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Teriparatide Associated Late Hypercalcemia: A Report of Two Cases and Literature Review

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Abstract

Introduction: Teriparatide, recombinant human parathyroid hormone (1–34), is a safe and usually well-tolerated medication. We describe two cases of late-onset hypercalcemia associated with teriparatide use and report current evidence of hypercalcemia during the treatment with PTH analogs.

Case report: Case 1 is a 54-year-old man with a history of osteoporosis, previously treated with 6 months of teriparatide, but had not been consistent in taking the medication. Before restarting teriparatide, his serum calcium, PTH and vitamin D were normal. Six months into the treatment, he developed asymptomatic hypercalcemia of 11.2 mg/dL 24 h after the last dose. Repeat serum calcium was normal and treatment was continued. Case 2 is a 75-year old woman with a history of osteopenia and severe scoliosis. Before starting teriparatide, her calcium, PTH and vitamin D were normal. Six months into the treatment, she developed asymptomatic hypercalcemia of 12.5 mg/dL. Teriparatide was held and subsequently her serum calcium normalized.

Discussion: Transient hypercalcemia can occur during treatment with teriparatide and usually resolves within 16 h after administration. Late hypercalcemia, occurring more than 24 h after the dose, is rarely seen. It is usually mild, asymptomatic and rarely occurs repeatedly. Hypercalcemia occurs more often in patients with pre-existing hypercalcemia or vitamin D deficiency. It is rarely a cause of treatment disruption (0.18–4%).

Conclusion: Clinicians should be aware of this side effect, especially in patients who may be at risk of complications of hypercalcemia.

Keywords: Teriparatide, Hypercalcemia, Adverse effects

1. Introduction

Teriparatide, recombinant human parathyroid hormone (1–34), has a long track record of safety and it is usually well-tolerated. Side effects of teriparatide are usually mild and include muscle pain, weakness, dizziness, headache and nausea.^{1–3} Hypercalcemia during teriparatide treatment has been described in the initial clinical trials. It usually occurs within 4–6 h and resolves by 16–24 h after dose administration.⁴ When late hypercalcemia occurs, it is of concern for clinicians. In this paper, we will report two cases of hypercalcemia during teriparatide therapy. Additionally, we will also review the available literature regarding hypercalcemia associated with the use of PTH analogs.

2. Case reports

Case 1 is a 54-year-old man with a history of osteoporosis, type 1 diabetes, hypothyroidism, hypertension and remote history of calculi and nephrolithiasis (more than 5 years ago). Medications included levothyroxine, simvastatin, bupropion, venlafaxine, insulin lispro via insulin pump, dulaglutide, ramipril, fluticasone inhaled and aspirin. Bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA) showed lumbar spine T-score of –2.8, with a corresponding Z score of –2.3, femoral neck T-score of –1.0, with a corresponding Z score of –0.2 and total hip T-score of –0.3 with Z-score of 0.1. He had been previously treated with bisphosphonates for approximately 5 years and had

Abbreviations: PTH, parathyroid hormone; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry.

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Table 1. Case 1 - summary of laboratory data.

Investigation	Prior to treatment	During the treatment	Repeat laboratory data	Reference range
Sodium (mmol/L)	138	145	140	135–145
Potassium (mmol/L)	4.2	5.8	4.5	3.5–5.1
BUN (mg/dL)	11	12	14	7–20
Creatinine (mg/dL)	0.91	1.0	0.86	0.5–1.3
Albumin (g/dL)	4.2	NA	4.5	3.4–5.0
Calcium (mg/dL)	9.3 (8.5–10.1)	11.2 (8.6–10.4)	10.7 (8.5–10.1)	–
25(OH)D (ng/mL)	49	NA	45.1	30.0–100.0
PTH (pg/mL)	41.3	NA	NA	8.7–77.1
24-h urine calcium (mg)	238	NA	NA	42–353
24-h urine creatinine (g)	1.7	NA	NA	0.6–2.5

Abbreviations: BUN = Blood Urea Nitrogen; 25(OH)D = 25-hydroxy-vitamin D; NA = not available.

been on a course of teriparatide for about 6 months, but had not been consistent in taking the medication. The decision was made to restart teriparatide 20 µg subcutaneously daily for an additional 18 months.

