Continuous rhPTH (1-34) treatment in chronic hypoparathyroidism

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Summary

Standard treatment of hypoparathyroidism consists of supplementation of calcium and vitamin D analogues, which does not fully restore calcium homeostasis. In some patients, hypoparathyroidism is refractory to standard treatment with persistent low serum calcium levels and associated clinical complications. Here, we report on three patients (58-year-old male, 52-year-old female, and 48-year-old female) suffering from severe treatment-refractory postsurgical hypoparathyroidism. Two patients had persistent hypocalcemia despite oral treatment with up to 4 µg calcitriol and up to 4 g calcium per day necessitating additional i.v. administration of calcium gluconate 2–3 times per week, whereas the third patient presented with high frequencies of hypocalcemic and treatment-associated hypercalcemic episodes. S.c. administration of rhPTH (1–34) twice daily (40 µg/day) or rhPTH (1–84) (100 µg/day) only temporarily increased serum calcium levels but did not lead to long-term stabilization. In all three cases, treatment with rhPTH (1–34) as continuous s.c. infusion via insulin pump was initiated. Normalization of serum calcium and serum phosphate levels was observed within 1 week at daily 1–34 parathyroid hormone doses of 15 µg to 29.4 µg. Oral vitamin D and calcium treatment could be stopped or reduced and regular i.v. calcium administration was no more necessary. Ongoing efficacy of this treatment has been documented for up to 7 years so far. Therefore, we conclude that hypoparathyroidism that is refractory to both conventional treatment and s.c. parathyroid hormone (single or twice daily) may be successfully treated with continuous parathyroid hormone administration via insulin pump.

Learning points:

- Standard treatment of hypoparathyroidism still consists of administration of calcium and active vitamin D.
- Very few patients with hypoparathyroidism also do not respond sufficiently to standard treatment or administration of s.c. parathyroid hormone once or twice daily.
- In those cases, continuous s.c. administration of parathyroid hormone via insulin pump may represent a successful treatment alternative.

Background

Hypoparathyroidism is characterized by hypocalcemia and hyperphosphatemia caused by the absence or deficiency of PTH. The most common cause of hypoparathyroidism is postsurgical after thyroidectomy (1). Patients typically suffer from paraesthesia, muscle cramps and tetany. Long-term complications consist of nephrocalcinosis and renal

insufficiency, as well as neurological manifestations, for example, seizures and basal ganglia calcifications (2). Hypoparathyroidism is an endocrine disease whose treatment is currently not based on replacement of the missing hormone. Instead, standard therapy consists of calcium and vitamin D supplementation which

generally restores serum calcium levels to normal ranges. However, in some cases, patients suffer from severe hypoparathyroidism resistant to conventional treatment regimens.

Parathyroid hormone preparations (rhPTH (1–84) or rhPTH (1–34)) administered as single s.c. injections were introduced in the market for treatment of osteoporosis several years ago. Since 2017, rhPTH 1–84 is also available for patients with treatment-refractory hypoparathyroidism in Germany. Recent trials studied substitution therapy in patients with primary hypoparathyroidism. Under treatment with PTH, serum calcium levels could be stabilized, sometimes leading to hypercalcemic episodes if PTH application followed a permanent treatment regimen, whereas skipping of PTH injection causes fast reduction of serum calcium. Patients also profit from the reduction of elevated serum phosphate levels (3). In a recent study, PTH administration was safe, tolerable and effective over a period of 5 years (4).

Because PTH injection once a day often does not lead to stable calcium concentration, PTH was applied multiple times a day leading to less fluctuations of serum calcium. Especially, PTH delivery via pump systems seems to provide good calcium control, normalization of bone-remodeling and reduction of daily PTH doses over the course of 3 months (5).

Here we report on three patients with uncontrolled postsurgical hypoparathyroidism. Despite high-dose oral calcium and calcitriol supplementation, frequent i.v. calcium administration, as well as daily rhPTH (1–34) or rhPTH (1–84) treatment, severe hypocalcemic episodes persisted. In all three cases, hypoparathyroidism could only be controlled by continuous s.c. administration of rhPTH (1–34). All patients gave written informed consent.

Case presentation

Patient 1

A 52-year-old female patient was referred to our Endocrinology Service for further evaluation and treatment of severe hypocalcemia. She suffered from postsurgical hypoparathyroidism after thyroidectomy and parathyroidectomy due to multinodular goiter in 1999. The patient presented with paraesthesia of upper and lower limbs, hand tremor and recurrent epileptic seizures under treatment with daily doses of 1.5 to 3 g calcium, 1.5 g magnesium and 4 µg calcitriol. In addition, she received i.v. calcium administrations two to three times per week via a central-venous port-system

