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Treatment of severe life threatening hypocalcaemia with recombinant human teriparatide in patients with postoperative hypoparathyroidism — a case series

Leczenie ciężkiej, zagrażającej życiu hipokalcemii ludzkim rekombinowanym teryparatydem pacjentów z pooperacyjną niedoczynnością przytarczyc — seria przypadków

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Abstract

Introduction: Hypocalcaemia is a common postoperative complication, both after the resection of parathyroid adenoma associated with primary hyperparathyroidism and after total thyroidectomy due to thyroid cancer or nodular goitre. For a few years, in patients with postoperative hypoparathyroidism and severe hypocalcaemia, who cannot discontinue intravenous calcium preparations even with the use of high vitamin D doses, attempts have been made to add recombinant human parathormone (rhPTH) to the treatment schedule. In this work, for the first time in Poland, we demonstrate the potential use of teriparatide for the treatment of severe hypocalcaemia based on three different cases of postoperative hypoparathyroidism.

Material and methods: Case 1. Female (52) with postoperative hypoparathyroidism, after total thyroidectomy and the removal of lower left parathyroid gland due to hyperparathyroidism, several weeks after the surgery still required intravenous calcium infusions because of tetany symptoms. Just one month of teriparatide treatment at 20 μg/0.08 mL given in daily subcutaneous injections proved sufficient to control calcium levels with oral calcium and vitamin D preparations during the next few days until total resolution of hypocalcaemia symptoms and the achievement and maintenance of laboratory normocalcaemia in the following weeks.

Case 2. Female (33) with hypoparathyroidism following total thyroidectomy in 1996 because of papillary thyroid cancer, with congenital tubulopathy associated with renal loss of calcium and magnesium, and the symptoms of tetany recurring since the day of surgery, requiring intravenous calcium administration every 2–3 days. Currently, the patient has been hospitalised because of venous port infection, the only venous access, which made intravenous therapy impossible. Because of the life-threatening condition of the patient, bridging teriparatide treatment was prepared (20 μg/0.08 mL). Complete resolution of clinical symptoms of hypocalcaemia was obtained with teriparatide doses given every 8–12 hours, which made dose reduction possible.

Case 3. Female (52) after major oncological surgery because of laryngopharyngeal and cervical oesophageal cancer with the removal of parathyroid glands, fed through PEG, was admitted to hospital with the symptoms of tetany. Despite treatment intensification, the patient experienced a hypocalcaemic crisis during hospitalisation. Teriparatide treatment at 2 × 20 μg/day resulted in the resolution of tetany symptoms, with gradual normalisation of calcium-phosphate balance parameters during the following days.

Conclusions: Based on the analysis of these cases, the conclusion was drawn that the use of recombinant human teriparatide allows for the control of severe hypocalcaemia requiring intravenous infusions of calcium in patients with postoperative hypoparathyroidism.
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Key words: *postoperative hypoparathyroidism; hypocalcaemia; teriparatide*

Streszczenie

Wstęp: Hipokalcemia jest częstym pooperacyjnym powikłaniem, zarówno po usunięciu gruczolaka przytarczyc w przebiegu pierwotnej nadczynności przytarczyc, jak i po całkowitej tyreoidektomii z powodu raka tarczycy lub wola guzowatego. Od kilku lat, u pacjentów z pooperacyjną niedoczynnością przytarczyc i ciężką hipokalcemią, u których nie można odstawić dożylnej terapii preparatami wapnia, nawet przy stosowaniu dużych dawek witaminy D, podejmowane są próby włączenia do leczenia ludzkiego rekombinowanego parathormonu (rhPTH). W niniejszej pracy, po raz pierwszy w Polsce, autorzy pracy wskazują na możliwość zastosowania teryparatydu w leczeniu ciężkiej hipokalcemii na podstawie trzech różnych przypadków pooperacyjnej niedoczynności przytarczyc.

