Hypocalcemia after Denosumab in a Pulmonary Hypertension Patient Receiving Epoprostenol

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Established Facts

- Severe hypocalcemia has been described after the use of denosumab in patients with osteomalacia and normal renal function.

Novel Insights

- To our knowledge, this is the first report of severe hypocalcemia due to the combination of denosumab with epoprostenol-induced diarrhea in a patient with pulmonary arterial hypertension.

Keywords

Denosumab · Hypocalcemia · Pulmonary arterial hypertension · Epoprostenol · Malabsorption · Nutritional osteomalacia

Abstract

We report the case of a 50-year-old woman with anorexigen-induced pulmonary arterial hypertension treated with epoprostenol, who presented with Trousseau's sign, leading to the diagnosis of severe hypocalcemia for which substitution was started (initially orally, followed by intravenous substitution). After further analysis, we assume that epoprostenol-induced diarrhea caused malabsorption (as other reasons were excluded), leading to nutritional osteomalacia with secondary hyperparathyroidism. We discovered that even

more severe hypocalcemia was induced by the treatment with the anti-osteoporotic drug denosumab, which was started after the diagnosis of osteoporosis on bone densitometry. In our opinion, clinicians have to be aware that in patients with malabsorption, antiresorptive therapy can induce dangerous and even life-threatening hypocalcemia, even in patients with normal renal function.

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Introduction

We present a case of severe hypocalcemia, induced by the anti-osteoporotic drug denosumab, in combination with epoprostenol-induced diarrhea in a patient with pulmonary arterial hypertension (PAH).

Table 1. Evolution of our patient's blood results over time

	Calcium, mmol/L	Phosphate, mmol/L	Albumin, g/L	Parathyroid hormone, ng/L ^a	25-hydroxyvitamin D, µg/L ^b	1,25-dihydroxyvitamin D, µg/L ^c	Calciuria	
							mmol/24 h	mg/24 h
Reference value	2.15–2.55	0.81–1.45	35–52	15–65	11–60	20–80	2.5–7.5	100–300
Day 0								
Morning	1.63	0.13	39.3					
Noon				442.7	36.4			
Evening	1.75	0.26	35.2					
Day 1	1.9	0.21	33.3					
Day 2	2.29	0.18	32.8				1.2	46.9
Day 3	2.14	0.53	30.5					
Day 5	1.81	0.37	31.7					
Day 7	1.94	0.34		311.1				
Day 9	2.25	0.33	38					
Day 15	2.17	0.68		154			0.7	26.9
Month 1.5	2.39	0.61	40.6	72.8			1.3	52.9
Month 3	2.37	0.79	41.5		41.1	27	1.8	72.1
Month 5	2.49	0.79	42.7		40.4	27.4	4.2	166.6
Month 7	2.48	0.95	42.9		45.9	29.1	3.8	151.8
Month 11	2.41	0.82	43.3				2.7	110.1

Day 0, day of hospitalization and start of therapy by means of intravenous calcium substitution.

^a Measured by electrochemiluminescence immunoassay; ^b measured by radioimmunoassay; ^c measured by liquid chromatography tandem mass spectrometry (LC-MS/MS) method.

Case Report

A 50-year-old woman with anorexigen-induced PAH, treated with oral anticoagulants, epoprostenol, and sildenafil since 19 and 12 years, respectively, was seen on a regular follow-up visit. She had a medical history of obesity and prostacyclin-induced hyperthyroidism treated with propylthiouracil and radioactive iodine in 1999 and 2001. In 2000, a mastectomy was performed because of a ductal carcinoma in situ of the right breast, and in 2011, she was treated for diverticulitis with Hartmann's procedure, which has been repaired in 2012. Eighteen months ago, she had a humeral traumatic fracture. Osteoporosis was diagnosed by bone densitometry (T score of −3.3 at the lumbar level), and anti-osteoporotic therapy with calcium carbonate (1,250 mg daily), vitamin D (25,000 IU monthly) as well as the antiresorptive drug denosumab (60 mg every 6 months) was started (16 months before presentation). Her other medication at the follow-up visit consisted of oral anticoagulants, pantoprazole (40 mg daily), iron substitution, potassium substitution, epoprostenol, and sildenafil.

Then, she presented to an affiliated hospital because of complaints of paresthesia of the hands and feet. Trousseau's sign was observed leading to the diagnosis of hypocalcemia for which calcium carbonate substitution was raised to 1,250 mg twice daily. At our follow-up visit 1 week later, paresthesia and jaw pain had resolved. Blood results revealed ion disorders with severe hypocalcemia (1.63 mmol/L, reference 2.15–2.55 mmol/L) and hypophosphatemia (0.13 mmol/L, reference 0.81–1.45 mmol/L) (Table 1). Magnesium, sodium, and potassium, as well as total protein and albumin level were within normal range. Her parathyroid hormone (PTH) level was highly elevated (442.7 ng/L, measured by electrochemiluminescence immunoassay). The ionized calcium

level on arterial blood gas was 0.84 mmol/L (corrected for pH 7.4, 0.90 mmol/L or 3.61 mg/dL).

A slow correction of the ionized calcium levels (0.92 mmol/L after 2 h, 0.94 mmol/L after 4 h) was obtained by administrating calcium gluconate 10% intravenously at a rate of 900 mg elementary calcium per 24 h, as well as 3 g magnesium sulfate under cardiac monitoring. After 48 h, normal calcium levels were achieved, and calcium substitution was continued per os (initially calcium carbonate but afterwards with calcium citrate), first with 3.5 g calcium daily, raised to 5 g and later 6 g daily because of recurrent hypocalcemia. Since the hypophosphatemia did not resolve despite the normalization of the calcium levels, per os substitution was started in increasing doses.

