Hypocalcemia Secondary to Denosumab: A Case Study

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Introduction

- Denosumab is a monoclonal antibody that inhibits osteoclast mediated breakdown of bone.1 Thus, it leads to prevention of bone resorption and potentially to hypocalcemia.
- Denosumab is primarily used in treatment of osteoporosis and prevention of adverse skeletal events in patient with metastatic disease of the bone.2
- In this case, a patient became hypocalcemic after receiving a single denosumab injection.
- We will review the patient presentation, hospital course, and details regarding denosumab's mechanism of action and how it leads to hypocalcemia.
- This case will be used to highlight importance of factors to consider before starting someone on denosumab as well as management of patients on denosumab to prevent likelihood of developing hypocalcemia.

Case Presentation

HPI: Pt was a 57 y.o. female who presented to the ER with some chest pressure and "felt funny". She was primarily presenting at request of PCP who advised her to go to ED after lab draw revealed calcium of 6.6. Patient was having this lab draw as follow up after receiving Prolia in previous weeks. Patient reported no other symptoms.

ROS: Unremarkable apart from chest pain. In particular, patient denied complaints including numbness or tingling, spasms, convulsions, weakness, difficulty swallowing, etc

PMH: CKD Stage 3, Systemic Lupus Erythematosus, Obesity with prior Roux-en-Y gastric bypass in 2005, Hypothyroidism, Vitamin D Deficiency, Anemia of Chronic Disease, COPD, Asthma, and Depression and Anxiety

PSH: Roux-en-Y gastric bypass in 2005, Salpingoopherectomy, Tubal ligation, Right and Left Shoulder repair, Bilateral total knee arthroplasties, Thyroidectomy

Social History: Didn't smoke, use illicit drugs, or drink alcohol

FH: No pertinent FH of CKD, autoimmune disorders, thyroid disorders, anemia were obtained.

Medications: Ativan, Benlysta, DuoNeb, Fluoxetine, Lamictal, Plaquenil, ProAir, Protonix, Synthroid, Vitamin D3 5000 IU, Allopurinol, Aspirin 81 mg, Bupropion, Bumetanide, Cyanocobalamin, Docusate-senna, Ferrous sulfate, Fluticasone, Gabapentin, Potassium chloride, Nortriptyline, Sucralfate, Trazadone
Allergies: Latex, tape

Physical Exam:
General: NAD, Alert and oriented x3
HEENT: NC/AT
CV: RRR, no m/r/g
Pulm: CTAB, no adventitious breath sounds
Abdomen: soft, NT, ND, BS present
MSK: Negative Chvostek and Trousseau sign, muscle tone intact
Neuro: No FND, no tingling, normal DTRs
Psych: Mood and affect appropriate

Pertinent Labs:
Calcium Ionized 0.88 (L)
BUN 14.2
Cr 1.27
GFR 46
Calcium 6.4 (7.2 when adjusted for Albumin) (L)
Albumin 3.0 (L)
Magnesium 2.8 (H)
TSH 4.93
Phosphorus 3.2
Vitamin D 38
PTH 467.5 (H)

Diagnostic Studies:
EKG- QTc prolongation

PLAN: Patient was admitted by hospitalist service for correction of hypocalcemia. Monitored with telemetry.

Hospital Course

The hospitalist team saw and evaluated patient and ordered repeat labs including CBC, metabolic panel, PTH, phosphorus, magnesium, TSH, Vitamin D Level. Repeat EKG was ordered as patient had QTc prolongation discovered on EKG performed in the ED. Patient received 2g of IV calcium gluconate. Serial measurements of ionized calcium and serum potassium were drawn every 6 hours. Patient telemetry monitored and also physical exams performed to ensure no signs hypocalcemia evident on exam.

Patient was in the hospital for two days total. She had a repeat calcium of 6.4 and then 7.0. Patient's Vitamin B12 was high at 6000, magnesium was 2.6, phosphorus was 3.2. Repeat EKG came back unremarkable with improvement of QTc prolongation. Patient was continued on IV fluids with calcium gluconate, placed on calcitriol 0.5 mcg daily, and put on oral replacement of Calcium Citrate with Vitamin D. Patient remained asymptomatic through her hospital course. Through the rest of the hospital stay, patient's ionized calcium increased from 0.88 up to 1.21 on day of discharge. Her serum calcium improved to normal range at 9.1 on day of discharge.

