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Teaching Point
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Recombinant PTH associated with hypercalcaemia and renal failure

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Introduction

Teriparatide (Forsteo®) is a recombinant drug of the parathyroid hormone (PTH) family (it is the N-terminal sequence of 34 amino acids of the endogenous human PTH) that promotes bone formation through its direct effect on osteoblasts, indirectly increasing calcium resorption by the tubules as well as phosphate excretion by the kidneys. Its main indication is the treatment of osteoporosis [1, 2]. The use of teriparatide has been associated with, among other potential side-effects, the infrequent induction of mild hypercalcaemic episodes. However, the possibility of acute renal insufficiency or worsening of prior chronic kidney disease (CKD) has not been sufficiently emphasized.

Here, we present the case of a 77-year-old male referred to our centre with acute impairment of renal function within the context of frequent use of nonsteroidal anti-inflammatory agents as well as drugs potentially causing hypercalcaemia, among which teriparatide was outstanding. This paper stresses some basic aspects of the diagnosis and current treatment of osteoporosis in patients with renal impairment and highlights the fact that teriparatide is contraindicated when CKD and secondary hyperparathyroidism are present.

Case description

A 77-year-old male was referred to our clinic by his primary care centre owing to acute deterioration of renal function and toxic syndrome.

The patient was a pacemaker bearer, former smoker, hypertensive and suffered from dyslipidaemia, hyperuricaemia, severe chronic obstructive pulmonary disease and ischaemic heart disease. The patient had been followed up in rheumatology for the last 2 years because of vertebral crushing at D6 and had been diagnosed with both osteoporosis and degenerative osteoarthropathy at several locations, all of which gave rise to systemic bone pain. Treatment with teriparatide 20 μg 1 vial/day and cholecalciferol/calcium (1000 mg/880 IU) one tablet/day had been started 1 year previously. The patient was also on acetylsalicylic acid 100 mg/day, allopurinol 100 mg/day, furosemide 20 mg/day, omeprazole 20 mg/day, tramadol/paracetamol 37.5/325 mg as needed, simvastatin 20 mg/day and valsartan 40 mg/day; furthermore, he inhaled bronchodilators and quite frequently took nonsteroidal anti-inflammatory agents.

The ambulatory follow-up lab tests showed a baseline creatinine of 104–121 μmol/L (1.18–1.37 mg/dL) and an eGFR (estimated glomerular filtration rate) by the CKD-EPI formula of 50–59 mL/min/1.73 m^2, which disclosed the presence of undiagnosed CKD in stage 3A. Neither baseline PTH nor vitamin D had been determined. Impairment of renal function was detected 1 year after follow-up, with creatinine 220 μmol/L (2.5 mg/dL) (eGFR 24 mL/min/1.73 m^2). The patient was referred to us owing to this deterioration in renal function. His vital signs and physical examination results were unremarkable.

At the blood tests initially performed at our centre, creatinine was 220 μmol/L (2.5 mg/dL), calcium 3.23 mmol/L (12.92 mg/dL), phosphorus 0.91 mmol/L (2.81 mg/dL) and haemoglobin 127 g/L. Urinalysis showed neither microhaematuria nor proteinuria. Urinary sodium was 55 mEq/L, with a 3% fractional excretion of sodium. Renal ultrasound scan was strictly normal.

The patient was admitted with the diagnosis of CKD probably secondary to nephroangiosclerosis, worsened within the context of hypercalcaemia. A blood proteinogram was requested and proved to be normal, as did levels of tumour markers. Other laboratory test results were intact PTH (iPTH) (12.2 ng/L; $N = 7–53$), 25(OH) vitamin D (calcidiol) (19.8 ng/mL; $N > 20–30$ ng/mL according to different guidelines), 1,25(OH)$_2$ vitamin D (calcitriol) (12 pg/mL; $N = 16–56$). Proteinuria was 0.13 g for 24 h and the Bence Jones proteinuria test was negative.

Chest, plain abdominal and spinal X-rays were obtained; the presence of severe scoliosis, vertebral crushes and osteophytes was outstanding.

