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Continuous Teriparatide Treatment in Chronic Hypoparathyroidism: A Case Report

Authors' Contribution:

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Funds Collection G

ABCDEF 1 **Miguel Saraiva**
AB 2 **Ana Catarina Chaves**
A 1 **Guilherme Assunção**
A 3 **Joana Saraiva**
A 1 **Rui Carvalho**

1 Division of Endocrinology, Diabetes, and Metabolism, Porto University Hospital Center, Porto, Portugal
2 Division of Endocrinology, Diabetes, and Metabolism, Hospital Center of Tâmega and Sousa (CHTS), Penafiel, Portugal
3 Division of Endocrinology, Diabetes, and Metabolism, Coimbra Hospital and University Center, Coimbra, Portugal

Corresponding Author: Miguel Saraiva, e-mail: miguelsaraiva.md@gmail.com

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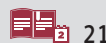
Patient: Female, 29-year-old
Final Diagnosis: Chronic hypoparathyroidism
Symptoms: Muscle cramps • numbness • tingling in fingers
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic

Objective: Unusual or unexpected effect of treatment**Background:** Hypoparathyroidism remains the only hormone deficiency-related disorder with a standard treatment that is not based on replacing a missing hormone. Growing evidence supports the use of recombinant human parathyroid hormone (PTH), mostly with subcutaneous injections. More recently, some clinicians have administered teriparatide, a pharmaceutical form of PTH, through continuous delivery systems.**Case Report:** A 31-year-old woman was referred to our department for further evaluation of chronic severe hypocalcemia due to iatrogenic postsurgical hypoparathyroidism. Despite being chronically medicated with high doses of calcium, vitamin D, and subcutaneous teriparatide injections, she still reported symptoms of hypocalcemia on a daily basis and frequently needed treatment with intravenous calcium perfusions. During hospitalization, we ruled out treatment noncompliance and documented 6 episodes of severe hypocalcemia. Our team then decided to implement a continuous subcutaneous perfusion of teriparatide through an insulin pump. After optimizing the infusion rate, no more severe hypocalcemia episodes occurred. Four months after hospital discharge, it was possible to fully suspend oral supplementation therapy, and the patient's serum calcium level consistently remained within normal range. No other episodes of hypocalcemia occurred.**Conclusions:** The only way to effectively restore long-term calcium homeostasis in our patient was to start a continuous subcutaneous infusion of teriparatide. There was no need to maintain calcium or vitamin D supplementation and we were able to halve the required daily dose of teriparatide. To our knowledge, this case represents one of the very few reports of successful treatment of hypoparathyroidism with a continuous perfusion of PTH.**Keywords:** Hypocalcemia • Hypoparathyroidism • TeriparatideFull-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/931739>

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Background

Hypoparathyroidism is an endocrine disorder characterized by hypocalcemia and hyperphosphatemia due to deficient or absent production of parathyroid hormone (PTH) [1]. The most common cause of this condition is iatrogenic [1,2]; ie, accidental removal of all or part of the parathyroid glands during thyroid surgery.

The symptoms associated with hypoparathyroidism are mostly related to hypocalcemia [2]. These include paresthesia of the fingertips, toes, and lips, and muscle cramps and twitching. Long-term hypoparathyroidism or its therapy may lead to several complications, including basal ganglia calcification and nephrocalcinosis [2].

Hypoparathyroidism still remains the only hormone deficiency-related disorder for which the standard treatment is not based on replacing the missing hormone [3,4]. Instead, standard treatment relies essentially on chronic replacement of calcium and vitamin D [3]. However, some cases of poor control of the disease have been published despite optimized supplementation [5,6].

Recombinant human PTH, amino acids 1 to 34 [rhPTH (1-34)], corresponding to the amino-terminal fragment of PTH, is a drug, known as teriparatide, that was initially approved for the management of osteoporosis. In the last few years, there has been growing evidence on the potential use of recombinant human PTH for the treatment of hypoparathyroidism. Teriparatide has been reported to be beneficial in the control of chronic hypoparathyroidism when administered as a once-daily subcutaneous injection and even more so when administered as a twice-daily regimen [7-9]. More recently, clinicians have developed a teriparatide continuous delivery system using an insulin pump, making it possible to treat patients with an infusion of teriparatide [10,11]. Studies have shown that this treatment modality is associated with lower urinary calcium excretion, lower required daily dosage of teriparatide, and improved quality of life when compared with treatment with once- or twice-daily subcutaneous injections [6,10,12]. An open-label, randomized, crossover trial compared rhPTH (1-34) delivery by insulin pump with a twice-daily subcutaneous injection regimen and reported that patients treated with the pump delivery method had lower urinary calcium excretion and lower required daily dosage of teriparatide to maintain eucalcemia [10]. Pump therapy also restored bone turnover to normal levels while avoiding the overstimulation of daily or twice-daily rhPTH (1-34) injections [10,12]. A reduced need for magnesium supplementation was also reported in this group [10,11].

