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Severe and Prolonged Hypocalcaemia Post Zoledronic Acid Infusion in a Patent with Sleeve Gastrectomy

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Abstract

Background: Zoledronic acid is commonly used to treat hypercalcaemia and osteoporosis, as well as to prevent skeletal complications from haematological and solid organ malignancies. Case presentation: We report the case of a 38 year old lady who presented with severe hypocalcaemia following the administration of zoledronic acid. Her significant background history included vitamin D deficiency and sleeve gastrectomy three years ago. She had prolonged hypocalcaemia requiring IV calcium replacement for two months. Her prolonged hypocalcaemia was attributed to her vitamin D deficiency at the time of zoledronic acid infusion as well as her history of bariatric surgery. Conclusion: This case emphasises the importance of ensuring vitamin D levels are replete prior to zoledronic acid infusion and ensuring the calcium levels are checked frequently in patients with a history of bariatric surgery obtaining zoledronic acid.

Keywords

Hypocalcaemia, Zoledronic Acid, Bariatric Surgery

1. Introduction

Zoledronic acid is commonly used to treat hypercalcaemia and osteoporosis, as well as to prevent skeletal complications from haematological and solid organ malignancies. It is a third generation nitrogen containing bisphosphonate that inhibits osteoclast function and prevents bone resorption. Zoledronic acid is usually favoured over other bisphosphonates due to its high potency and the ease of administration. There is a risk of prolonged and severe hypocalcaemia after treatment with zolendronic acid. The hypocalcaemia can be difficult to

control despite aggressive calcium replacement [1]. Bariatric surgery has been associated with micronutrient deficiency, especially vitamin D deficiency [2] [3]. These deficiencies could be present post bariatric surgery due to decreased vitamin D intake as well as altered metabolism. In our patient, the administration of zoledronic acid after sleeve gastrectomy led to prolonged hypocalcaemia.

2. Case Presentation

A 38 year old lady presented to the emergency department with dizziness accompanied by pain and paraesthesia in her hands and feet. She had a history of obesity with a sleeve gastrectomy three years ago, after which she lost 47 Kg. Her other medical conditions included osteoporosis, hypertension, hypercholesterolemia, chronic pain, depression, gastroesophageal reflux disease and fibromyalgia. One year ago, she was investigated for normocalcaemic hyperparathyroidism (parathyroid hormone (PTH): 20 pmol/L (normal range 2 - 6 pmol/L)). The cause for this was attributed to vitamin D deficiency. Her sestamibi scan at the time showed no parathyroid adenoma. On ultrasound, she was noted to have a thyroid nodule, which was not biopsied.

Her medications at presentation were amitriptyline 10 mg nocte (for depression), atenolol 50 mg nocte, gabapentin 300 mg bd, indapamide 1.5 mg daily, paroxetine 20 mg nocte, sodium valproate 100 mg tds, telmisartan 40 mg daily, amlodipine 5 mg daily, pantoprazole 40 mg daily and nizatidine 300 mg daily. She had been administered zoledronic acid to treat osteoporosis and two months later presented with severe hypocalcaemia of 1.57 mmol/L (normal range 2.1 - 2.6 mmol/L).

On examination, she was clinically euvolemic with blood pressure 145/76 mmHg and heart rate 77 beats per minute. Her weight was 108 Kg and height was 1.64 m, with a body mass index (BMI) 40.15 kg/m^2. There was mild sensory loss to light touch in a glove and stocking distribution affecting upper and lower limbs, with no saddle paraesthesia. The remainder of her neurological examination and general examination was unremarkable. She was admitted to hospital and her calcium normalised with calcium infusions and Vitamin D replacement. Two weeks later, she was seen at a hypertension clinic, complaining of weakness, paraesthesia and pain in all limbs. She was again hypocaclcaemic and hypophosphataemic. She was re-admitted and the prior receipt of zolendric acid was identified as the cause for her hypocalcaemia.

2.1. Investigations

On her latest admission, she had severe hypocalcaemia with calcium of 1.57 mmol/L (normal range 2.1 - 2.6 mmol/L), corrected calcium of 1.57 mmol/L (normal range 2.1 - 2.6 mmol/L), magnesium 1.03 mmol/L (normal range 0.70 - 1.1 mmol/L), phosphate 0.5 mmol/L (normal range 0.75 - 1.5 mmol/L) and albumin 40 g/L (normal range 33 - 48 g/L).

