic with a corrected calcium level of 1.98 mmol/l. The serum iPTH of 14.4 pmol/l was even higher than the previously reported value of 8.1 pmol/l immediately prior to her receiving the Zoledronic acid. Potassium and magnesium levels were normal. An elevated 24-hour urinary phosphate secretion of 40.61 mmol/day (reference range 8.1-22.6 mmol/day) confirmed urinary loss of phosphate. Urinary glucose, uric acid and amino acid were negative. She had not been on any chronic treatment with aminoglycosides, anti-virals or chemotherapeutic agents, neither was she taking aluminium or magnesium containing antacids. There was no family history of hypophosphatemia or bone diseases.

Further examination of her medical records revealed that she had been admitted to another hospital one day after her IV Zoledronic acid infusion, for symptoms suggestive of an acute phase reaction with myalgias and fever that lasted less than 24 hours. During that admission, both her serum phosphate and corrected calcium levels were noted to be slightly low at 0.73 mmol/l and 2.10 mmo/l respectively with a serum iPTH level of 8.3 pmol/l. The transient hypophosphatemia resolved with 20 mmol of IV phosphate replacement as did the myalgias and she was discharged.

During the current admission, the patient required multiple daily doses of both intravenous as well as oral phosphate supplementation (**Table 1)**. She required between to 20 to 120 mmols of IV phosphate replacement per day. This is equivalent to 0.43-2.61 mmol phosphate/kg/day. In addition to that, she received 20.75 to 103.75 mmols of oral phosphate supplementation per day. The combined oral and IV phosphate replacement amounted to 0.43-4.86 mmol phosphate/kg/day. On the 12th day post hospitalization (Day 67 after receiving IV Zoledronic acid) her serum phosphate level was still 0.71 mmol/l and she was still requiring intravenous phosphate supplementation. However, the patient decided to leave the hospital against medical advice at this point and has not returned for a follow-up visit.

Table 1. Evolution of laboratory abnormalities pre and post intravenous Zoledronic acid and phosphate supplementation that patient received.

						Phosphate replacement			
	Corrected calcium	Phosphate	25 OH Vit D	PTH	Mg	Oral PO4*	IV PO4 (mmol)	mmol/kg of IV PO4	mmol/kg of total PO4
	2.09-2.46 mmol/l	0.94-1.50 mmol/l	(ng/ml)	0.9-6.2 pmol/l	0.74-0.97 mmol/l	(mmol)			
Prior to administration of 5 mg ZA									
	2.22	1.15	20.1	8.1					
First admission to hospital (1 day after ZA administration)									
Day 1	2.04	0.73		8.3	0.92		20		
Day 2	2.13	0.97			0.84				
Second admission to hospital									
Day 56	1.98	0.28	35.6	14.4	0.94		40	0.87	0.87
Day 57	1.93-2.11	0.59-0.89		18.1		20.75	60	1.3	1.76
Day 58	1.97-2.12	0.91-0.92			0.83	41.5	70	1.52	2.42
Day 59	2	0.67				41.5	40	0.87	1.77
Day 60						62.25	70	1.52	2.88
Day 61	2	0.54				62.25	80	1.74	3.09

Day 62	2.08	0.50-1.08				103.75	120	2.61	4.86
Day 63	2	0.66			0.66	41.5	20	0.43	1.33
Day 64	2.14	0.58			0.93	41.5	60	1.3	2.21
Day 65	2.17	0.63				41.5	60	1.3	2.21
Day 66		0.63				Nil	20	0.43	0.43
Day 67	2.21	0.71			0.85				
*Oral phosphate replacement: 1ml contains 128.6 mg or 4.15 mmol of phosphate									

Discussion

All bisphosphonate shares a characteristic Phosphate-Carbon-Phosphate (PCP) bond, which causes these compounds to bind avidly onto hydroxyapatite crystals on the surface of actively remodeling bones. The hydroxyl group attached to the carbon atom confers a high affinity for calcium on bone surfaces as well as in the circulation making it a calcium chelator and thus bisphosphonates may induce hypocalcemia [1]. ZA is unique in that it can cause a more profound hypocalcemic state compared to other bisphosphonates due to its superior efficacy [2].

Another electrolyte abnormality that can be caused by ZA is hypophosphatemia. The mechanism of ZA induced hypophosphatemia has been postulated to be due to secondary hyperparathyroidism from the hypocalcemia [3]. Another explanation would be that the inhibition of bone resorption by bisphosphonate reduces the release of phosphate from the bone [4]. The manufacturer's prescribing information cites an incidence of Grade 3 hypophosphatemia (serum phosphate <0.65 mmol/l) as 51% in HCM and 12% in bone metastases. As for Grade 4 hypophosphatemia (serum phosphate<0.32mol/l), this rate is 1% and <1% respectively. Since the hypophosphatemia is typically transient, the manufacturer recommends only short term supplemental therapy with phosphate as necessary. Clark et al. reported a case of a patient with refractory hypophosphatemia after receiving a single dose of 4 mg IV ZA for treatment of HCM. This patient required IV phosphate replacement for a total of 33 days [5]. That patient also had severe and profound vitamin D deficiency with serum vitamin D levels of only 6.8 ng/ml.