and 100 000 IU cholecalciferol intramuscularly twice a week. Serum calcium levels of 1.5–1.7 mmol/L (reference range (RR): 2.2–2.7 mmol/L), hyperphosphatemia (1.77 mmol/L, RR: 0.8–1.3 mmol/L), hypocalciuria (1.45–3.72 mmol/24 h, reference value: 4.00–8.00 mmol/24 h) and low 1,25-OH-vitamin-D levels were found. To rule out a potential malabsorption of calcitriol, D-xylose absorption test and endoscopic procedures were performed, showing no abnormalities. We started the additional off-label treatment with 100 µg rhPTH (1–84) daily and s.c. injection of 1 µg calcitriol/day which together with up to 3 g oral calcium supplementation resulted in short-term stabilization of serum calcium levels (2.2 mmol/L). Four months later she was readmitted because of severe recurrent hypocalcemia (1.6 mmol/L) requiring i.v. calcium supplementation. Due to low 1,25-OH-vitamin-D levels (15 ng/L, RR: 35 – 80 ng/L) and normal 25-OH-vitamin-D levels (55.8 µg/L, RR: 30 – 70 µg/L), the daily s.c. calcitriol dosage was increased to 2 µg. Additional treatment with PTH (1–84) 100 µg/day was switched to 20 µg PTH (1–34) daily with division into up to five single injections distributed over the day. However, these adjustments still did not provide amelioration of serum calcium, phosphate and vitamin D levels. Our patient still experienced severe paraesthesia and epileptic seizures and developed slight renal insufficiency (GFR (MDRD)=64 mL/min/1.73 m²). Renal ultrasound showed no signs of nephrocalcinosis. Potential compliance issues were ruled out by supervised drug intake. All treatment modifications described previously were conducted during several inpatient visits of up to 8 weeks during which the patient's therapy was directly observed, PTH was administered by trained healthcare professionals to rule out poor adherence or errors in administration and serum calcium was measured every 1 to 3 days.

Patient 2

A 58-year-old male had developed hypoparathyroidism after thyroidectomy due to multinodular goiter in 2008. He presented with paraesthesias of his face, arms and legs as well as muscle cramps of the hands. He further suffered from intermittent nausea and vomiting. He also had to be treated at the intensive care unit twice because of loss of consciousness and tetanias caused by hypocalcemic crises. On admission, the patient was under treatment with 1.5 µg calcitriol/day, 4 g calcium/day and magnesium. The patient did not experience any gastrointestinal symptoms under high calcium doses. Low serum calcium of 1.2 mmol/L and increased serum

phosphate of 1.87 mmol/L were found. By addition of 20 µg rhPTH (1-34), increasing calcitriol dosage to 4 µg/day and adding 3000 IU vitamin D/day, calcium and phosphate levels improved, but did not fully normalize. Therefore, rhPTH (1-34) dosage was increased to two daily doses administered in the morning and evening and calcium i.v. was administered weekly. Despite this intensified therapy regimen, the highest measured serum calcium level was found to be still low (1.9 mmol/L) and clinical symptoms recurred only few weeks after changes in therapy had been made.

Patient 3

The third patient (48 years, female) also developed postsurgical hypoparathyroidism after thyroidectomy due to symptomatic goiter in 1983. In 1999, she was admitted to the hospital because of severe treatment-associated hypercalcemia requiring dialysis. Since 2002, however, frequent admissions for hypocalcemic episodes had been necessary. Hypocalcemia was assumed to have been caused by recurrent diarrhea due to fructose intolerance. Because of poor calcium control, she received rhPTH (1-34) treatment starting in 2004. However, even during treatment with 40 µg rhPTH (1-34) daily (2 × 20 µg) and 3 µg calcitriol/day, calcium levels highly fluctuated. To improve the patient's quality of life, she was referred to us for initiation of continuous s.c. rhPTH (1-34) administration.

Treatment and outcome

S.c. rhPTH (1-34) (Forsteo, 20 µg/80 µL, Lilly) was diluted with Aqua destillata (Braun, Melsungen, Germany) and administered continuously via Omnipod pump (patient 1, Insulet Corporation, Acton, Massachusetts, USA), Medtronic pump (patient 2, Medtronic GmbH, Meerbusch, Germany) and Vibe pump (patient 3, Animas, Johnson&Johnson Medical GmbH). In patient 1, initial infusion rate was set at 10.8 µg PTH 1-34/24 h and further adapted to 15.3 µg/24 h, whereas patient 2 immediately received a starting dose of 15 µg/24 h. In patient 3, rhPTH (1-34) treatment was started at a dosage of 25.2 µg/day. After intermittent dose reduction, she showed stable calcium levels at a slightly increased dose of 29.4 µg/day. Within 1 week after start of pump therapy, normalization of serum calcium and phosphate levels could be observed in all three patients (Figs 1, 2 and 3). Clinical symptoms gradually improved. Frequency of seizures decreased (patient 1) and no more hypo- and hypercalcemic crises occurred (patient 2+patient 3). Under continuous administration of rhPTH (1-34) additional medication could be reduced to 1000 IU cholecalciferol/day (patient 1), 20 000 IU cholecalciferol weekly + 80 mg magnesium/day (patient 2) and calcitriol 0.5 µg/day + calcium 500 mg/day (patient 3). For the first time, in all three patients, we were able to control a severe therapy refractory hypoparathyroidism with very low rhPTH (1-34) doses for 7 (patient 1), 6.5

Figure 1

Serum calcium, phosphate and urinary calcium levels before and during rhPTH (1-34) – pump therapy in patient 1.

