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CASE REPORT

Delayed and significant hypercalcaemia due to teriparatide therapy: a case report and review

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Abstract

Introduction Transient hypercalcaemia due to teriparatide occurs in up to 11% of patients though delayed hypercalcaemia (> 24 h post injection) is rare. We report the case of a female who developed significant delayed hypercalcaemia after teriparatide treatment for osteoporosis and review other cases in the literature to date.

Case report A 72-year-old female on teriparatide for the treatment of osteoporosis was found to have hypercalcaemia (3.30 mmol/l) on routine testing approximately 3 months after starting therapy. Serum calcium pretreatment was normal at 2.39 mmol/l. She was admitted to the hospital for investigations which identified a serum 25-hydroxyvitamin D of 94 nmol/l, a low parathyroid hormone of 6.0 pg/ml, and normal test results for 1,25 dihydroxyvitamin D (115 pmol/l), parathyroid hormone-related peptide (< 1.4 pmol/ml), serum electrophoresis and angiotensin-converting enzyme (39 IU/l). CT abdomen, pelvis, and thorax revealed no evidence of malignancy and an isotope bone scan ruled out skeletal metastases. Serum calcium normalised (2.34 mmol/l) several days after stopping teriparatide and calcium supplements and administering intravenous fluid. On restarting teriparatide, delayed hypercalcaemia reoccurred and treatment was switched to denosumab.

Discussion Delayed moderate to severe hypercalcaemia (serum calcium > 3.0 mmol/l) due to teriparatide is rare but may lead to therapy withdrawal. The underlying predisposing risk factors remain unclear and highlight the importance of a routine serum calcium assessment on therapy.

Keywords Case report · Hypercalcaemia · Teriparatide therapy

Introduction

Teriparatide is recombinant human parathyroid hormone (1–34) and is indicated for the treatment of patients with osteoporosis at high risk of fracture, including steroid induced osteoporosis [1]. It is the first anabolic therapy developed and has been in use for over 20 years, being generally well tolerated. Mild transient hypercalcaemia is an adverse effect that occurs in up to 11% of patients. This usually resolves within 16 to 24 h and is infrequently a cause of therapy cessation. However, delayed hypercalcaemia (persisting > 24 h after teriparatide administration) has been rarely reported with unclear predisposing risk factors [2]. We report a patient who developed a delayed moderate hypercalcaemia after teriparatide therapy and review other case reports in the literature to date.

Case history

A 72-year-old female with osteoporosis attending our bone health clinic was started on teriparatide (Sondelbay™) 20 mcg daily after sustaining a low-trauma L1 vertebral fracture. She had been on a 2-year drug holiday after 10 years of alendronate, with recent densitometry (DXA) showing a T-score of − 2.5 in spine and − 1.9 in total hip. Medical history included hypertension, hyperlipidaemia, and treated hepatitis C. Medications included aspirin, bisoprolol, amlodipine, rosuvastatin, and calcium 500 mg/vitamin D3 400 IU once daily. Serum calcium at baseline was 2.39 mmol/l, though delayed hypercalcaemia (3.30 mmol/l) was

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identified on routine testing after 3 months of teriparatide and on retesting (3.33 mmol/l) one day after stopping. She was admitted to hospital for investigations which found evidence of mild dehydration, serum 25-hydroxyvitamin D of 94 nmol/l, suppressed parathyroid hormone (PTH) of 6.0 pg/ml, and normal test results for 1,25 dihydroxyvitamin D (1,25(OH)D) (115 pmol/l), parathyroid hormone-related peptide (PTHrP) (< 1.4 pmol/l), and serum electrophoresis and angiotensin-converting enzyme (39 IU/l). CT abdomen, pelvis, and thorax revealed no evidence of malignancy. Isotope bone scan ruled out skeletal metastases but showed increased uptake at the site of her L1 fracture and in her skull. After stopping teriparatide and calcium supplements, and treatment with intravenous fluids, serum calcium normalised (2.34 mmol/l) after several days (see Table 1). She remained off calcium tablets and restarted teriparatide 19 days after it was stopped. However, delayed hypercalcaemia (serum calcium 2.70 mmol/l) was re-identified after the 4th injection and treatment was switched to denosumab. The 24-h urinary calcium was subsequently tested and was normal at 5.32 mmol (2.5–7.5 mmol).

