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Case Report

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Denosumab Induced Hypocalcaemic Seizures

Will Jervis[1], Najeeb Shah[2]* and Kamrudeen Mohammed[2]

[1]Scunthorpe General Hospital, Cliff Gardens, DN15 7BH

[2]Hull Royal Infirmary, Anlaby road, HU3 2JZ

***Corresponding Author:** Najeeb Shah, Hull Royal Infirmary, Anlaby road, HU3 2JZ.

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Abstract

Denosumab is a monoclonal antibody that is approved in the United States and Europe for the treatment of osteoporosis. Denosumab is typically given every 6 months and there is no current requirement for monitoring or dose adjustment in renal impairment. We present a case of a patient with chronic kidney disease stage 4 who presented with a generalised tonic clonic seizure and prolonged QT secondary to severe hypocalcaemia (1.43 mmol/L) 13 days after receiving a single dose of denosumab as treatment for osteoporosis. The patient was therefore commenced on an intravenous calcium infusion, which restored her calcium to near normal range and she had no further seizure activity. This report highlights the severe hypocalcaemia that can develop from a single dose of denosumab. We recommend that further monitoring of eGFR/serum calcium/vitamin D is required prior and post dosing of denosumab to help immediately recognise and treat life-threatening hypocalcaemia following denosumab administration.

Keywords: *Denusomab; Osteoporosis; Hypocalcaemia; Seizure; Chronic kidney disease.*

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Background

Denosumab is a monoclonal antibody that binds RANKL, reducing the activation of RANK on the surfaces of osteoclasts, decreasing bone reabsorption in trabecular and cortical bone [1,2]. Denosumab is approved in the United States and Europe and is used for the treatment of osteoporosis and is typically given every 6 months [3,4]. Hypocalcaemia is a recognised side effect of denosumab, however the degree of this is uncertain and might be expected in patients with severe/end stage renal disease. Currently calcium levels are suggested for monitoring before and after dosing but there is no current requirement for monitoring of renal function or dose adjustment with denosumab. We report a case of life-threatening hypocalcaemia presenting as a seizure and prolonged QT following a single dose of denosumab in a 70-year-old female with chronic kidney disease (CKD).

Case

A 70-year-old female with history of asthma, osteoarthritis, low impact right shoulder and wrist fracture, spondylosis, CKD stage 4 and osteoporosis presented to accident and emergency with a single episode of a generalized tonic clonic seizure lasting 10 minutes. She remained post ictal subsequently for a number of hours and after coming around fully had no recollection of events leading to admission.

She was not a known epileptic and did not consume alcohol. There was no history of head injury or infective symptoms. Her blood tests revealed serum adjusted calcium 1.43 mmol/L (2.2-2.6), magnesium 0.52 mmol/L (0.7-1.0), potassium 4.0 mmol/L (3.5-5.3), urea 13 mmol/L (3.0-7.6), creatinine 203 umol/L (55-87), eGFR 20ml/min/1.73m2 and vitamin D 68.9 nmol/L. ECG revealed sinus rhythm with a QTc of 516ms. Given the post ictal state clinical signs associated with hypocalcaemia could not be elicited.

She was treated with intravenous calcium infusion on an emergency basis together with intravenous magnesium and was subsequently started on combined calcium and vitamin D tablets. This treated her hypocalcaemia to near normal range and there was no further seizure activity [table 1].

Prior to this episode the patient had osteoporosis with a previous DEXA scan revealing AP spine (L2-4) T score -1.4 Z score 0.3 and right neck of femur T score -3.2 Z -1.6. She was commenced on denusomab injections 13 days prior to this presentation; chosen in view of her poor renal function. At the time of her injection a complete secondary osteoporosis screen including parathyroid hormone level was normal. Her serum adjusted calcium level was 2.42 mmol/L (2.20-2.60) and Vitamin D was 59.1 nmol/L.

Days following admission	Day 1 (admission)	Day 2	Day 3	Day 4	Day 5	Day 6
Adjusted calcium mmol/L	1.43	1.54	1.74	2.03	1.97	1.96

Table 1: *adjusted calcium each day following initial admission.*

Discussion

Denosumab is not known to be nephrotoxic however is known to cause hypocalcaemia in patients with an eGFR <30 [5]. Previous studies including the FREEDOM study originally concluded that denosumab was suitable and safe treatment for osteoporosis [1]. The study did not report hypocalcaemia in patients with CKD stage 1-4, however patients with stage 5 CKD were excluded [6]. Another study involving single dosing of denosumab demonstrated no cases of serious adverse effects from hypocalcaemia in patients with CKD stages 1-4 however a small sample size was used and stage 5-kidney disease was again excluded [7]. Despite reporting no serious adverse effects from hypocalcaemia, around 15% of the patients in the study experienced a degree of hypocalcaemia. Hypocalcaemia to a certain degree has therefore been shown to be prevalent in patients with CKD receiving denosumab in previous studies, however previous research has been unable to establish the severity of denosumab induced hypocalcaemia in CKD stage 1-4. Whilst denosumab is licenced for use in patients with CKD stage 5, previous evidence has not examined the safety of its use in end stage renal disease.

Previous cases have reported severe hypocalcaemia in patients following denosumab administration [4,8]. Many of these case reports involved patients with renal impairment including CKD stage 4 and 5 who had a normal calcium prior to denosumab administration. These cases have reported a similar reduction in calcium and time spans of hypocalcaemia developing range between 10 days to 3 weeks following denosumab administration. Despite similar previously reported levels of hypocalcaemia following denosumab administration, this report is the first to describe a patient experiencing seizure secondary to the hypocalcaemia induced by a single dose of denosumab. The presentation of a seizure demonstrates the life-threatening risks of severe hypocalcaemia that can be induced by a single dose of denosumab.

Key Points

Denosumab should be used with great caution in patients with an eGFR <30 and life-threatening severe hypocalcaemia can be expected to develop around 10 days to 3 weeks following administration.

The current recommendation of measuring sole serum calcium following administration is insufficient to ensue the prevention of hypocalcaemia.

We recommend monitoring eGFR/serum calcium/vitamin D prior and post-dosing of denosumab in particular patients with CKD.

Further studies are required to explore the severity of hypocalcaemia following denosumab administration in patients with CKD stage 1-5. Patients should be counselled about this extreme life-threatening side effect.

Ethical Responsibilities of Authors

Will Jervis, Najeeb Shah and Kamrudeen Mohammed declare they have no conflict of interest. The authors declare no competing financial interest. Informed consent was obtained from all individual participants included in the study.

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