Severe hypocalcemia and hypophosphatemia following Denosumab administration in a multi-comorbidity patient

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Abstract

The case is presented of an elderly patient (DCP) with extensive medical history, including osteoporosis, who developed hypocalcaemia and hypophosphataemia whilst treated with denosumab, while prescribed concomitant calcium and vitamin D therapies. The management of this complex case involved a multidisciplinary team (MDT) approach, incorporating the patient's wishes. It included discontinuation of denosumab and intravenous (IV) and oral mineral supplementation that yielded gradual amelioration of calcium and phosphate levels. This case demonstrates the importance of vigilant monitoring and appropriate management in patients receiving denosumab, particularly those with multiple comorbidities. It carries important considerations for using denosumab for osteoporosis treatment in patients with complex medical backgrounds. Ethical clearance waiver was granted by the Trust Research Ethics Committee on 18/01/2024.

Keywords: osteoporosis, Denosumab, hypocalcaemia, hypophosphatemia

Background

Denosumab is a human monoclonal IgG2 antibody, primarily used to treat osteoporosis [1]. It acts by blocking receptor activator nuclear factor kB ligand (RANKL) that activates receptor activator nuclear factor kB (RANK) on osteoclasts, therefore competitively inhibiting other RANKLs [2]. RANKL is expressed by osteoblasts to stimulate bone resorption and activation of RANK stimulates osteoclastogenesis [2]. This reduces bone breakdown and prevents the progression of osteoporosis [1]. Osteoprotegrins are another receptor to RANKL, which affects several mechanisms, such as bone resorption, inflammatory responses and apoptosis [3].

Denosumab has World Health Organisation (WHO) type 1 side effects (attributable to its known mode of action) including electrolyte abnormalities, musculoskeletal pain and osteonecrosis of the jaw [1]. According to the manufacturer's product information, denosumab-induced electrolyte imbalances appear to be rarely reported in the literature, while the most reported complication is infection [2]. Denosumab-induced hypocalcaemia reportedly occurs in 5-10% of patients treated for bony metastases, and in up to 10-45% of patients with renal dysfunction [4,5]. This occurs around 10 days after the initiation of therapy, and it may take up to 8 weeks for serum calcium to return to normal levels, given the half-life of denosumab is around 30 days [5,6]. Hypophosphatemia can co-exist in these patients, particularly with impaired vitamin D metabolism secondary to CKD.

It is also reported that cases of hypophosphatemia and hypocalcaemia have occurred after initiation of denosumab in patients with metastatic cancer [5,7]. It is speculated that an underlying electrolyte imbalance is unproven but is believed

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to be due to the calcium-parathyroid-vitamin D axis [6]. Through denosumab's inhibition of osteoclastic activity and bone resorption, there is a decrease in serum calcium, with calcium being bound to bone [8]. Serum hypocalcaemia could lead to induction of the parathyroid gland to secrete parathyroid hormone. However, where this would usually increase serum calcium levels, if a patient is vitamin D deficient due to CKD, phosphate excretion and subsequent hypophosphatemia will occur and calcium levels would not be appropriately restored by gut resorption [7].

At the time of writing, this NHS Trust has 1003 patients prescribed denosumab. Based in a rural area of small, closely integrated communities, the detail we can present is limited because patients may be identified from the history. Of these, four experienced severe hypocalcaemia and hypophosphatemia (3.99/1000 patients) with one death (0.99/1000 patients), and three who recovered on cessation of treatment.

The aim of bringing this case to wider attention is to raise the awareness of medical practitioners and consultants of the need to be vigilant when prescribing denosumab to a patient with concurrent CKD diagnosis, and inform the future development of strategies to spot the development of complications earlier.

Case Presentation

DCP has a complicated medical history including recurrent iron deficiency anemia, mild folic acid deficiency, atrial fibrillation, sarcoidosis, type II diabetes mellitus, obstructive sleep apnoea, chronic kidney disease (CKD stage 3b) and prostate cancer for which he underwent prostatectomy. Denosumab 60 mg by slow subcutaneous injection every 6 months was commenced on 24/03/2022. In July 2023, DCP was first admitted to hospital with low calcium. Bowel cancer was considered but was not scheduled for further investigations due to his high risk of life-threatening perforation and blood loss. In addition, with a possible diagnosis of cancer, he would not be a candidate for dissection or chemotherapy due to his age, complex medical history and the absence of obstructions or adhesions. It was decided by his treating team that performing further invasive investigations carried too great a risk. Calcium and Vitamin D results are shown in figures 1A and B.