Figure 2

Serum calcium, phosphate and urinary calcium levels before and during rhPTH (1-34) – pump therapy in patient 2.

(patient 2) and 5.5 (patient 3) years, respectively, without observing significant side effects. After treatment with continuous PTH administration for 4.5 years, patient 1 presented with severe hypercalcemia (serum calcium 3.4 mmol/L) requiring dialysis. Hypercalcemia persisted after discontinuation of rhPTH (1-34) and oral calcium and vitamin D. The patient's history revealed the presence of sarcoidosis. Therefore, treatment with oral prednisone was initiated resulting in rapid decline in serum calcium

levels due to reduced sarcoidosis activity. After reinitiation of continuous rhPTH (1-34) administration, calcium and phosphate levels could be maintained stable.

Twenty-four-hour urinary calcium was measured in patient 1 and 3 before and in all patients during treatment with continuous rhPTH (1-34). None of the patients showed hypercalciuria during administration of rhPTH (1-34), but rather a tendency toward a reduction of urinary calcium levels, whereas periodic increases in

Figure 3

Serum calcium, phosphate and urinary calcium levels before and during rhPTH (1-34) – pump therapy in patient 3.

calcium excretion in patient 1 can most likely be attributed to periods of hypercalcemia due to active sarcoidosis.

In the long-term period, single episodes with hypocalcemia during stressful events or infectious episodes were noted in all three cases, requiring intermittent dose increase of rhPTH (1–34) and additional oral calcium intake.

Regarding treatment safety, in all patients, creatinine levels and glomerular filtration rate remained stable. Renal ultrasound was performed every 1 to 2 years. Nephrocalcinosis was present in patient 3 prior to initiation of continuous PTH therapy, whereas patient 1 and 2 did not develop nephrocalcinosis during PTH treatment. Additionally, bone density measurement and skeletal scintigraphy were carried out every 1 to 2 years in patient 1 and 2 revealing neither significant changes in bone mass nor skeletal lesions over time.

Discussion

We describe three cases in which continuous s.c. administration of rhPTH (1–34) via insulin pump was the only effective way to achieve long-term stabilization of calcium homeostasis and clinical symptoms of postsurgical hypoparathyroidism.

In the majority of patients with hypoparathyroidism, hypocalcemia and associated symptoms can be treated sufficiently by active vitamin D and calcium supplementation. However, there are some limitations to this current standard treatment, especially regarding the frequent risk of hypercalcemia and hyperphosphatemia, hypercalciuria, potentially leading to nephrocalcinosis and renal dysfunction, as well as persistent mood impairment (1).

More recently, treatment with rhPTH (1–84) or rhPTH (1–34) as replacement therapy has been evaluated. Previous studies show stabilization of serum calcium and phosphate levels, reduction of calcium and vitamin D supplementation (3, 4). In our cases, single s.c. injections were not sufficient to restore calcium and phosphate homeostasis over a longer time period. However, we were able to normalize serum calcium and phosphate levels by continuous s.c. rhPTH (1–34) administration, reducing severe clinical manifestations in all three patients without causing hypercalcemic episodes and hypercalciuria.

This phenomenon has also been observed in two other patients, both suffering from chronic vitamin D unresponsive hypoparathyroidism which could only be sufficiently treated with continuous PTH administration, but not with PTH injections (6, 7). PTH therapy via

insulin pump vs injections has previously been evaluated. Winer *et al.* compared twice-daily s.c. injections to pump treatment, both administered for 3 months followed by crossover, in 12 children and young adults with congenital hypoparathyroidism as well as in 8 adults with chronic hypoparathyroidism. In both groups, rhPTH (1–34) pump led to less fluctuation in serum calcium, greater reduction of urine calcium, significant reduction of PTH dose and magnesium supplements as well as normalization of bone turnover markers (5, 8). Therefore, pump treatment currently provides the closest approach to physiological calcium homeostasis.

Regarding safety and risk evaluation, development of osteosarcoma after long-term treatment with PTH in rats has been noted (9). Until now, based on data regarding PTH treatment in osteoporosis, there is no evidence of increased risk for osteosarcoma in humans (10). In our patients, no adverse events have been observed over a course of up to 7 years.

In conclusion, in cases where even PTH injections do not allow sufficient disease control, long-term PTH pump therapy represents an alternative option, providing long-term stabilization of calcium and phosphate homeostasis.

Declaration of interest

C T F is a member of the Advisory board and speaker engagement – Shire/Takeda. The other authors have nothing to disclose.

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Author contribution statement

C T F, A M and S Horn performed data collection. C T F and S Hahner drafted the manuscript. C T F, S B S, A M, A C K, S Horn and S Hahner revised the manuscript content. C T F, S B S, A M, A C K, S Horn and S Hahner approved the final version of the manuscript. C T F, S B S, A M, A C K, S Horn and S Hahner were involved in the care of the patients.

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