Her renal function was normal with a serum creatinine of 46 umol/L and es-

timated glomerular filtration rate (eGFR) > 90 ml/min/1.73m^2. Her PTH was elevated at 24.6 pmol/L (normal range 2 - 6 pmol/l). The urine calcium excretion was less than 0.2 mmol/L (normal range 0.2 - 0.58 mmol/L), and the calcium: creatinine ratio was less than 0.1mmol/day (normal range 2.5 - 7.5 mmol/day). Her urine pH was 5 and urine phosphate was 23.9 mmol/L. The calcitonin level was less than 2 pg/ml (normal range < 10 pg/ml) and the vitamin D level was 33 nmol/L (normal range > 50 mmol/L). Her bone mineral density showed osteopenia with a T score of −2.3 in the lumbar spine.

A dotatate positron emission tomography (PET) scan was performed to rule out rare mesenchymal bone tumours and medullary thyroid carcinoma. This revealed a poorly defined inferior pole of the left thyroid lobe demonstrating moderate dotatate activity. A biopsy of the lesion revealed a benign follicular pattern in keeping with a colloid nodule with associated haemorrhagic degeneration (Bethesda category 2).

2.2. Differential Diagnosis

We postulated that her hypocalcaemia was likely secondary to zoledronic acid that had been administered for osteoporosis. The increase in PTH was appropriate for her hypocalcaemia and excluded a diagnosis of hypoparathyroidism. Her urine calcium was low, which excluded renal tubular acidosis. The normal bone scans and Dotatate PET scan excluded neuro endocrine tumours (**Figure 1**). The low calcitonin and thyroid biopsy excluded a medullary thyroid carcinoma.

2.3. Treatment

She was administered daily intravenous (IV) calcium in addition to oral rocaltrol and caltrate tablets. Drugs that can impede calcium and/or vitamin D absorption were ceased including sodium valproate, nizatidine and pantoprazole. Her calcium trend is demonstrated in **Figure 2**. Over the course of her month-long admission,

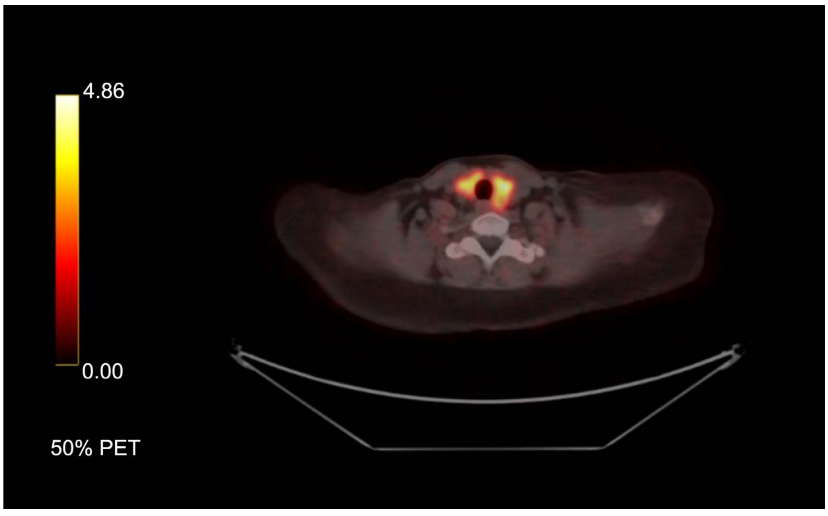

Figure 1. G68 Dotate Pet scan: Revealed no neuro endocrine tumours. However, revealed a poorly defined inferior pole of the left thyroid lobe of moderate glucose uptake.