According to the most recent European guidelines for the treatment of chronic hypoparathyroidism in adults, in Europe the

routine use of replacement therapy with PTH or PTH analogs is still not widely recommended because of lack of evidence for long-term beneficial effects on outcomes such as hypercalciuria, renal complications, and quality of life [3]. However, teriparatide is available for commercialization in Europe and there have been reports of its successful usage in the treatment of chronic hypoparathyroidism, both with the subcutaneous injections regimen [13,14] and with pump delivery systems [6,15,16], when the hypoparathyroidism is refractory to standard treatment.

Case Report

We present the case of a 31-year-old female patient referred to our endocrinology department for further evaluation and treatment of chronic severe hypocalcemia. She suffered from postsurgical hypoparathyroidism after being subjected to a total thyroidectomy in 2018 to treat a papillary thyroid carcinoma.

Prior to admission to our ward, the patient was chronically medicated for her hypoparathyroidism with oral calcium supplementation (calcium carbonate, 1500 mg thrice daily and 1250 mg 4 times daily, which is equivalent to 3.8 g of elemental calcium daily); oral inactive vitamin D supplementation (cholecalciferol, 400 IU thrice daily); oral active vitamin D supplementation (calcitriol, 0.25 mcg thrice daily), oral magnesium supplementation (400 mg, thrice daily through a multivitamin and mineral complex); indapamide (1.5 mg once daily) and teriparatide injections (20 mcg thrice daily).

Despite this complex and optimized therapeutic regimen, which was progressively titrated in her regular endocrinology followup appointments, the patient still reported muscle spasms, cramps, and numbness and tingling sensations in the perioral area and in the fingers on a daily basis. She was frequently admitted to the emergency room of her home area hospital because of these complaints, where severe hypocalcemia was systematically documented and intravenous (IV) calcium perfusion was administered. The high frequency of these episodes even led to the placement of a long-term central venous (subclavian) catheter for IV calcium administration. Therefore, the patient was electively admitted to our ward to assess therapeutic compliance and to further optimize the therapeutic regimen.

During hospitalization, it was initially decided to suspend teriparatide injections and only keep the oral supplementation therapy with calcium (we used calcium carbonate) and vitamin D (we used cholecalciferol and alphacalcidol simultaneously). The doses were progressively titrated to up to 5 g/day of elemental calcium and 4 mcg/day of alphacalcidol. Despite the progressive optimization of these doses, with supervised