Prior to restarting teriparatide, his initial laboratory data were notable for normal serum calcium of 9.3 mg/dL and normal vitamin D (Table 1). Additionally, due to history of calciuria, 24-h urine calcium studies were obtained and were normal. Six months into the treatment, he was noted to have asymptomatic hypercalcemia of 11.2 mg/dL (obtained approximately 24 h after the last injection). Four days later, a repeat laboratory panel was obtained, showing serum calcium of 10.7 mg/dL with normal vitamin D. Patient remained on teriparatide therapy. On subsequent follow-up visits, his serum calcium remained within normal limits (9.1 mg/dL).

Case 2 is a 75-year-old woman with a history of osteopenia and severe progressive scoliosis. She had previously been on a course of raloxifene and then preventive doses of alendronate. Medications included 1000 mg calcium and 1000 IU vitamin D daily, vitamin D 50,000 IU monthly and aspirin daily. Due to osteopenia, at risk for fracture and severe debilitating scoliosis, she was started on 20 µg/day of teriparatide. A DXA scan later revealed

lumbar spine T-score of –0.7 with a corresponding Z score of 1.8, femoral neck T-score of –2.5 with a Z-score of –0.4, total hip T-score of –1.7 with Z-score of 0.1 and the distal forearm T-score of –2.9 with Z-score of –0.2.

Prior to treatment start, calcium levels were normal at 9.3 mg/dL with normal PTH and vitamin D levels (Table 2). Six months into the treatment, the patient was noted to have asymptomatic hypercalcemia of 12.5 mg/dL (24 h after the last teriparatide dose). Subsequently, teriparatide treatment was held. On follow-up visits, serum calcium remained within normal ranges. Additionally, three months before the hypercalcemic event, she was noted to have low 25-hydroxy-vitamin D of 24.2 ng/mL. However, on a repeat laboratory panel after resolution of hypercalcemia, the vitamin D levels were normal.

3. Discussion

Given the physiological effects of PTH and hypercalcemia seen in hyperparathyroidism, there was a natural concern of hypercalcemia with the use of PTH analogs. Transient increase in serum calcium can occur within the first 4–6 h after 20 µg dose of teriparatide, with a median increase of 0.4 mg/dL.

Table 2. Case 2 - summary of laboratory data.

Investigation	Prior to treatment	During the treatment	Repeat laboratory data	Reference range
Sodium (mmol/L)	140	141	139	135–145
Potassium (mmol/L)	4.5	4.0	4.1	3.5–5.1
BUN (mg/dL)	24	29	23	7–25
Creatinine (mg/dL)	0.64	0.85	0.65	0.6–0.93
Albumin (g/dL)	4.3	4.3	3.9	3.6–5.1
Calcium (mg/dL)	9.5	12.5	9.3	8.6–10.4
25(OH)D (ng/mL)	33	NA	32	30.0–100.0
PTH (pg/mL)	24	NA	83, repeat 43	14–64
ALP (U/L)	57	143	214	33–130
24-h urine calcium (mg)	210	NA	31	35–250
Calcium/creatinine ratio in 24-h urine (mg/g)	230	NA	57	30–275

Abbreviations: BUN = Blood Urea Nitrogen; 25(OH)D = 25-hydroxy-vitamin D; ALP = alkaline phosphatase; NA = not available.