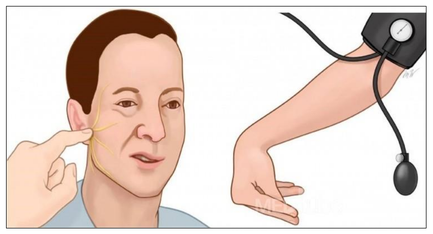

Figure 1: MedTube.net
Chvostek Sign (1st Image); Trousseau Sign (2nd Image)

Management Post Hospital Course

Patient was discharged on Calcium Citrate with Vitamin D four times daily and calcitriol 0.5 mcg daily. Outpatient labs were ordered including repeat ionized calcium, magnesium, phosphorus, and CMP. Strong recommendation was made that she shouldn't receive any further denosumab injections.

Patient's calcium continued to be monitored in the outpatient setting. Her calcium decreased back to 7.9 ten days after discharge. They remained in the 7.6 to 8.4 range for two months. Corrected for albumin, the range was 8.2 to 8.6. After two months calcium levels stabilized between 8.5 and 9.0 with corrected values of 9.0 to 10.0. Patient was maintained on the same dose of calcitriol and calcium supplementation. She has received no further denosumanb injections since.

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Discussion

There are numerous causes for hypocalcemia in addition to denosumab use present in this case including the patient's prior history of gastric bypass surgery, patient's Vitamin D deficiency, and patient's stage CKD and resultant secondary hyperparathyroidism.

Calcium in the serum is normally effected by 1,25 Dihydroxy vitamin D and PTH, which leads to increased serum calcium by (1) absorption of calcium in the GI system, (2) bone remodeling and release of calcium by breaking down bone, as well as (3) decreased urinary excretion of calcium.3 Factors that can contribute to increased risk of hypocalcemia thus include high bone turnover, renal insufficiency, absence of vitamin D and calcium supplementation.4 Gastrectomy with Roux-en-Y led to increased chance of hypocalcemia secondary to malabsorption.4

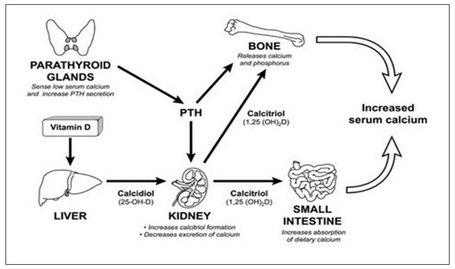

Figure 2: *Disorder of Calcium Metabolism*
Demonstrates factors promoting calcium release

Denosumab is a monoclonal antibody that inhibits osteoclast mediated resorption of bone.1,5 It acts by binding RANKL, which normally binds to the RANK receptor on osteoclasts and leads to bone resorption.5,6 Normally, the breakdown of bone by osteoclasts decreases bone density and leads to skeletal related events that are adverse.1 This inhibition of the breakdown of bone decreases fracture risk.1 The prevention of breakdown of bone also leads to decreased serum calcium by way of bone resorption. Denosumab is primarily indicated for use in osteoporosis.1,5,7

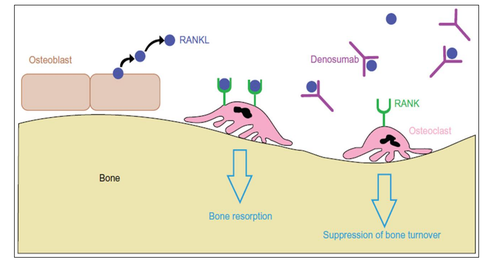

Figure 3: *Osteoporosis in men: epidemiology and treatment with denosumab*
Demonstrating osteoblasts, osteoclasts, and effect of denosumab.

It is important to keep an eye on patients and monitor their calcium levels after they are started on denosumab. There is a noted benefit to obtaining a baseline of calcium, vitamin D, PTH, magnesium, phosphate, albumin, and kidney function.1,3,6 It is important that a physician discusses the potential risks and benefits of denosumab as well as the risk of hypocalcemia before starting denosumab. Consideration should be given to other drugs that could be used to treat osteoporosis such as alendronate and whether they might be more suitable for use over denosumab based on the patient's medical history. If the decision is reached to start a patient on denosumab, patients should have baseline labs drawn before starting the medicine and then again within a couple of weeks. They should have continued monitoring of their calcium levels and appropriate supplementation as necessary. There is noted benefit to Calcium and Vitamin D supplementation in these patient as well.12,13

Conclusion

In summary, while denosumab is a useful medicine in treating osteoporosis, caution should be taken into consideration with patients who are predisposed to hypocalcemia. Hypocalcemia can lead to potential severe life threatening consequences if not recognized and treated. For this reason, it is crucial to check levels of calcium, vitamin D, and other markers prior to starting a patient on denosumab. Levels should be monitored throughout the patient's course of taking the medicine and they should be appropriately supplemented to avoid hypocalcemia and the complications from it.

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