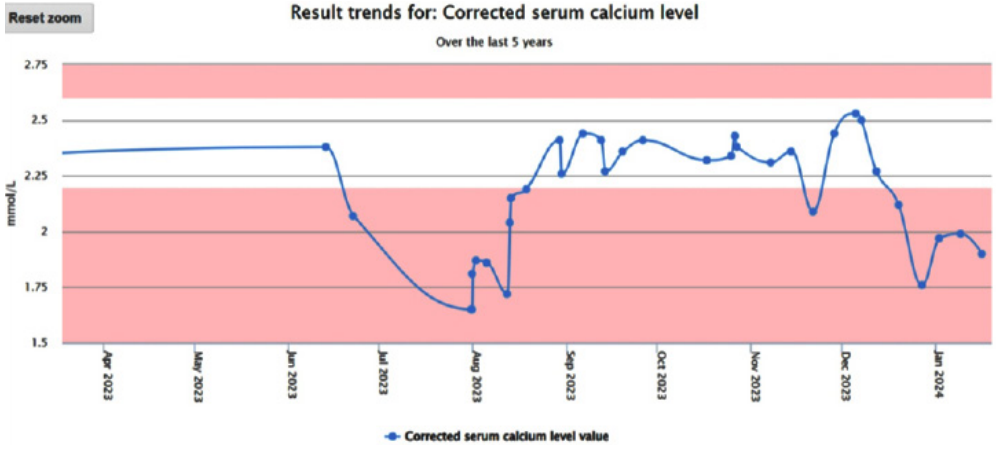

Figure 1 A. Calcium trend for MR DCP.

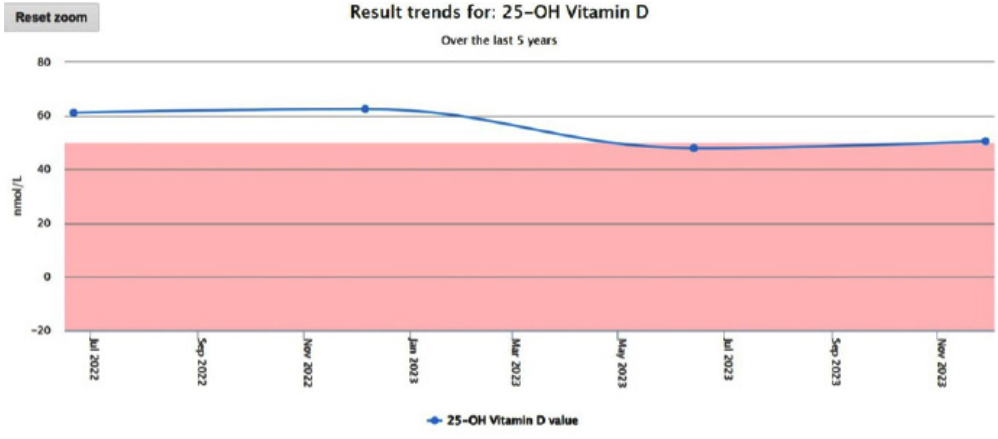

Figure 1B. Vitamin D trend for MR DCP.

Table I. Cases medical and medication history.