Discussion

This case adds to the few reports of hypercalcaemia (> 24 h) attributed to teriparatide (see Table 2). In our patient, the Naranjo criteria (score 9) for definite causality between teriparatide and delayed hypercalcaemia were met [3] with other causes of high calcium excluded and re-occurrence

Table 1 Biochemical test results

	Baseline	Day 1[a]	Day 2[b]	Day 3	Day 4	Day 5	Day 11	Day 24[c]	Day 77[d]	Range
Calcium (mmol/l)	2.39	3.30	3.33	3.05	2.75	2.64	2.34	2.70	2.43	2.10–2.50
Phosphate (mmol/l)	1.14	0.90	0.84	1.0	0.77	0.82	1.07	1.18	0.92	0.81–1.45
Albumin (g/l)	50	48	50	46	42	40	48	48	46	35–50
PTH (pg/ml)	20.9	6.0	-	-	-	-	-	-	16.4	15.0–65.0
ALP (IU/ml)	60	55	53	57	44		50	49	42	80–120
eGFR (ml/min)	76	46	51	48	53	54	59	-		> 60
25(OH)D (nmol/l)	130	94	-	74	-	-	-	-	-	> 50
1,25(OH)D (pmol/l)	-	-	-	115	-	–	-	-		15–150
PTHrP (pmol/l)	-	-	-	< 1.4	-	–	-	-		< 1.4

Calcium corrected calcium (Roche Cobas c701 assay), *PTH* parathyroid hormone (Elecys Roche Assay}, *ALP* alkaline phosphatase, *eGFR* estimated glomerular filtration (MDD formula), *25(OH)D 25* hydroxyvitamin D (Liquid Chromatography tandem Mass Spectrometry—LCMS), *1,25(OH)D* 1,25 dihydroxyvitamin D (LCMS), *PTHrP* Parathyroid Hormone-related Peptide (LCMS).

[a]110 days after teriparatide started and day when stopped.

[b]Day admitted to hospital.

[c]5 days after restarting teriparatide.

[d]53 days after teriparatide stopped and on denosumab therapy

Table 2 Case reports of delayed hypercalcaemia attributed to teriparatide

	Age (years)	Sex	Calcium (mmol)		Time on TPD (weeks)	Resolution (days)	Management
			Baseline[a]	On TPD			
Karatoprak et al. (2012) [6]	74	F	2.32	3.62*	28	18	Stopped, Hospitalised, IVF, Frus
Ayasreh et al. (2012) [7]	77	M	-	3.23	52	> 7	Stopped, Hospitalised, IVF, Frus
Koo et al. (2012) [8]	78	F	2.34	3.64*	8	> 3	Stopped, Hospitalised, IVF
Thiruchelvam (2014) [9]	65	F	2.32	3.44*	20	> 2	Stopped Hospitalised, IVF
Hajime et al. (2014) [10]	49	F	2.32	2.74	8	> 14	Stopped
Sistla et al. (2019) [11]	74	F	-	4.32*	16	-	Stopped, Hospitalised, IVF, BP, Calc
Milosavljevic (2022) [2]	54	M	2.32	2.79	24	> 4	Continued and normalised
	75	F	2.37	3.12	24	-	Stopped and monitored

Calcium values converted into mmol/l using Unitlabs.com. Teriparatide dose was 20 mcg daily though was not reported by Sistla et al.

[a]normocalcaemic at baseline, *symptomatic hypercalcaemia.

F female, *M* male, *TPD* teriparatide, *IVF* intravenous fluids, *Frus* frusemide, *BP* bisphosphonate, *Calc* calcitonin,—data not available

of hypercalcaemia on restarting treatment. In particular, we ruled out conditions associated with extra-renal production of 1,25(OH)D such as sarcoidosis and lymphoma and other causes including multiple myeloma, skeletal metastases and PTHrP-secreting tumours. An isotope bone scan revealed increased uptake in the skull as described elsewhere on teriparatide [4] and consistent with a change in bone density at this site on treatment [5]. The patient was educated by the nurses at our unit on injection technique and was able to correctly administer the injection, with no concerns that she could have overdosed.

Only eight case reports of delayed hypercalcaemia were identified, with it being noted on the first calcium check performed between 8 and 52 weeks after starting teriparatide [2, 6–11]. All patients were normocalcaemic at baseline and where checked serum PTH [6–11] and 1,25(OH)D levels [8, 9, 11] at the time of hypercalcaemia were suppressed or normal. Four patients were asymptomatic and had serum calcium between 2.74 and 3.23 mmol/l [2, 7, 10], with one resolving on continuing treatment and stopping calcium supplements [2]. However, in all other cases teriparatide was stopped, three of whom had severe hypercalcaemia (> 3.50 mmol/l) [6, 8, 11] and two moderately high calcium levels (3.00–3.50 mmol/l) [2, 7]. Five patients were hospitalised and treated with intravenous fluids [6–9, 11] with two receiving frusemide [6, 7] and one also a bisphosphonate and calcitonin [11]. The highest calcium was 4.32 mmol/l though hypercalcaemia recurred off teriparatide despite extensive investigations (CT neck and whole body, PTHrP, 1,25(OH)D) suggesting other contributory causes [11]. One patient also had acute renal failure though frequent use of anti-inflammatories was a contributing factor [10].