Materiał i metody: Przypadek 1: 52-letnia kobieta, z pooperacyjną niedoczynnością przytarczyc, po całkowitej tyreoidektomii i usunięciu przytarczycy dolnej lewej z powodu nadczynności przytarczyc, kilkanaście tygodni po operacji, z powodu objawów tężyczki, wciąż wymagająca stosowania dożylnych wlewów wapnia. Zastosowano jedynie miesięczną kurację teryparatydem w dawce 20 μg/0,08 ml w codziennych iniekcjach podskórnych, która okazała się wystarczająca do kontrolowania stężenia wapnia doustnymi preparatami wapnia i witaminy D, w ciągu następnych dni do całkowitego ustąpienia objawów hipokalcemii, a w kolejnych tygodniach uzyskania i utrzymania laboratoryjnych parametrów normokalcemii.

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Przypadek 2: 33-letnia kobieta, z niedoczynnością przytarczyc po całkowitej tyreoidektomii w 1996 roku z powodu raka brodawkowatego tarczycy, z wrodzoną tubulopatią przebiegającą z nerkową utratą wapnia i magnezu, od dnia operacji z nawracającymi objawami tężyczki wymuszającymi dożylne podawanie wapnia co 2–3 dni. Aktualnie hospitalizowana z powodu zakażenia portu naczyniowego, jedynego dostępu dożylnego, co uniemożliwiało dożylną terapię. Z uwagi na stan zagrożenia życia pacjentki, przygotowano leczenie pomostowe teryparatydem (20 μg/0,08 ml). Uzyskano całkowite ustąpienie klinicznych objawów hipokalcemii przy podawaniu dawki teryparatydu co 8–12 godzin, co pozwoliło na redukcję dawki leku.
Przypadek 3: 52-letnia kobieta po rozległej operacji onkologicznej z powodu raka gardła dolnego i szyjnej części przełyku z usunięciem przytarczyc, odżywiana za pomocą PEG, przyjęta na oddział z objawami tężyczki. Mimo intensyfikacji leczenia, podczas hospitalizacji wystąpił u chorej przełom hipokalcemiczny. Zastosowany teryparatyd w dawce 2 × 20 μg/dobę spowodował ustąpienie objawów tężyczki, ze stopniową normalizacją parametrów gospodarki wapniowo-fosforanowej w następnych dniach.
Wnioski: Na podstawie analizy przedstawionych przypadków wyciągnięto wniosek, że zastosowanie ludzkiego rekombinowanego teryparatydu pozwala na opanowanie ciężkiej hipokalcemii wymagającej dożylnych wlewów wapnia u pacjentów z pooperacyjną niedoczynnością przytarczyc. **(Endokrynol Pol 2016; 67 (4): 403–412)**

Słowa kluczowe: *pooperacyjna niedoczynność przytarczyc; hipokalcemia; teryparatyd*

Introduction

Hypocalcaemia is a frequent postoperative complication, following both the resection of parathyroid adenoma associated with primary hyperparathyroidism, and total thyroidectomy due to thyroid cancer, Graves' disease, or nodular goitre [1–3]. In most cases, hypocalcaemia is of a temporary nature, although it does require calcium supplementation: initially by intravenous route, followed by oral administration with concomitant vitamin D supply [1, 3, 4]. The incidence of permanent postoperative hypoparathyroidism reported by reference surgical sites does not exceed 1–2% among operated patients. This group includes cases of severe hypocalcaemia, a life-threatening condition that cannot be managed by standard treatment with active vitamin D3 and calcium preparations. It requires intravenous infusion of calcium chloride repeated several times during a 24-hour period [5, 6]. Particularly severe hypocalcaemia may be observed in patients with postoperative hypoparathyroidism and an underlying condition making calcium deficiency even worse. These underlying conditions include, in particular: impaired calcium absorption from gastrointestinal tract or excessive calcium loss with urine associated with kidney disease [7, 8].

Scant literature, mainly based on case studies, indicate that recombinant human parathormone (rhPTH) may be added to treatment in patients with severe hypocalcaemia in whom intravenous calcium therapy cannot be discontinued, even when high doses of alphacalcidol or calcitriol are used [4, 9, 10]. During the last few years, there were reports on teriparatide treatment of severe hypocalcaemia following surgery for both primary hyperparathyroidism and secondary hyperparathyroidism in renal post-transplant patients and in the treatment of chronic hypoparathyroidism, including in children [8, 11–14].