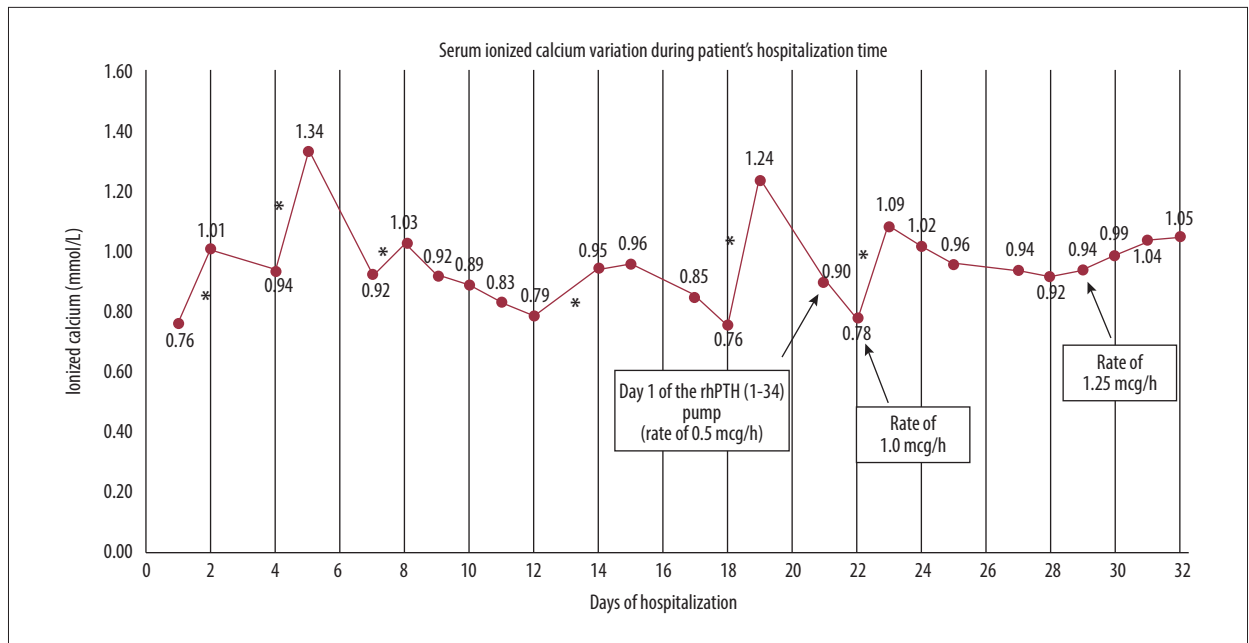


Figure 1. Serum ionized calcium variation during the patient's hospitalization time. * Indicates treatment with intravenous calcium perfusion.

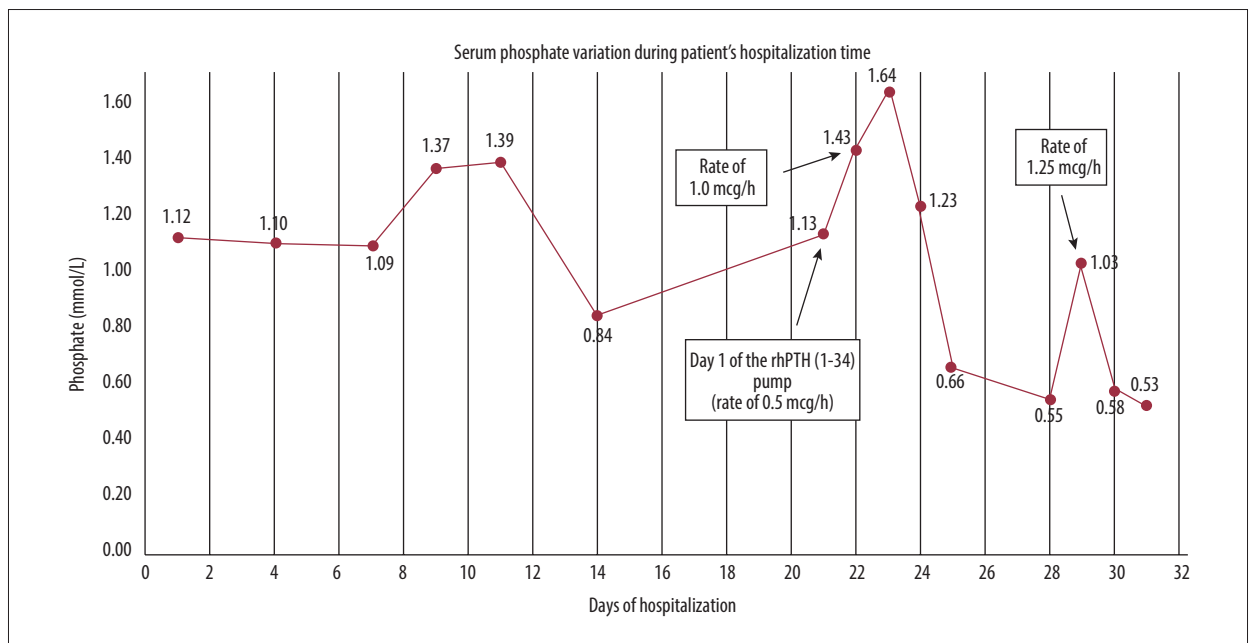


Figure 2. Serum phosphate variation during the patient's hospitalization time.

therapy to rule out noncompliance, the patient had 6 episodes of symptomatic severe hypocalcemia (ionized calcium <0.8 mmol/L, reference range 1.13-1.32 mmol/L) with both positive Trousseau and Chvostek signs during the hospitalization period, necessitating therapy with intravenous calcium gluconate infusion 6 times.