	Case 1 (DCP)	Case 2	Case 3	Case 4
Age at time of hypocalcaemia	84	84	93	89
Baseline adjusted calcium (mmol/L)	2.2	2.3	2.47	2.26
Baseline GFR	42	12	12	44
Post-treatment calcium (mmol/L)	2.36	1.5	1.7	1.78
Time to hypocalcaemia (weeks) after first dose	12 months	4 weeks	2 weeks	6 weeks
Co-administered drugs	Allopurinol 100 mg OD Sodium Bicarbonate 500 mg BD Atorvastatin 20 mg Nocte Omeprazole 20 mg OD Warfarin - stopped. Calcium Carbonate 1.25G and Colecalciferol 400IU Daily Goserelin 10.8 mg / 12 weeks Ferric carboxymaltose every 2 weeks	Citalopram 20 mg OD Furosemide 20 mg OD Ferrous sulphate 200 mg OD Nortriptyline 10 mg nocte Lactulose Gaviscon Omeprazole 20 mg OD Oxycodone MR 10 mg BD Oxycodone solution PRN Paracetamol PRN Pravastatin 20 mg OD	Amlodipine 10 mg OD Atorvastatin 10 mg OD Calcium Carbonate 1.25G and Colecalciferol 400IU Daily Prednisolone 5mg OD	Furosemide 40mg OD Diltiazem 10 mg OD Spironolactone 100 mg OD Isosorbide mononitrate 40 mg BD Clopidogrel 300 mg OD Travoprost eye drops BD
Possible drug-drug interactions No severe or life threatening interactions detected for any of the 4 patients [9]	**Calcium carbonate and iron:** oral calcium carbonate decreases the absorption of oral iron.	**Calcium carbonate and iron**: oral calcium carbonate decreases the absorption of oral iron. **Citalopram and esomeprazole**: esomeprazole increases the exposure to citalopram. **Citalopram and furosemide:** furosemide is predicted to cause hypokalaemia when given with citalopram. Both drugs can increase the risk of hyponatraemia. **Citalopram and nortriptyline, citalopram and oxycodone, nortriptyline and oxycodone**: both drugs can cause sedation which may affect the ability to perform skilled tasks. **Frusemide and nortriptyline:** both drugs can increase the risk of hyponatraemia and hypotension. **Paracetamol and pravastatin:** can increase the risk of hepatotoxicity.	No interactions documented	**Diltiazem, furosemide,** isosorbide, and spironolactone combination can increase the risk of hypotension.
Comorbidities	Recurrent Iron deficiency Anaemia Mild Folic acid deficiency Suspected bowel cancer Atrial fibrillation Sarcoidosis Type II diabetes mellitus. Obstructive sleep apnoea on CPAP CKD stage 3B Prostate cancer – prostatectomy	Osteoporosis Fractured hip 2021 CKD stage 5 Spinal stenosis Bronchiectasis Suspected bowel cancer	Osteoporosis Fractured sternum in 1986 CKD stage 5 Spinal stenosis Gout HTN	Osteoporosis: fracture left wrist 2013, T8-9 vertebra 2015 and sternum in 2017 CKD stage 3b CLL Atrial fibrillation Ischaemic heart disease History of recurrent chest infections (cryptogenic pneumonia 2015)
Severity	Severe	Severe	Severe	Moderate
Continued or ceased therapy	Ceased	Ceased	Ceased	Ceased
End outcome	Recovered	Recovered	Recovered	Deceased due to other unrelated complications

*DCP: the patient discussed in this report, OD: once daily, BD: twice daily, Nocte: at night, CKD: chronic kidney disease, MR: modified release, PRN: as required, HTN: hypertension, CLL: chronic lymphocytic leukaemia

Investigations and differential diagnosis

One year after the initiation of denosumab, DCP presented to his GP with severe fatigue. On investigation he had seriously reduced calcium and phosphate levels (corrected calcium 2.2 mmol/L and serum inorganic phosphate 0.33 mmol/L). Parathyroid hormone level was 9.9 pmol/L and levels of 25-OH Vitamin D were low at 47.9 nmol/L. His eGFR was 42 mL/min (stable CKD). Due to his CKD he had been prescribed calcium and vitamin D supplements, but had chosen to discontinue them over the summer and had not informed his carers. Interventions were initiated to ensure rigorous management of the patient's electrolyte imbalances while being mindful of his concurrent conditions. Given the history of chronic kidney disease and parathyroid disorder, the impact of concurrent self-discontinuation of calcium and vitamin D and the known relationship between denosumab administration and onset of hypocalcaemia, denosumab was discontinued. Drug-drug interactions as a cause were ruled out (Table I).

