Hypercalcaemia to Hypocalcaemia- Tetany as a side effect of intravenous bisphosphonate treatment

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TITLE

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SUMMARY

A woman in her forties with advanced bladder cancer was admitted to hospital with hypercalcaemia of malignancy. Initially she presented with non-specific symptoms of malaise, fatigue, and general deterioration. She was treated with intravenous fluids and zoledronic acid in order to bring her calcium levels down, but subsequently developed significant hypocalcaemia. This manifested as tetany in the hands in the form of bilateral carpopedal spasm. She also reported perioral paraesthesia. Bloods during her admission revealed deranged electrolytes, and her vitamin D level was on the lower scale of normal (25 nmol/l). The patient's symptoms improved with electrolyte replacement and oral baclofen for her symptomatically distressing wrist and hand muscle spasms. This case report is a reminder that bisphosphonates can cause significant hypocalcaemia with symptoms of tetany, even when they are given for initial hypercalcaemia. Baclofen worked well to improve symptoms.

BACKGROUND

Hypercalcaemia of malignancy is an oncological emergency and should be treated urgently and bisphosphonates are a primary treatment strategy for people who develop it.[1] We report the case of a woman in her forties, who received intravenous bisphosphonate treatment for hypercalaemia. This resulted in a very low calcium level and associated carpopedal spasm of the hands and perioral anaesthesia.

The patient was admitted to hospital and treated initially with intravenous fluids and then given an infusion of zoledronic acid 4 mg. Several days after the infusion, she developed symptoms of tetany in the hands (manifesting as bilateral carpopedal spasms) as well as perioral paraesthesia. Her calcium had gone from high (3.53 mmol/L) to low (1.79 mmol/L). She was found to be vitamin D deficient during her admission.

The UK's British National Formulary (BNF) lists muscle spasms and electrolyte imbalances as a side effect of zoledronic acid, but neither the drug's profile page, nor the bisphosphonate chapter list carpopedal spasm secondary to hypocalcaemia.[2] Hypocalcaemia can be caused by bisphosphonate treatment, which can result in symptoms of cardiac arrhythmias and neurological symptoms such as convulsions, tetany and hypoaesthesia. Existing literature predominantly lists bisphosphonates causing hypocalcaemia when patients are receiving them for causes *other* than hypercalcaemia (ie administered to initially normocalcaemic patients, whilst our patient had a hypercalcaemia at the outset) [3] Tetany is a syndrome

characterised by painful flexion of wrist and ankle joints (carpopedal spasm). It can also be associated with muscle cramps, twitching, seizures, laryngospasm, syncope, or myocardial dysfunction. It occurs due to hyperexcitable nerves and muscles in the setting of decreased extracellular ionised calcium.[4]

On reviewing the literature, we found a case report describing a patient having received bisphosphonates who subsequently developed tetany of the legs and feet, rather than the hands as was the case in our patient.[5] Low vitamin D levels can constitute an additional risk factor for developing hypocalcaemia, but our patient had a serum vitamin D level of 25 nmol/l, which is on the lower side of the normal reference range. Existing literature suggests that vitamin D deficiency can exacerbate bisphosphate-induced hypocalcaemia.[6-9] It is recommended to assess calcium vitamin D and PTH status prior to commencing treatment with bisphosphonates.

CASE PRESENTATION

A woman was admitted to the cancer hospital inpatient ward from the oncology clinic, due to newly deranged blood test results of hypercalcaemia (3.53 mmol/L; reference range 2.20-2.60) and hypokalaemia (2.1 mmol/L; reference range 3.5-5.0). She also had magnesium and phosphate deficiency.

The patient had been diagnosed with transitional cell carcinoma of the bladder (grade 3) invading through the posterior wall of the bladder. Her diagnosis came a year previously with initial lower urinary tract symptoms and severe flank pain. The CT urogram at this point revealed a right-sided hydronephrosis and hydroureter secondary to a primary bladder tumour. She underwent extensive treatment including a radical cystectomy and ileal conduit with a resulting urostomy and four cycles of adjuvant Gemcitabine and Cisplatin chemotherapy. Post-treatment scans revealed local recurrence of the right pelvic side wall. As such, she was offered local radiotherapy to the right pelvic wall and three cycles of Atezolizumab immunotherapy thereafter, with the aim of control rather than cure. She had no other past medical history and had never required treatment for hypercalcaemia prior to this.