However, by 16–24 h after the dose, serum calcium returns to predose levels, thus hypercalcemia prior to the morning dose is rarely seen.^{1,4}

The pivotal study in postmenopausal women reported a rate of postdose hypercalcemia at least once in 11% of women treated with 20 µg/day of teriparatide, compared to 2% of women in the placebo group.¹ Similar postdose hypercalcemia occurred in men with osteoporosis with an incidence of 6.2%.⁵ On the other hand, initial clinical trials did not observe predose hypercalcemia, i.e., serum calcium levels above the upper limit of normal measured more than 16 h after the last dose. Nonetheless, EUROFORS, a randomized clinical trial done in 95 centers in Europe, reported 4.3% of women developing predose hypercalcemia during a 2-year treatment with 20 µg of teriparatide.⁶

Both of our patients had asymptomatic elevation of predose calcium. Due to the overall low number of cases of hypercalcemia in the clinical trials, a more detailed analysis of factors association with similar hypercalcemia was limited. However, review of the literature provides some information. When present, hypercalcemia is usually mild with 95% of elevated serum calcium levels remaining less than 11.2 mg/dL in women treated with a 20 µg/day dose of teriparatide.¹ Case 1 patient had asymptomatic elevation of predose calcium of 11.2 mg/dL, however our second patient had elevation to 12.5 mg/dL. In a study by Kendler et al. only 0.6% of the study population (total of 4 women) developed similar severe hypercalcemia with levels greater than 12.5 mg/dL.⁷

Repeated hypercalcemia rarely occurs.^{5,8} Orwoll et al. reported only 2 out of 151 in the 20 µg/day group and 8 out of 139 men in the 40 µg/day group experienced hypercalcemia more than once.⁵ Nevertheless, at month 1 and 3 of treatment, a statistically significant increase in serum calcium was observed (0.2 mg/dL and 0.3 mg/dL respectively). However, this was thought not to be clinically significant. By 12 months of treatment, calcium levels returned to baseline, pretreatment concentrations.⁹ Similarly, both of our patients had normalizations of calcium levels upon retesting.

Hypercalcemia occurred more often in patients with pre-existing hypercalcemia or vitamin D deficiency. In the study done by Greenspan et al., the rate of predose hypercalcemia was 28% while on treatment with full-length recombinant PTH (1–84).¹⁰ Although previous studies on full-length recombinant PTH showed overall higher incidence of hypercalcemia,⁹ this study included women with mild hypercalcemia at baseline (8.9% of the study population), as well as patients with vitamin D insufficiency. These patients were thought to have increased endogenous PTH, which could

precipitate hypercalcemia. The current drug label is recommending avoidance of teriparatide in patients with hypercalcemia, vitamin D deficiency, hyperparathyroidism or unexplained elevation of alkaline phosphatase (ALP).¹¹ Interestingly, our second patient was found to have elevated ALP during a follow-up visit, despite normal pretreatment levels. Nevertheless, treatment was discontinued due to moderate hypercalcemia.

Our first patient did have a remote history of calculi and nephrolithiasis (more than 5 years ago). Although no contraindications exist regarding the use of teriparatide in patients with history of kidney stones, the medication has not been studied in those with urolithiasis.¹¹ Nevertheless, we obtained 24-h urine calcium studies prior to treatment, which resulted as normal. Despite that, our patient developed asymptomatic hypercalcemia during the follow-up.

Similar to our patients, none of the patients in the clinical trials were reported to have clinical effects of hypercalcemia.^{1,5,9} However, several case reports exist in the literature of severe persistent elevation of serum calcium (Table 3). Reported cases vary in their presentation from mild, self-limiting to severe symptomatic hypercalcemia requiring hospital admission. Calcium levels in the above case reports ranged from 10.4 to 17.3 mg/dL. Hajime et al. reported co-occurrence of severe hypophosphatemia as well.¹² Those admitted were treated with intravenous fluids, diuretics and/or intravenous bisphosphonates.^{13–16} Sustained hypercalcemia persisting for a week after teriparatide discontinuation has been reported as well.¹⁴ In three patients, PTH was measured during the hypercalcemic episode. Levels were suppressed in all cases, which was thought to be consistent with the physiological response.^{12,14,16} In all reported cases, teriparatide was discontinued (Table 3).