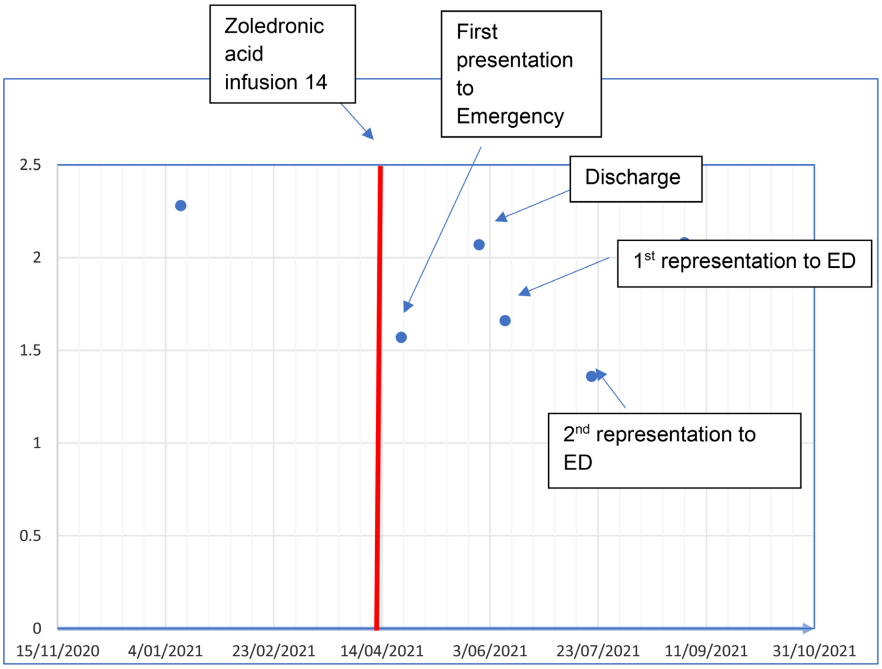

Figure 2. Trends of the calcium levels over a 4-month period.

her calcium levels stabilised. However, she still required occasional IV calcium infusions in the outpatient setting to maintain her corrected calcium above 1.8 mmol/L. Her serum phosphate was very low and was replaced orally with SandoPhosphate. She had multiple presentations post discharge with hypocalcaemia despite being on regular outpatient IV calcium infusions.

2.4. Outcome and Follow-Up

Eight weeks following her initial presentation she remained on twice weekly calcium infusions. Her calcium levels were 1.8 to 1.9 mmol/L. Her symptoms from hypocalcaemia had improved. The patient continued to be followed up every fortnight, with a plan to reduce the frequency of the calcium infusions once the corrected calcium rose above 2 mmol/L. Her phosphate levels continued to be low, ranging from 0.3 to 0.5 mmol/L and she received oral phosphate supplementation.

Three months following her initial presentation, she no longer required intravenous calcium and her calcium remained normal. Phosphate supplements were ceased and her rocaltiol dose was reduced without resulting in recurrent hypocalcemia. Her neurological symptoms continue to improve. She remains on maintenance rocaltrol and vitamin D supplements.

3. Discussion and Conclusion

We report a rare case of prolonged hypocalcaemia following the administration of zoledronic acid in a patient with previous gastric sleeve surgery. At the time of her administration of zoledronic acid, her vitamin D level was not checked. During her first admission, her vitamin D level was low, thus indicating a likely

vitamin D deficiency at the time of administration of the zoledronic acid.

Prolonged hypocalcaemia following infusion of zoledronic acid has been rarely reported. A case study in 2015 presented a patient with hypocalcaemia that required IV replacement for 28 days following administration of zoledronic acid [1]. Similarly to our case, there was concurrent hypophosphatemia. However, there was no record of vitamin D levels and the patient had renal impairment prior to the zoledronic acid administration. Most retrospective studies have looked at the short-term risk of hypocalcaemia following zoledronic acid administration [4] [5]. There was one case report that reported hypocalcaemia post zoledronic acid for paget disease nine months post infusion. However, this patient did not have severe hypocalcaemia and was only on oral replacement [6]. Furthermore, none of these cases reports prolonged hypocalcaemia needing intravenous replacement lasting greater than 28 days.

Our case appears unique in comparison to the other cases which have reported hypocalcaemia post zoledronic acid, given the normal renal function and the longer duration of the hypocalcaemia [6]. Our patient was likely at higher risk of hypocalcaemia given the previous gastric sleeve surgery leading to decreased calcium and vitamin D absorption. Recommendations exist to monitor vitamin D routinely both before and after bariatic surgery. On the other hand, there are no clear guidelines on the calcium monitoring post bariatric surgery [7].

Bisphosphonates attach to the hydroxyapatite site on bones and inhibit osteoclastic-mediated bone resorption in a variety of ways. They are used extensively in clinical practice for the management of osteoporosis as well as bony metastases and hypercalcaemia secondary to malignancy. IV bisphosphonates are usually preferred over oral bisphosphonates, given their increased bioavailability, faster onset of action and lower risk of gastrointestinal side effects [8]. Amongst the intravenous options, zolendronic acid is considered one of the most potent bisphosphonates [9]. It can be infused over a shorter period of time compared to other bisphosphonates, making it more convenient for medical practitioners and patients [10].

Bisphosphonates are associated with hypocalcaemia, as they disrupt the mobilisation of calcium in addition to their inhibition of osteoclastic activity [11]. The side effects of hypocalcaemia can be exacerbated due to factors such as vitamin D deficiency and reduced (gastric) calcium absorption. Our patient was also on pantoprazole and nizatidine, both of which suppress gastric acid and thereby reduce calcium absorption [12]. Furthermore, she was also on sodium valproate which could have impaired her vitamin D metabolism [13].