Her symptoms on admission were unsteadiness, weakness, feeling muddled, fatigue, poor appetite, and a general decline in function. On arrival, she received initial intravenous fluids with electrolyte replacements. IV Zoledronic acid was given on day 2 of her admission, due to persistent hypercalcaemia refractory to iv fluids.

On day 6 of her admission, she developed acute carpopedal spasms of both hands and wrists, with bilateral rigidity in both hands. On the day these symptoms developed, she was found to be hypocalcaemic (1.82 mmol/L). Her left hand was affected worse than her right hand. The rigidity was severe enough that all her fingernails (bar those of her thumb) were painfully indenting into the skin of her left palm. The muscle contraction itself was not painful, but she was unable to open her left hand and

hence her functional ability (such as holding cups etc.) was severely diminished. In addition, this new clinical presentation was distressing to her. There was no redness of swelling to the hands or wrists, apart from the indentations made by her fingernails. She also reported new perioral paraesthesia.

INVESTIGATIONS

The patient had sequential blood tests during her nine days of admission as summarized in Table 1. She remained persistently hypokalemic despite IV and oral supplementation. On day 6 of admission, the symptoms of tetany were found in both hands and a repeat set of bloods confirmed hypocalcemia. Subsequently, a vitamin D level was added on to the bloods which came back showing a mild deficiency. An ECG showed ST depression in leads V2-V4, T wave inversion and u waves, albeit a normal qTC interval. These findings were consistent with her hypokalaemia.

Electrolytes measured over the admission					
	Potassium	eGFR	Calcium	Phosphate	Magnesium
Day 1	**2.1**	**55**	**3.53**	1.01	0.93
Day 2	**3.1**	>90	**3.07**	-	0.77
	Zoledronic Acid 4mg infusion on day 2 of admission				
Day 3	**2.5**	>90	**2.72**	**0.42**	**0.66**
Day 4	**2.8**	>90	2.33	**<0.23**	-
Day 6	**2.1**	>90	**1.82**	**0.71**	**0.34**
	Patient developed symptoms of tetany as carpopedal spasms on day 6 of admission. Vitamin D was added onto the bloods of day 6 revealing normal level at the lower end of normal reference range (25nmol/L; reference range 25-50 nmol/l) Parathyroid Hormone Level was also normal 1.9 pmol/L				
Day 9	**2.6**	>90	**1.79**	**0.41**	**0.60**

Table 1: Blood results throughout admission. Those highlighted in bold are abnormal. No bloods taken on day 5, 7 or 8 of admission. References ranges: Potassium 3.5-5.0 mmol/L. eGFR: >90. Calcium: 2.20-2.60 mmol/L. Phosphate: 0.80-1.50 mmol/L. Magnesium: 0.71-1.00 mmol/L

DIFFERENTIAL DIAGNOSIS

Differential diagnoses considered by the clinical team included focal epileptic seizures, although the presentation would have been atypical. [7] Other electrolyte disturbances, including hypomagnesaemia,

hypokalaemia, and hypophosphatemia could have been causative or contributory causes for her symptoms, including the muscle spasm and contractures, however her symptoms improved when calcium was replaced. Her other electrolytes were resistant to the replacement regimens instituted. [10]

Her low adjusted calcium in fact persisted until day 9 and the refractory nature of the deficiency, despite best efforts to replace it, may have been contributed to by other electrolyte deficiencies. Low magnesium at the outset, for instance, can lead to a significant challenge in correcting hypokalemia, hypocalcemia and hypophosphatemia. [10]

TREATMENT

On admission from oncology clinic, she received initial fluid resuscitation and electrolyte replacements as summarised in Table 2. Subsequently her eGFR improved from day 2. Zoledronic acid 4mg was given on day 2 due to persistent hypercalcaemia refractory to adequate fluid replacement.