Profound and protracted hypophosphatemia following IV Zoledronic acid administration for osteoporosis has not been reported previously. Though the reason for this discrepancy is not clear it may likely be because Zoledronic acid is more actively adsorbed onto the hypermetabolic osseus surfaces of malignancy thus producing more severe hypocalcemia and hypophosphatemia. However, in the setting of pre-existing and unrecognized comorbid conditions such as hyperparathyroidism with its capacity to induce phosphate loss sub-clinical and non-overt though it may be, IV Zoledronic acid may cause abrupt reductions in calcium that can worsen hyperparathyroidism and also potentially aggravate the phosphate loss. This is what we postulate was responsible for the protracted and profound hypophosphatemia that occurred in our patient. She had elevated levels of serum iPTH in the setting of normal serum calcium levels without any other reason for the hyperparathyroidism such as renal failure or overt hypercalciuria [6]. Though low vitamin D levels may contribute to secondary hyperparathyroidism and hypovitaminosis D must be ruled out before making a diagnosis of normocalcemic primary hyperparathyroidism, in our patient the vitamin D levels though probably insufficient were not profoundly low enough to cause secondary hyperparathyroidism. It is likely that the pre-existing modestly raised PTH levels (8.3 pmol/l) prior to IV Zoledronic acid administration became further elevated from the hypocalcemia induced by the Zoledronic acid infusion as was evidenced by her serum iPTH level of 14.1 pmol/l at the time of admission with profound hypophosphatemia 56 days after receiving the infusion. Hypocalcemia is a recognized side effect of Zoledronic acid use, and is usually transient. In the HORIZON Pivotal Fracture Trial, transient and asymptomatic hypocalcaemia occurred 9–11 days after the first infusion of once yearly 5 mg Zoledronic acid [7]. The manufacturers insert (Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936, revised April 2016) recommends that patients being treated for osteoporosis ensure that their daily calcium intake should be at least 1200 mg. While supplemental calcium is advised if the dietary intake is inadequate, this may further worsen hypophosphatemia by binding dietary phosphate. It is likely that the already elevated PTH levels that the patient had prior to infusion continued to rise in the 2 months following it, with progressive phosphaturia resulting in the severe hypophosphatemia.

We did not have reasons to suspect an extra-renal cause such as malabsorption for the hypophosphate since in our patient such as malabsorption since there had not been any recent or significant weight loss and she did not have a history of diarrhea. Intracellular shifts, such as that which occurs with refeeding syndrome or insulin therapy were also ruled out given that the patient was not malnourished nor was she diabetic. The source of phosphate loss was thought to be

renal, and this was confirmed by the elevated 24-hour urinary phosphate levels. Conditions that cause a proximal renal tubulopathy such as Fanconi's syndrome, excess alcohol intake and the use of chemotherapeutic agents were not present in our patient. FGF-23 dependent hypophosphatemia as seen in TIO [8] was also deemed to be unlikely, given the fact that the patient had a sub-acute presentation and had a normal phosphate level prior to ZA administration. After very careful review of all her medications, we have concluded that her severe and protracted hypophosphatemia was most likely caused by the ZA given 56 days prior to her presenting to our institution.

Brown et al. recommend that patients with severe hypophosphatemia (serum phosphate <0.48 mmol/l) be treated with intravenous replacement of 1 mmol phosphate/kg/day [9]. Our patient persistently needed much higher doses than this; with requirements on some days during hospitalization of 1.5-2 mmol/kg/day. This did not include the oral phosphate supplementations that she needed in addition. Despite this, her phosphate levels failed to normalize even more than 2 months after the administration of Zoledronic Acid.

To our knowledge, this is the first case report that describes such profound and protracted hypophosphatemia following a single intravenous administration of Zoledronic acid for the treatment of osteoporosis. This case drives home the importance of monitoring of electrolytes especially that of calcium and phosphate levels in even osteoporotic patients treated with ZA especially in those with concurrent conditions such as primary hyperparathyroidism that can worsen urinary phosphate losses. Other conditions such as Vitamin D deficiency that contribute to phosphate malabsorption must be treated prior to administration of this potent bisphosphonate. It must be borne in mind that the presentation may be delayed and that the abnormalities can persist for a long period of time, as seen in our case.

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