The bariatric surgery could have reduced both her calcium and vitamin D levels. Firstly, Vitamin D deficiency has been widely reported prior to bariatric surgical procedures in obese patients [14] [15]. This has been postulated to be secondary to low sun exposure, reduction in bioavailability of vitamin D due to its sequestration in adipose tissues as well as inadequate oral intake of vitamin D rich foods despite high overall calorie intake [16] [17] [18]. Vitamin D deficien-

cy has also been widely reported following bariatric surgery. The main cause of this is thought to be inadequate vitamin D supplementation during the period of weight loss post bariatric surgery. Other potential factors include bile acid deficiency associated with bariatric surgeries [19] [20] and malabsorption of vitamin D due to intestinal bacterial overgrowth [21].

The body's normal response to hypocalcaemia is to increase secretion of PTH, which increases the release of calcium from bone, renal reabsorption of calcium, production of vitamin D and intestinal reabsorption of calcium. In this case, the patient probably had a blunted response to the hypocalcaemia due to zolendric acid inhibiting osteoclast activity and reabsorption of calcium from bone. Other contributing factors to her hypocalcaemia were a reduced vitamin D level and poor intestinal calcium absorption as a result of her previous gastric sleeve surgery. Proton pump inhibitors and sodium valproate also may have impaired calcium absorption. This likely affected her calcium homeostasis and precipitated her prolonged hypocalcaemia. The limitation of this case was that were not able to confirm her compliance with her oral calcium supplements.

In summary, we report the case of a 38 year old lady with severe persistent hypocalcaemia following the infusion of zoledronic acid, six weeks prior to presentation. This was likely precipitated by her history of gastric sleeve surgery as well as vitamin D deficiency at the time of the zoledronic acid infusion. In conclusion it is important to consider and monitor for prolonged hypocalcaemia following the use of bisphosphonate in patients with baratric surgery due to the effect on calcium and vitamin D absorption. Routine vitamin D and calcium supplementation following bariatric surgery are required to prevent osteoporosis.

Ethics and Consent to Participate

None required. Consent was obtained from the patient.

Consent for Publication

Consent from all the authors and the patient informed for the publication.

Authors' Contribution

Idea: AJ, ED, AI, HN, Data collection: AJ, Write up AJ, manuscript edition ED, HN, AI.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Narechania, S., Thiruchelvam, N., Lokhande, C., Kistangari, G. and Daw, H. (2015) Prolonged Zoledronic Acid-Induced Hypocalcemia in Hypercalcemia of Malignancy. *Journal of Community and Supportive Oncology*, **13**, 374-377. https://doi.org/10.12788/jcso.0166

[2] Borges, J.C., Miranda, I.S.M., Sarquis, M.M.S., Borba, V., Maeda, S.S., Lazaretti-Castro, M., *et al.* (2018) Obesity, Bariatric Surgery, and Vitamin D. *Journal of Clinical Densitometry*, **21**, 157-162. https://doi.org/10.1016/j.jocd.2017.03.001

[3] Lupoli, R., Lembo, E., Saldalamacchia, G., Avola, C.K., Angrisani, L. and Capaldo, B. (2017) Bariatric Surgery and Long-Term Nutritional Issues. *World Journal of Diabetes*, **8**, 464-474. https://doi.org/10.4239/wjd.v8.i11.464

[4] Chennuru, S., Koduri, J. and Baumann, M.A. (2008) Risk Factors for Symptomatic Hypocalcaemia Complicating Treatment with Zoledronic Acid. *Internal Medicine Journal*, **38**, 635-637. https://doi.org/10.1111/j.1445-5994.2007.01580.x

[5] Breen, T.L. and Shane, E. (2004) Prolonged Hypocalcemia after Treatment with Zoledronic Acid in a Patient with Prostate Cancer and Vitamin D Deficiency. *Journal of Clinical Oncology*, **22**, 1531-1532. https://doi.org/10.1200/JCO.2004.99.013

[6] Ferraz-de-Souza, B., Martin, R.M. and Correa, P.H. (2013) Symptomatic Intracranial Hypertension and Prolonged Hypocalcemia Following Treatment of Paget's Disease of the Skull with Zoledronic Acid. *Journal of Bone and Mineral Metabolism*, **31**, 360-365. https://doi.org/10.1007/s00774-012-0395-8

[7] Osland, E., Powlesland, H., Guthrie, T., Lewis, C.A. and Memon, M.A. (2020) Micronutrient Management Following Bariatric Surgery: The Role of the Dietitian in the Postoperative Period. *Annals of Translational Medicine*, **8**, S9. https://doi.org/10.21037/atm.2019.06.04