In Europe, recombinant human parathormone products are approved only for the treatment of postmenopausal osteoporosis, idiopathic osteoporosis, osteoporosis associated with hypogonadism in men, and glucocorticosteroid-induced osteoporosis [15, 16–20]. Two rhPTH formulations are available on the market: one of them contains full rhPTH amino acid chain 1-84 (Preotact 1, approved only in EU), while the other, contains only the N-terminal active PTH fragment 1–34 (teriparatide — FORTEO™, Forsteo™). The biological activity of rhPTH is associated with N-terminal fragment, which binds to PTH 1 receptor and mimics the activity of endogenous parathormone [21]. Full-length rhPTH 1-84 contains not only the N-terminal fragment, but also the C-terminal one, which binds to CPTHR receptor and displays different biological activity — it enhances the apoptosis of osteocytes [22]. Following subcutaneous injection, the rhPTH preparations are absorbed rapidly and the half-life is 1 hour for rhPTH 1-34 and 2.5 hours for rhPTH 1-84, with bioavailability of 95% and 55%, respectively [23, 24]. It has been observed that 4–6 hours after subcutaneous injection of teriparatide, a peak increase in serum calcium levels by approx. 0.4 mg/dL occurs, and that it persists for about 6 hours and returns to baseline levels after 16–24 hours, which has been used in the treatment of hypocalcaemia [19, 25]. Initially, teriparatide makes bone formation markers increase and after some time, and bone resorption markers are elevated, which is related to intensive bone remodelling and the dominance of resorption process; therefore, long-term use of rhPTH products in osteoporosis is not indicated — the treatment should not exceed 18–24 months [7, 26].

This article is the first Polish presentation of possible teriparatide use in the treatment of severe hypocalcaemia based on three different cases of postoperative hypoparathyroidism.

Material and methods

Case no. 1

A female patient (52) with postoperative hypoparathyroidism, following total thyroidectomy and the removal

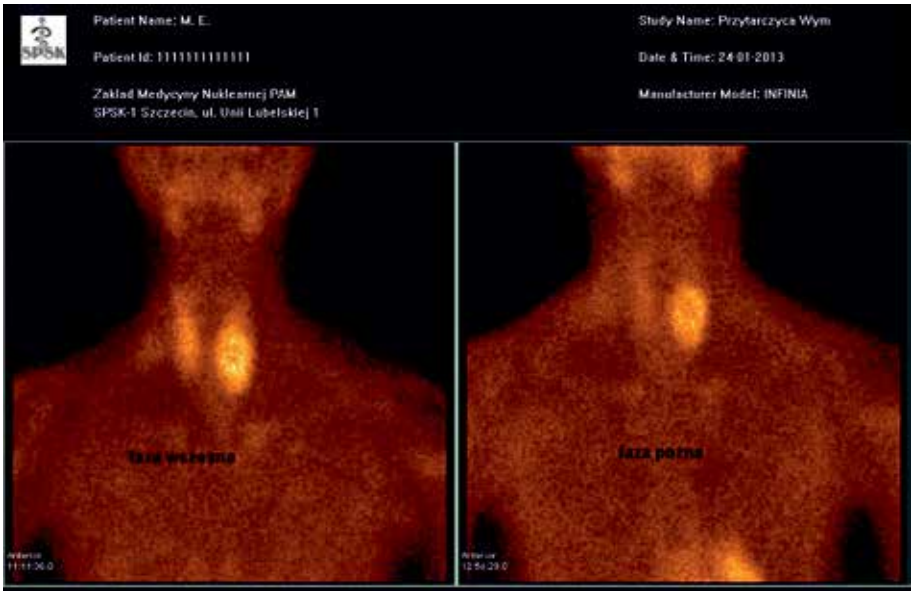


Figure 1. *Pathological marker accumulation focus in parathyroid scintigraphy MIBI-TC99m in the lower pole of left thyroid lobe — left parathyroid adenoma*