Miller noted pre-dose hypercalcaemia (> 2.99 mmol/l) in only 5 out of over 1000 patients (< 0.5%) treated with teriparatide with the highest level of 3.49 mmol/l. Additionally, about 5% had a level above 2.74 mmol/l [12]. However, persistent mild hypercalcaemia (serum calcium levels of 2.74–2.87 mmol/l) was noted in three patients by Licato [13] though no clinical details were provided in the former or latter cases.

By comparison, the incidence of transient hypercalcaemia in randomised controlled trials was up to 11% with the vast majority being mild [2, 14–17]. Serum calcium measurements in trials were generally taken 4–16 h after teriparatide administration. In the pivotal trial by Neer et al., 95% with transient hypercalcaemia (> 6 h) had levels below 2.79 mmol/l [14] whilst Black et al. found median increases in calcium of 0.05 and 0.07 mmol/l at 1 and 3 months, returning to baseline at 1 year [17]. However, in the VERO trial where serum calcium was checked between 16 and 24 h post teriparatide injection, 9.7% had hypercalcaemia, with 0.6% having a level above 3.12 mmol/l (0.47 mmol/l above normal) [16]. Overall, discontinuation rates due to hypercalcaemia in trials were low (0.18–4.0%) [2, 14, 15]. This transient rise in calcium (peaking at 4–6 h) and usually normalising by 16–24 h is consistent with the rapid absorption and short half-life (2–4 h) of teriparatide [18].

The predisposing factors for delayed hypercalcaemia are unclear. Calcium supplement use in patients on teriparatide has been associated with transient hypercalcaemia which resolves on their cessation or on dose reduction [2, 14]. One mechanism whereby teriparatide may cause hypercalcaemia is by increasing synthesis of 1,25(OH)D consistent with the actions of endogenous PTH. Higher 1,25(OH)D after teriparatide are reported in clinical trial [19] and real-world settings [13]. In fact, median 1,25(OH)D were found to increase by 22–27% at 1 month and 14–19% at 1 year [19], whilst levels above normal were found 6 h after teriparatide administration [13]. A trend for a positive correlation between higher 1,25(OH)D and increases in serum calcium has also been reported [13]. In our patient and other case reports, 1,25(OH)D was not elevated but this might be explained by its short half-life (4 h) [18] and levels being drawn days after stopping teriparatide. Our patient's 1,25(OH)D level was in the upper limit of normal though, which could be considered inappropriately high in the presence of hypercalcaemia and a low PTH. It is therefore possible that her supratherapeutic baseline 25(OH)D of 130 nmol/l could have resulted in excessive synthesis of 1,25(OH)D. Another proposed mechanism for hypercalcaemia was reduced hepatic clearance of teriparatide, though this was in a patient with acute porphyria and significant liver disease [10].

Whilst teriparatide product literature does not stipulate a routine serum calcium check on treatment, this is recommended after 1 month of therapy, by which time hypercalcaemia should be apparent [12]. However, in most case reports, hypercalcaemia was identified much later or only after testing symptomatic patients [6, 8, 9, 11], suggesting that routine calcium checks are not standard. Importantly, blood sampling should occur at least 16 h postinjection [12] as identification of transient hypercalcaemia could lead to unnecessary investigations.

For patients with hypercalcaemia, a first approach would to be stop or lower the dose of calcium supplements to ensure a total intake of < 1000 mg per day [12]. Indeed, in clinical trials where this was done, hypercalcaemia on repeat blood testing was uncommon (1.3%) [2, 14]. Additionally, avoiding supplemental vitamin D when serum 25(OH)D > 50 nmol/ has been proposed [13] and predicated on reducing vitamin D activation to 1,25(OH)D. This strategy remains uncertain, though levels above 75 nmol/l are probably best avoided. Secondly, consideration should be given to changing to alternate day teriparatide [12] though definitive evidence on anti-fracture efficacy is lacking. However, a reduction in vertebral fractures has been identified in trials of once weekly teriparatide using 28.2 μg or higher doses

[20]. Finally, therapy could be switched to abaloparatide which has a lower incidence of hypercalcaemia, though is not approved in Europe. Given the significant hypercalcaemia (0.83 mmol/l above normal) in our patient, we decided to switch therapy to denosumab.