The initial treatment consisted of intense fluid replacement, to which intravenous furosemide was added 24 h later and maintained for 5 days. Teriparatide and the calcium and vitamin D supplements were discontinued, after which a slow but steady improvement in renal function and the blood calcium values were observed. The patient was discharged 1 week after admission with

Table 1. Evolution of patient's biochemical data[a]

	Baseline	Admission	3 days later	Discharge (7 days later)	6 months later	12 months later	18 months later
Creatinine (mg/dL)	1.18-1.37	2.50	2.10	1.79	1.51	1.41	1.39
eGFR (mL/min/1,73 m2)	60-51	25	32	37	45	48	49
Calcium (mg/dL)	NA	12.9	11.5	10.5	9.5	9.1	9.0
Phosphorus (mg/dL)	NA	2.8	2.9	2.9	2.9	2.9	2.9
Intact PTH (ng/L)	NA	12	28	32	50	61	57
Calcidiol (pg/mL)	NA	12	NA	NA	20	25	23

[a]eGFR, estimated glomerular filtration rate by the CKD-EPI formula; NA, not available.

creatinine 158 μmol/L (1.79 mg/dL) (eGFR 37 mL/min/1.73 m^2) and calcium 2.64 mmol/L (10.5 mg/dL), with progressive clinical and lab test improvement. On the last control, performed 18 months later, creatinine was 123 μmol/L (eGFR 49 mL/min/1.73 m^2), calcium 2.26 mmol/L (9.0 mg/dL), iPTH 57 ng/L (N = 7–53) and 25(OH) vitamin D 23.2 ng/L. (Table 1).

Discussion

We have presented a case referred to our centre with toxic syndrome, acute impairment of renal function and significant hypercalcaemia, the major inducer of which was his new treatment for osteoporosis—teriparatide. Frequent use of anti-inflammatory drugs and calcium, even at low doses, may have played a promoting (but not a causative) role.

The importance of publishing this case is manifold. In the first place, osteoporosis is a bone disease that is progressively being diagnosed by means of easily affordable techniques, such as bone densitometry. In view of its high prevalence among the general population, much effort has been invested in achieving therapeutic advances, which include the recently launched teriparatide or recombinant PTH [1–3].

Although from a nephrologic viewpoint it would seem a paradox that teriparatide is a bone 'anabolic' agent, it was approved by the Food and Drug Administration (FDA) in November 2002 for single or combined treatment of osteoporosis in men and postmenopausal women with high risk of fractures [2]. It is administered as a 20-μg daily subcutaneous injection, over a maximum of 24 months. Other potential indications for teriparatide are corticoid-induced osteoporosis or other secondary forms [2]. We now know that PTH administered as 'subcutaneous' pulses stimulates bone formation through its direct effect on the bone-forming cells, further stimulating osteoblasts rather than osteoclasts [1]. Thus, teriparatide triggers an increase in the volume of bone deposited at each remodeling cycle, increases trabecular thickness, improves trabecular connectivity and increases cortical thickness and bone size [2]. On the other hand, consideration needs to be given to the consequences of 'persistent' elevation of PTH, such as development toward CKD with secondary hyperparathyroidism, where a continuously elevated PTH has noticeable 'catabolic' effects on bones [4].

Teriparatide, when compared with PTH (1–84), the complete PTH sequence [5], has been shown to be capable of reducing non-vertebral in addition to vertebral fractures, has been available for longer and has been associated with fewer instances of side-effects including hypercalcaemia [6, 7].