Due to the high recurrence of these worrisome episodes, our team decided to try to control the patient's refractory hypoparathyroidism with a continuous subcutaneous perfusion of rhPTH (1-34) through an insulin pump. Specifically, we assembled the circuit and started the continuous administration of subcutaneous rhPTH (1-34) (Forsteo®, 20 µg/80 µL, Lilly) via a Roche® pump. We started the perfusion with a rate of 0.2 IU/h (equivalent to 0.5 mcg of teriparatide/h or 12 mcg

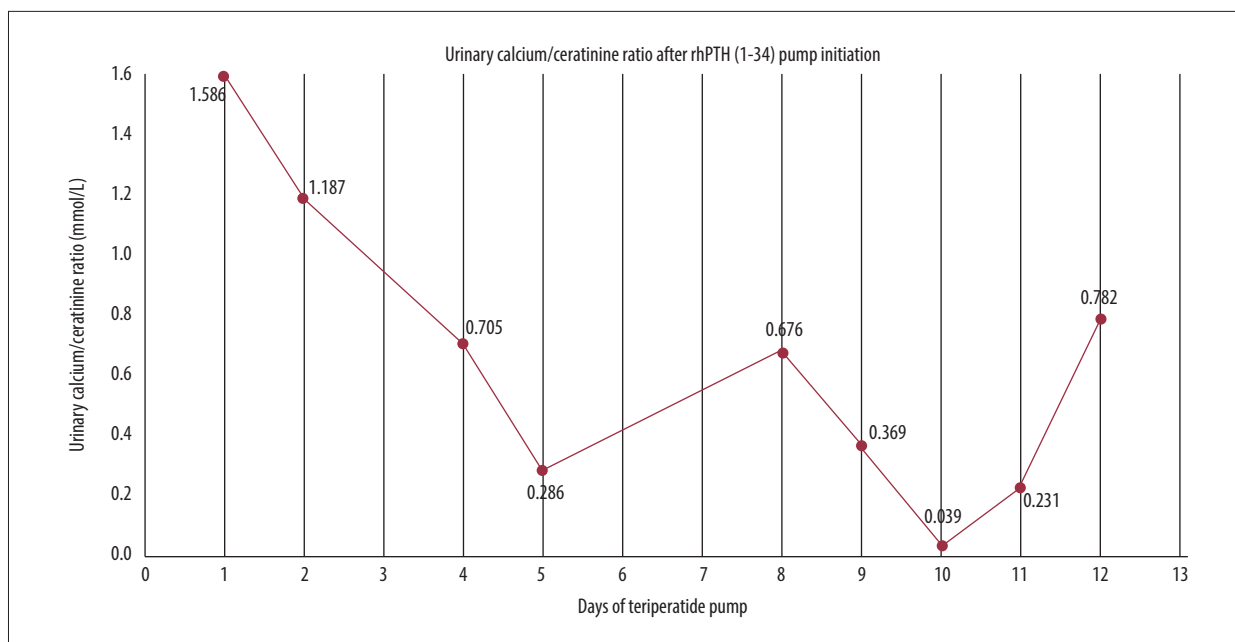


Figure 3. Urinary calcium/creatinine ratio variation after initiation of teriparatide perfusion.

of teriparatide/day) and initially maintained the previous calcium and vitamin D supplementation doses. On the second day of rhPTH (1-34) perfusion (rate, 0.2 IU/h), another calcium gluconate infusion was needed to correct yet another episode of severe symptomatic hypocalcemia. After that, the infusion rate was slowly titrated up to 0.5 IU/h (equivalent to 1.25 mcg of teriparatide/h or 30 mcg of teriparatide/d) and we were able to reduce the oral elemental calcium supplementation dose to 4 g/day. With the adjustment of the rhPTH (1-34) perfusion rate, no further severe hypocalcemia episodes occurred during the remaining time of the patient's hospitalization. The treatment was monitored by daily clinical evaluation (symptoms and Chvostek and Trousseau signs) and frequent assessment of urinary calcium: creatinine ratio, ionized calcium, and serum phosphate. After rhPTH (1-34) pump implementation, the ionized calcium was increased up to a steady state of an internal target level (lower part slightly below the lower limit of the reference range, with patient remaining free of symptoms or signs of hypocalcemia [3]) (Figure 1). In concert with the ionized calcium increase, the serum phosphate gradually decreased (Figure 2), and the urinary calcium: creatinine ratio slowly decreased (Figure 3). At the time of hospital discharge, the patient was medicated with 4 g/d of elemental calcium (through a calcium carbonate formula), 2 mcg/d of calcitriol (equivalent to the 4 mcg/d of alphacalcidol she was medicated with during hospitalization) and 30 mcg of teriparatide/d through a continuous subcutaneous perfusion system. Magnesium oral supplementation was suspended.