Treatment, outcome and follow-up

After ceasing Denosumab, IV calcium gluconate, oral phosphate two tablets three times a day (TDS), calcium carbonate 1.25 g/ cholecalciferol 400 iu, two tablets BD. After discussion with the metabolic bone disease consultant at the regional Metabolic Bone Centre, the strategy was changed to add calcitriol (activated vitamin D) 0.25 mcg BD, with monitoring of calcium in 2 weeks, 6 weeks and 3 monthly thereafter if stable. Calcitriol was to be titrated up to 1 mcg if necessary. With this treatment plan, the patient's corrected serum calcium reached 2.36 mmol/L and serum inorganic phosphate was 0.84 mmol/L within 8 weeks. This strategy served to gradually recalibrate calcium and phosphate levels, whilst maintaining a delicate balance of the patient's complex clinical picture. He had also previously received ferric carboxymaltose infusions, which were ceased, as it could be a confounding and contributing factor to the low phosphate. This regimen notably improved DCP's metabolic imbalance, but it took around 8 weeks for the calcium levels to stabilize. The patient was monitored through agreed, scheduled blood tests, ensuring a vigilant watch over electrolyte levels, and facilitating prompt intervention as required.

Discussion

Our four patients with hypocalcaemia shared the following in common: advanced age, chronic kidney disease (two with stage 5 and one with stage 3b) and multi comorbidities. Hypocalcaemia became apparent after first dose of denosumab dose (2-6 weeks) in three cases and after a year in one (Table I).

CKD, vitamin D deficiency and chronic iron deficiency are known major risk factors [5], of which all were present in DCP, and could have contributed to these complications.

Additionally, his previous medical history of iron and folic acid deficiency, previous prostate cancer, current colorectal cancer and stage 3B CKD, osteoporosis and type 2 diabetes, sarcoidosis and obstructive sleep apnea should also be considered as contributing factors due to their impact on further altering key homeostatic responses of the body when under stress and represent a challenging clinical dilemma in modern medicine [10]. Therefore, knowledge of complications such as those experienced in this case provide valuable learning as these cases become more common. DCP presented to the department of acute medicine on multiple occasions over a period of three months, during which his corrected calcium ranged from 2.05 to 1.65 to 2.19 mmol/L. Following the initiation of activated Vit D in the form of calcitriol after discussion with metabolic bone disease specialist, DCP's calcium stabilized, although it is of note that the team was not aware that he had previously chosen to discontinue his prescribed combined calcium with cholecalciferol tablets. The management of electrolyte abnormalities in the context of denosumab administration at present is to promptly stop denosumab and commence electrolyte replacement.

It must be noted however, that cessation of denosumab has its own consequences. A recent review by Sølling et al. [11] sets out in great detail the current evidence on the effects of cessation. They concluded that discontinuation rapidly leads to increased in bone turnover and loss, with increased fracture risk. They concluded a case could be made that treatment with denosumab should be life-long, but occurrence of side-effects may necessitate discontinuation. They suggest that patients stopping denosumab be offered other antiresorptive treatment with close monitoring in the first year as this is the period where most of the bone loss occurs.

Despite the risks, the potential benefits of denosumab in patients, even with end stage renal disease were well summarized in a recent review by Gu et al [12]. In their review of 12 studies covering 348 cases, the majority of patients saw a beneficial increase in bone mineral density with most not experiencing electrolyte disturbance. The potential benefits appear to outweigh the potential risks of therapy even in ESRD.

In conclusion, our patient manifests hypocalcaemia and hypophosphatemia, a relatively uncommon but important complication of denosumab treatment. Managing osteoporosis in patients with concurrent CKD, early withdrawal of denosumab and prompt, closely monitored treatment with IV calcium gluconate and oral phosphate, calcium and activated vitamin D was crucial to a successful outcome.

Conclusion

Denosumab is now widely used in the management of osteoporosis with high rates of success and low rates of adverse events, even in patients such as DCP, so similar presentations are likely to occur in the future.

In deciding to prescribe denosumab in patients with concurrent pathologies, notably CKD, consideration of the potential to develop hypocalcaemia should be considered and monitored.

Discussion of this case is intended to lead to further case presentations that will inform development of strategies to better monitor such patients aiming for earlier detection and intervention.

Discussion with appropriate specialists and initiation of appropriate doses and formulations of vitamin D and calcium was the turning point in the progress of this patient.

The evaluation of the risk-benefit profile of denosumab should be considered, noting concurrent pathologies and potential interactions. Discontinuation of denosumab and appropriate supplementation can lead to the resolution of hypocalcaemia and hypophosphatemia, but also results in rapid loss of any benefit from the denosumab therapy, which will need to be addressed. Patient education is paramount in continuing with calcium and vitamin D supplementation when denosumab is to be used as a long-term treatment of osteoporosis.

Adherence to prescribed therapy by the patient should not be assumed.

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