Independently of the effects of these drugs on plasma calcium, the technical data sheets limit their use, from a pharmacologic–pharmacokinetic viewpoint, only to cases of 'severe' kidney disease and patients with hypercalcaemia. However, from the nephrologic viewpoint it is important to stress that no studies have been carried out on their effects in patients with baseline secondary hyperparathyroidism (so common in CKD patients); for this reason their use should be limited in this population, as occurs with bisphosphonates [8]. Furthermore, as stated by both international and national guidelines on the alterations of mineral metabolism in chronic kidney disease (CKD-MBD), it is a well-known fact that bone mineral density (BMD) does not reflect the underlying bone pathology in CKD patients, and thus bone densitometry should not be usually indicated but in transplant patients [8, 9]. In fact, BMD may be reduced in CKD patients with either high or low bone remodelling, with completely different appropriate therapeutic approaches in each of these circumstances [8, 9].

In this context, it should be recalled that the prevalence of both osteoporosis and CKD increases with age. The recently published Kidney Disease: Improving Global Outcomes guidelines [8] recommend that stage 1–3 CKD patients with osteoporosis and PTH in the normal range should be treated similarly to the general population. On the other hand, it is advisable that in patients with stage 3 CKD who have also CKD-related abnormalities of mineral metabolism treatment decisions should consider the possibility of performing a bone biopsy, and that in stages 4–5 CKD a 'bone biopsy' is recommended before deciding upon treatment with an antiresorptive medication, particularly bisphosphonates, owing to the fear of perpetuating an adynamic bone disease. Beyond the limits of the technical data sheet, a recombinant PTH might be recommended on compassionate grounds as a potential treatment only for 'low-turnover' bone disease in CKD patients [9], according to sporadically reported cases [10, 11].

Among the other side-effects of recombinant PTH, hypercalcaemia should of course be mentioned [12, 13]. Hypercalcaemia >2.76 mmol/L (11.04 mg/dL) is considered rare ($\geq$1/1000 to <1/100), and hypercalcaemia >3.25 mmol/L (13 mg/dL) is considered very rare. Other infrequent nephrourologic adverse reactions associated with the use of teriparatide are urinary incontinence, polyuria and urinary urgency, potentially related to high serum calcium levels as well [2]. Teriparatide is contraindicated in patients with tumours or known bone metastases [5–7, 14].

Hypercalcaemia has been reported in 5% of patients and basically in transient form, is limited to 4–6 h after its subcutaneous injection [1]. Actually, sustained hypercalcaemia lasting long enough to develop severe

complications due to hypercalcaemia *per se* has only recently been reported [15] and, according to both the FDA and the product's technical data sheet, calcium monitoring is not necessary throughout the treatment. Hypercalcaemia has mostly been seen in patients concomitantly on calcium and vitamin D [12, 16]. We should stress that the presence of an undiagnosed diminished eGFR or the use of nephrotoxic drugs could be important contributing factors, as in our case. Finally, it is noteworthy that hypercalcaemia presented in our patient with a suppressed intact PTH due to PTH inhibition as a result of the presence of hypercalcaemia, and the absence of teriparatide interaction with the measurement of intact PTH (iPTH Roche Diagnostics), as would be expected from a truncated molecule. The levels of calcidiol and calcitriol ruled out vitamin D as the cause of hypercalcaemia and showed renal 1-α-hydroxylase inhibition due to hypercalcaemia, which exceeded the potential stimulating effect of PTH on this enzyme.

Conclusions

The presented case highlights the fact that teriparatide may be the cause of significant hypercalcaemia and acute impairment of renal function. It is possible that this adverse effect, hardly described in the literature, is more frequent in elderly patients where undiagnosed CKD is usual. For this reason we believe that, beyond the recommendations of the technical data sheet, before teriparatide is prescribed, both a screening for CKD and measurement of basal PTH should be performed, and that a periodic control of renal function and plasma calcium levels should also be guaranteed.

Teaching points

  (i) Teriparatide, a N-terminal sequence of PTH, is a new bone anabolic treatment for osteoporosis.
 (ii) Teriparatide may be a cause of hypercalcaemia and renal failure.
(iii) It should be stressed that bone densitometry does not reflect the underlying bone pathology in CKD patients.
(iv) Teriparatide prescription should be preceded by creatinine and eGFR evaluation, as well as basal levels of PTH, to rule out both CKD and secondary hyperparathyroidism.

Conflict of interest statement. None declared.

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