We continued to frequently monitor the patient's hypoparathyroidism through followup appointments. Two months after

hospital discharge, the patient's rhPTH (1-34) infusion rate remained at 0.5 IU/h (30 mcg/d) but it had been possible to decrease oral supplementation to only 1 g/d of elemental calcium and 0.25 mcg/d of calcitriol. Four months after hospital discharge, it was possible to fully suspend oral supplementation with calcium and vitamin D. Her serum calcium level consistently remained within normal range and no other episodes of hypocalcemia occurred.

Discussion

Despite the fact that most cases of postsurgical hypoparathyroidism can be securely and effectively managed with optimized oral calcium and vitamin D supplementation, some patients require treatment with PTH analogs [6,13]. According to the guidelines of the Expert Panel of the First International Conference on the Management of Hypoparathyroidism [17], PTH analogs are already a valid option. Such PTH analogs include rhPTH (1-84), a PTH analog containing the full amino acid structure of the human PTH and commercialized under the brand name Natpara®. Natpara® is already approved by the Food and Drug Administration for adults (although not for children or adolescents) with hypoparathyroidism of any etiology, except autosomal dominant hypoparathyroidism, which cannot be well controlled on calcium and active vitamin D [17]. These guidelines go even further and postulate that the use of rhPTH (1-84) should be considered for any hypoparathyroidism patient with any of the following conditions: inadequate control of serum calcium concentration (due to intercurrent illness, noncompliance, or malabsorption); adequate

control of serum calcium concentration but requiring a daily dose of calcium above 2.5 g or of active vitamin D above 3 mcg; hypercalciuria, nephrocalcinosis, or reduced estimated glomerular filtration rate of <60 mL/min; hyperphosphatemia and/or calcium-phosphate product exceeding 55 mg²/dL², or reduced quality of life [17]. However, Natpara[®] has been removed from the market and is currently not available in the United States or in Canada.

In Europe, Natpara[®] has been given 'conditional approval' by the European Medicines Agency and its marketing has been authorized since 2017 [18]. However, in Portugal, the national agency that regulates drug commercialization has not given rhPTH (1-84) a green light yet [19]. Therefore, Portuguese patients can only be treated with rhPTH (1-34).

Several studies have reported that continuous infusion of rhPTH (1-34) is more effective than daily treatment with rhPTH (1-34) injections [10,11]. Furthermore, other authors have already published cases in which long-term calcium homeostasis was only achievable with a subcutaneous PTH infusion system [6,15,16].

Our patient's hypoparathyroidism remains well controlled after 4 months of teriparatide subcutaneous perfusion. So far, no other episodes of hypocalcemia have occurred and no adverse effects of teriparatide were reported. We were able to fully suspend the oral supplementation therapy and she requires only half the daily dose of teriparatide compared with the dose she needed with the subcutaneous injections regimen (30 mcg/d vs 60 mcg/d). Moreover, the patient now reports a much better quality of life.

After determining the ideal rhPTH (1-34) perfusion rate for our patient during hospitalization, there was no need for further adjustment of this parameter (the pump was set at a rate of 0.5 IU/h). The patient learned how to autonomously fill the reservoir of the pump from the pre-filled teriparatide pens and how to change the infusion set (reservoir connector, tubing, and cannula). We initially worried that teriparatide would not remain stable for many days in the pump reservoir, as it is normally located close to the patient's body surface and thus exposed to a higher than desirable temperature. However, we verified that the efficacy of the infusion did not deteriorate with time and, therefore, there was no need to dilute the teriparatide and refill the reservoir more often to guarantee its stability.

Studies using rodents pointed out that long-term use of teriparatide might lead to increased incidence of osteosarcoma [20]. However, based on data on patients being treated with teriparatide for osteoporosis, there is no evidence that this phenomenon also occurs in humans [21]. Case reports about patients using continuous teriparatide infusions for up to 7 years have been published without any reported occurrence of adverse effects (including decreased glomerular filtration rate, nephrocalcinosis, reduced mineral bone density, or bone lesions) [6].

We will continue to monitor our patient both clinically and analytically, and we expect to periodically perform renal ultrasounds and bone-density measurements through dual-energy X-ray absorptiometry.

Conclusions

We present a case of chronic postsurgical hypoparathyroidism refractory to standard treatment with oral supplementation therapy and teriparatide injections. The only way to effectively restore long-term calcium homeostasis and to relieve hypocalcemia symptoms was to assemble a continuous rhPTH (1-34) subcutaneous perfusion system. To our knowledge, this case represents one of the very few reports of successful treatment of hypoparathyroidism with a continuous perfusion of PTH, shedding a light on this novel treatment for severe cases of chronic hypoparathyroidism.

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Conflict of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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