A trial of Baclofen 5mg tablets orally was commenced with good effect on day 6 of her admission to help ease the carpopedal muscular spasms in the hands and wrists. Occupational therapists were also involved to provide splints for the hands for comfort.

Summary of treatments given during admission	
Day 1	NaCl 0.9% 1L with KCL 40 mmol 4 hourly (x3) Commenced on 1 week of oral Sando K (2 sachets TDS)
Day 2	Zoledronic acid 4mg/100ml IV over 15 mins NaCl 0.9% 1L with KCL 40mmol 8 hourly NaCl 0.9% 1L 6 hourly (x2)
Day 3	NaCl 0.9% 1L with KCL 40 mmol 8 hourly NaCl 0.9% 1L with KCL 20 mmol 8 hourly
Day 4	Phosphate polyfuser 250ml with 25mmol 12 hourly
Day 5	Phosphate polyfuser 100ml with 10mmol 12 hourly
Day 6 *Symptoms of hypocalcaemia	Started Calcichew D3 2 tablets BD. NaCl 0.9% 500ml 20mmol MgSO4 4 hourly NaCl 0.9% 100ml IV calcium gluconate 10% 20ml 4.5mmol 1 hourly Started Baclofen 5mg TDS for carpopedal spasms
Day 7	NaCl 0.9% 1L IV 40mmol potassium and 10mmol magnesium 10 hourly NaCl 0.9% 1L with KCL 40 mmol 6 hourly

Day 9	5% Dextrose 100ml IV with 10% calcium gluconate 20ml of 4.5mmol 1 hourly 0.9% 1L IV 40mmol potassium and 10mmol magnesium 4 hourly. 0.9% 1L IV 10% calcium gluconate 100mls 22.5mmol 10 hourly.

Table 2: Summary of treatments patient received as an inpatient.

OUTCOME AND FOLLOW-UP

The patients carpopedal spasm resolved one hour after receiving oral baclofen, and she was able to hold a glass of water (she had not been able to do this during the acute episode). Her perioral anaesthesia improved once calcium had been supplemented. Her hand symptoms had gone by day 7 of the admission, however her other electrolytes (potassium, phosphate and magnesium) remained low despite supplementation.

Baclofen works as a GABA-B agonist in the central and peripheral nervous system. It reduces muscle spasticity through inhibition of synaptic transmission in motor neurons that innervate muscle spindles [11] For this reason it is commonly used to treat muscle spasms and spasticity in conditions such as multiple sclerosis, cerebral palsy and spinal cord injury, typically at a starting dose of 5mg orally three times a day. A trial of baclofen was commenced in this patient at a dose of 5mg TDS. The patient showed good response within an hour of administration, with a considerable reduction in the level of carpopedal spasticity caused by the hypocalcaemia.

Other members of the multidisciplinary team who contributed to an improvement in her symptoms were the occupational therapists, who were quick to suggest hand splints to reduce discomfort.

The patient was transferred to the inpatient hospice for symptom control as per the patient's expressed wishes mainly for pain control (she had pain from her metastatic disease). She continued oral calcium supplementation on discharge. By her own request she did not wish to receive further blood tests after transfer to the hospice.

We reported this side effect via the Medicines and Healthcare products Regulatory Agency (MHRA) yellow-card scheme.

DISCUSSION

Tetany manifesting as carpopedal spasm can be a serious and unpleasant side effect of bisphosphonate treatment, when the intended decrease in blood calcium becomes too pronounced. Whilst she received calcium and other electrolyte replacements, the main symptom relief she got for the carpopedal spasm

was after administration of oral Baclofen, which allowed her to get back to writing as well as picking up cutlery and glasses of water.

LEARNING POINTS/TAKE HOME MESSAGES

- Ensure that all patients with deranged calcium levels have a vitamin D level checked.
- Recognise that hypocalcaemia can be a side effect of treating hypercalcaemia with bisphosphonate treatment, particularly if vitamin D deficient.
- Careful monitoring of electrolytes is required when treating someone with bisphosphonates.

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