At first, the etiology of the hypocalcemia was unclear: the patient had been taking vitamin D and calcium substitution correctly since starting the treatment with denosumab, as confirmed by her serum 25-hydroxyvitamin D levels which were within the normal range (36.4 µg/L, reference 11–60, measured by radioimmunoassay). In addition, as recommended by the European Medicines Agency (EMA), the calcium levels were checked 2 and 4 months after starting the treatment with denosumab and were within the normal range (2.32 and 2.28 mmol/L, respectively). Retrospectively, at the start of the denosumab treatment, hyperparathyroidism (129.2 ng/L, reference 15–65) had already been present with a borderline vitamin D level of 19.5 µg/L. Hence, calcium malabsorption was suspected. Since calciuria remained extremely low 36 h after starting calcium substitution (46.9 mg/24 h or 1.2 mmol/24 h) in combination with low folic acid and vitamin A, malabsorption was confirmed. The previous diagnosis of "osteoporosis" was revised to "osteomalacia," presumably secondary to malabsorption. Our patient's history indeed revealed at least once

daily episodes of diarrhea since starting the treatment with epoprostenol.

Other screening tests (by means of IgA and tissue transglutaminase antibodies, gastroscopy with gastric and duodenal biopsies, mixed triglyceride breath test, and 3 times 24-h fecal collections for fat dosage) could exclude other etiologies of malabsorption.

We assume that because of malabsorption (probably epoprostenol induced as other reasons were excluded), nutritional osteomalacia occurred with secondary hyperparathyroidism. Even more severe hypocalcemia was induced by the treatment with the antiresorptive drug denosumab, with even higher PTH levels and consequently hypophosphatemia, as was confirmed by a calcium level that stayed within the normal range 7 months after stopping denosumab (Table 1).

Discussion

Osteomalacia is a disorder characterized by bone demineralization that can be induced by malabsorption of calcium, vitamin D deficiency, insufficient calcium intake, or/and phosphate deficiency. Typical biochemical abnormalities include low or normal calcium levels, decreased levels of vitamin D, and normal or elevated PTH levels, as well as discretely elevated alkaline phosphatase levels [1]. In this case, we suspect that diarrhea, which is a frequent side effect of epoprostenol, a synthetic prostacyclin analogue given by continuous intravenous administration in severe PAH patients, is the ultimate cause of calcium malabsorption [2, 3].

Denosumab is a human monoclonal antibody, which inhibits the receptor activator of nuclear factor kappa-B ligand (RANK-ligand). By this, it prevents binding of the RANK-ligand to RANK. This drug strongly reduces bone resorption by inhibiting osteoclast activity as well as osteoclast generation. It is used as a treatment for osteoporosis in postmenopausal women with a persistent high risk of bone fractures (despite the treatment with bisphosphonates or in those with intolerance to bisphosphonates), as a treatment for bone loss related to hormonal ablation in prostate cancer as well as for the treatment of bone metastases of solid tumors. Hypocalcemia is an important (usually mild and therefore asymptomatic and transient) side effect in patients with bone metastases, though not withheld as a side effect in the study of denosumab used for the treatment of osteoporosis in postmenopausal women. Before starting treatment with denosumab, calcium and vitamin D levels need to be optimized, and hypocalcemia needs to be corrected. A potential well-recognized risk factor facilitating hypocalcemia is chronic kidney disease with a clearance <50 mL/

min (as well as end stage renal disease) [4–9]. In addition, it has been shown that prostacyclin itself has an effect on bone modelling: it inhibits osteoclasts, and an overproduction of prostacyclin can reduce osteoblast differentiation [10, 11]. Since both denosumab and prostacyclin (which both inhibit osteoclast activity) were used in this patient, we assume that the risk of inducing hypocalcemia may have been even higher.

In this case, we discovered that calcium malabsorption can exist even with normal 25-hydroxyvitamin D levels, as was demonstrated by the low calcium excretion (despite normal renal function) and secondary hyperparathyroidism. It is important to acknowledge that, under these circumstances, a strong inhibition of bone resorption can cause hypocalcemia with even higher PTH levels.

To our knowledge, only one other case of severe hypocalcemia has been described after the use of denosumab in a patient with osteomalacia and normal renal function. However, this is the first report of severe hypocalcemia in a patient treated with epoprostenol. Clinicians have to be aware that in patients with malabsorption, antiresorptive therapy can induce dangerous and even life-threatening hypocalcemia [12]. Therefore, we presume that the vigilance of calcium levels is important in patients with risk factors for hypocalcemia, even during intervals between 2 consecutive administrations of denosumab; furthermore, patients should be educated to recognize and report symptoms of hypocalcemia.

Financial Disclosure and Conflicts of Interest

Dr. De Muynck reports financial support for one congress from Pfizer, outside the submitted work. Dr. Leys, Dr. Cuypers, and Dr. Vanderschueren have nothing to disclose. Dr. Delcroix reports grants from Actelion, personal fees from Bayer, and personal fees from Actelion, outside the submitted work. Dr. Belge reports personal fees from GSK (GlaxoSmithKline) and personal fees from Actelion, outside the submitted work.

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