Management of hypercalcemia in the studies with PTH analogs was done according to an algorithm. If hypercalcemia persisted on the repeat analysis, researchers would decrease calcium supplementation to less than 1000 mg daily.¹⁷ If persisting hypercalcemia was found, the dose of PTH analog was reduced by 50%.^{1,9,18} Hypercalcemia was rarely a cause of treatment disruption when used as a treatment of postmenopausal osteoporosis (Neer et al. 1 out of 541 [0.18%] in 20 µg/day, 9 out of 552 [1.6%] in 40 µg/day; Body et al. 1 out of 73 [1.36%], 40 µg/day).^{1,18} One study in men with osteoporosis reported the rate of discontinuation of 2% in 20 µg/day and 4% in 40 µg/day of teriparatide.⁵ As yet, there are no clinical practice recommendations regarding the treatment discontinuation. In Case 2,

Table 3. Case reports of teriparatide associated hypercalcemia.

Author (year)	Age, sex	Pretreatment calcium	Laboratory Data	Comments
Thiruchelvam (2014) ¹³	65, F	9.3 mg/dL	Calcium 13.8 mg/dL	Admitted to the hospital and treated with calcitonin, i.v. pamidronate and i.v. fluids. TPTD discontinued.
Hajime (2014) ¹²	49, F	9.3 mg/dL	Calcium 10.4 mg/dL Phosphorus 0.9 mg/dL iPTH 6 pg/mL	Occurred two weeks after treatment initiation. TPTD was discontinued and calcium subsequently normalized.
Karatoprak (2012) ¹⁴	47, F	9.3 mg/dL	Calcium 14.5 mg/dL Cr 2.24 mg/dL* iPTH 4.5 pg/mL	Occurred 7 months after TPTD start. Admitted to hospital with constipation, nausea, heartburn. Treated with i.v. fluids and furosemide. TPTD was discontinued and calcium subsequently normalized.
Ayasreh (2012) ¹⁵	77, M	NA	Calcium 12.92 mg/dL Phosphorus 2.81 mg/dL Cr 2.5 mg/dL** iPTH 12.2 pg/mL 25(OH)D 19.8 ng/mL	One year after treatment start. Admitted to the hospital and treated with i.v. fluids, furosemide. TPTD was discontinued and calcium subsequently normalized.
Sistla (2019) ¹⁶	74, F	NA	Calcium 17.3 mg/dL iPTH 3 ng/L	Admitted to the hospital with confusion and bone pain. Treated with i.v. fluids, i.v. bisphosphonates and calcitonin. TPTD was discontinued. Hypercalcemia persisted 3–4 weeks post-discharge.

Abbreviations: TPTD = teriparatide; iPTH = intact PTH; 25(OH)D = 25-hydroxy-vitamin D, Cr = creatinine, i.v = intravenous. Reference range: calcium 8.5–10.5 mg/dL, iPTH 10–65 pg/mL, 25-hydroxy vitamin D 30–100 ng/mL.

*baseline creatinine 0.78 mg/dL; **baseline creatinine 1.18–1.37 mg/dL.

we did permanently discontinue teriparatide treatment, due to level of hypercalcemia.

It has been suggested that serum calcium should be assessed before PTH analog use.¹⁹ There are currently no guidelines regarding when to measure serum calcium. In the clinical trials, usually, serum calcium was assessed at baseline, 1, 6 and 12 months after treatment start. It is also important to be aware of the timing of serum calcium measurement with teriparatide administration. Measurements post-injection are more likely to reveal transient hypercalcemia. This could potentially lead to more testing, patients' concerns and avoidable expense.

Although none of the clinical trials reported symptomatic hypercalcemia, current drug label instructions include a recommendation to educate patients on hypercalcemic symptoms and when to contact a healthcare provider.¹¹

4. Conclusion

Hypercalcemia can occur during treatment with teriparatide. It is usually mild and asymptomatic. Although rarely a cause of discontinuation of treatment, it is important to be aware of this side effect in patients who may be at risk of complications of hypercalcemia. Further studies are necessary to identify patients for hypercalcemia.

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Conflicts of interest

The authors have no multiplicity of interest to disclose.

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