[8] Do, W.S., Park, J.K., Park, M.I., Kim, H.S., Kim, S.H. and Lee, D.H. (2012) Bisphosphonate-Induced Severe Hypocalcemia—A Case Report. *Journal of Bone Metabolism*, **19**, 139-145. https://doi.org/10.11005/jbm.2012.19.2.139

[9] Sanfilippo, K.M., Gage, B., Luo, S., Weilbaecher, K., Tomasson, M., Vij, R., *et al.* (2015) Comparative Effectiveness on Survival of Zoledronic Acid versus Pamidronate in Multiple Myeloma. *Leukemia & Lymphoma*, **56**, 615-621. https://doi.org/10.3109/10428194.2014.924117

[10] Drake, M.T., Clarke, B.L. and Khosla, S. (2008) Bisphosphonates: Mechanism of Action and Role in Clinical Practice. *Mayo Clinic Proceedings*, **83**, 1032-1045. https://doi.org/10.4065/83.9.1032

[11] Rosen, C.J. and Brown, S. (2003) Severe Hypocalcemia after Intravenous Bisphosphonate Therapy in Occult Vitamin D Deficiency. *The New England Journal of Medicine*, **348**, 1503-1504. https://doi.org/10.1056/NEJM200304103481521

[12] Ito, T. and Jensen, R.T. (2010) Association of Long-Term Proton Pump Inhibitor Therapy with Bone Fractures and Effects on Absorption of Calcium, Vitamin B12, Iron, and Magnesium. *Current Gastroenterology Reports*, **12**, 448-457. https://doi.org/10.1007/s11894-010-0141-0

[13] Xu, Z., Jing, X., Li, G., Sun, J., Guo, H., Hu, Y., *et al.* (2019) Valproate Decreases Vitamin D Levels in Pediatric Patients with Epilepsy. *Seizure*, **71**, 60-65. https://doi.org/10.1016/j.seizure.2019.06.009

[14] Pereira-Santos, M., Costa, P.R., Assis, A.M., Santos, C.A. and Santos, D.B. (2015) Obesity and Vitamin D Deficiency: A Systematic Review and Meta-Analysis. *Obesity Reviews*, **16**, 341-349. https://doi.org/10.1111/obr.12239

[15] Yao, Y., Zhu, L., He, L., Duan, Y., Liang, W., Nie, Z., *et al.* (2015) A Meta-Analysis of the Relationship between Vitamin D Deficiency and Obesity. *International Journal of Clinical and Experimental Medicine*, **8**, 14977-14984.

[16] Hypponen, E. and Power, C. (2007) Hypovitaminosis D in British Adults at Age 45 y: Nationwide Cohort Study of Dietary and Lifestyle Predictors. *The American Journal of Clinical Nutrition*, **85**, 860-868. https://doi.org/10.1093/ajcn/85.3.860

[17] Williams, S.E., Cooper, K., Richmond, B. and Schauer, P. (2008) Perioperative Management of Bariatric Surgery Patients: Focus on Metabolic Bone Disease. *Cleveland Clinic Journal of Medicine*, **75**, 333-334. https://doi.org/10.3949/ccjm.75.5.333

[18] Wortsman, J., Matsuoka, L.Y., Chen, T.C., Lu, Z. and Holick, M.F. (2000) Decreased Bioavailability of Vitamin D in Obesity. *The American Journal of Clinical Nutrition*, **72**, 690-693. https://doi.org/10.1093/ajcn/72.3.690

[19] Riedt, C.S., Brolin, R.E., Sherrell, R.M., Field, M.P. and Shapses, S.A. (2006) True Fractional Calcium Absorption Is Decreased after Roux-en-Y Gastric Bypass Surgery. *Obesity* (*Silver Spring*), **14**, 1940-1948. https://doi.org/10.1038/oby.2006.226

[20] Schafer, A.L. (2017) Vitamin D and Intestinal Calcium Transport after Bariatric Surgery. *The Journal of Steroid Biochemistry and Molecular Biology*, **173**, 202-210. https://doi.org/10.1016/j.jsbmb.2016.12.012

[21] Koch, T.R. and Finelli, F.C. (2010) Postoperative Metabolic and Nutritional Complications of Bariatric Surgery. *Gastroenterology Clinics of North America*, **39**, 109-124. https://doi.org/10.1016/j.gtc.2009.12.003

Abreviations

Body mass index (BMI)
Estimated glomerular filtration rate (eGFR)
Parathyroid hormone (PTH)
Positron emission tomography (PET)
Intravenous (IV)