To conclude, delayed and non-mild hypercalcaemia (> 24 h) is a rare side effect of teriparatide. Hypercalcaemia may persist despite stopping calcium supplements and lead to therapy cessation. Routine serum calcium checks between 1 and 3 months after starting teriparatide should be standard for all patients, by which time any hypercalcaemia should be apparent.

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Declarations

Conflicts of interest None.

References

1. Lindsay R, Krege JH, Marin F et al (2016) Teriparatide for osteoporosis: importance of the full course. Osteoporos Int 27:2395–2410. https://doi.org/10.1007/s00198-016-3534-6
2. Milosavljevic J, Thomas AM (2022) Teriparatide associated late hypercalcemia: a report of two cases and literature review. J Community Hosp Intern Med Perspect 12(1):54–58
3. Naranjo CA, Busto U, Sellers EM, Sandor P et al (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30:239–245
4. Moore AE, Blake GM, Taylor KA, Ruff VA, Rana AE, Wan X, Fogelman I (2012) Changes observed in radionuclide bone scans during and after teriparatide treatment for osteoporosis. Eur J Nucl Med Mol Imaging 39(2):326–336
5. Paggiosi MA, Yang L, Blackwell D, Walsh JS, McCloskey E, Peel N, Eastell R (2018) Teriparatide treatment exerts differential effects on the central and peripheral skeleton: results from the MOAT study. Osteoporos Int 29(6):1367–1378
6. Karatoprak C, Kayatas K, Kilicaslan H, Yolbas S, Yazimci NA, Gümüskemer T, Demirtunç R (2012) Severe hypercalcemia due to teriparatide. Indian J Pharmacol 44(2):270–271
7. Ayasreh N, Fernandez-Llama P (2013) MJ Lloret, Iara Da Silva, Jose Ballarín, Jordi Bover, Recombinant PTH associated with hypercalcaemia and renal failure. Clin Kidney J 6(1):93–95. https://doi.org/10.1093/ckj/sfs148
8. Koo JW, Lee JH, Jang NE, Kim H, Seok HY, So YR, Shin AR, Cho JH, Lee SH (2012) A case of severe hypercalcemia after treatment with teriparatide for osteoporosis. Korean J Bone Metabol 19(1):53–58
9. Thiruchelvam N, Randhawa J, Sadiek H, Kistangari G (2014) Teriparatide induced delayed persistent hypercalcemia. Case Rep Endocrinol 2014:802473. https://doi.org/10.1155/2014/802473
10. Hajime M, Okada Y, Mori H, Tanaka Y (2014) A case of teriparatide-induced severe hypophosphatemia and hypercalcemia. J Bone Miner Metab 32(5):601–604
11 Sistla D, Mehrotra N, Mon SY (2019) SAT-505 A A rare case of teriparatide induced persistent hypercalcemia. J Endoc Soc 3:SAT-505
12. Miller PD (2008) Safety of parathyroid hormone for the treatment of osteoporosis. Curr Osteoporos Rep 6(1):12–16
13. Licata AA (2005) Osteoporosis, teriparatide, dosing of calcium and vitamin D. N Engl J Med 352:1930–1931
14. Neer RM, Arnaud CD, Zanchetta JR et al (2001) Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 344(19):1434e1441
15. Orwoll E, Scheele W, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman J-M, Clancy A, Gaich G (2003) The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 18:9–17
16. Kendler DL, Marin F, Zerbini CAF et al (2018) Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 391(10117):230e240
17 Black DM, Greenspan SL, Ensrud KE et al (2003) The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med. 349(13):1207e1215
18. Satterwhite J, Heathman M, Miller PD et al (2010) Pharmacokinetics of teriparatide (rhPTH[1–34]) and calcium pharmacodynamics in postmenopausal women with osteoporosis. Calcif Tissue Int 87:485–492
19. Cosman F, Dawson-Hughes B, Wan X, Krege JH (2012) Changes in vitamin D metabolites during teriparatide treatment. Bone 50(6):1368–1371
20. Kim KM, Lee SY, Rhee Y (2017) Influence of dosing interval and administration on the bone metabolism, skeletal effects, and clinical efficacy of parathyroid hormone in treating osteoporosis: a narrative review. JBMR Plus 1(1):36–45