Rycina 1. *Ognisko patologicznego gromadzenia znacznika w scyntygrafii przytarczyc MIBI-TC99m w dolnym biegunie lewego płata tarczycy — gruczolak lewej przytarczycy*

of left lower parathyroid gland due to hyperparathyroidism (16 April 2013) was referred to the Department of Endocrinology, Metabolic Diseases, and Internal Diseases at Pomeranian Medical University in Szczecin because of persistent symptoms of severe hypocalcaemia despite continuous, high-dose supplementation with calcium and vitamin D. The patient was also hospitalised twice at the internal diseases ward because tetany symptoms recurred as soon as intravenous calcium substitution treatment was discontinued, despite the use of oral calcium products — calcium carbonate 4 g/day, alphacalcidol 3 μg/day, magnesium hydroaspartate 900 mg/day, and hydrochlorothiazide 25 mg/day.

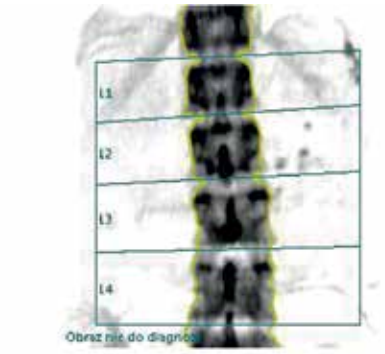
Based on the patient's medical history, the diagnosis of left lower parathyroid adenoma took about two years. Because of increasing fatigue, weight loss, generalised osteoarticular pain, extensive atrophic paradontitis, nephrolithiasis with recurrent infections, and depression, the patient was admitted to different hospital departments — lung tumour and myeloma were ruled out, and the patient even received palliative radiation therapy on both scapulas, but bone metastases were eventually ruled out. Antidepressant treatment was also started. Further diagnostic tests demonstrated hypercalcaemia, and consequently the parathormone levels were determined (PTH, 1522.4 pg/mL) and MIBI-TC99m scintigraphy of parathyroid glands was performed. The findings included a focus of increased marker uptake visualised in the lower pole of left thyroid lobe, suggestive of left lower parathyroid adenoma (Fig. 1). Total thyroidectomy and the resection of left lower parathyroid gland were performed resulting in intraoperative decline of PTH levels from 1500 pg/mL to 85 pg/mL. After that, low PTH and calcium levels were observed as well as hyperphosphataemia, despite intensive use of calcium, magnesium, and vitamin D with recurrent severe symptoms of tetany.

On the day of admission to the Department, the patient complained of continuous tingling and numbness as well as periodic muscle cramps in the limbs and face, generalised bone pain, dry skin, hair loss, nail brittleness, and depressed mood.

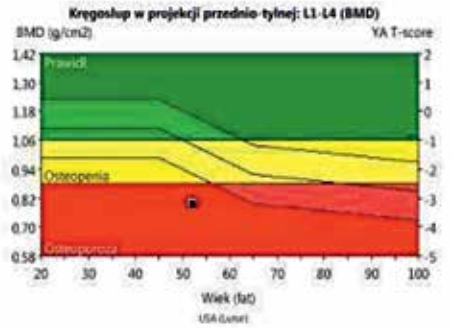
Physical examination findings included the following deviations: cachexia — BMI = 15.9 kg/m^2, dry skin, thinning of hair, increased thoracic kyphosis, positive Chvostek sign and Trousseau's sign, and advanced dental caries.

Laboratory tests demonstrated hypocalcaemia, hyperphosphataemia, low PTH levels, low 24-hour elimination of calcium and phosphorus and elevated bone turnover parameter, and alkaline phosphatase (ALP) (Table I). Treatment was based on 11 g/day calcium carbonate, 3000 mg/day magnesium citrate, vitamin D (6 μg/day alphacalcidol and 0.075 mg/day cholecalciferol) and 25 mg/day hydrochlorothiazide, and because of recurrent symptoms of tetany intravenous calcium infusions were given every two days (2 g calcium chloride). Attempts to switch to oral-only therapy resulted in the symptoms of hypocalcaemia with very low calcium and high phosphorus levels. Endoscopy of upper gas-

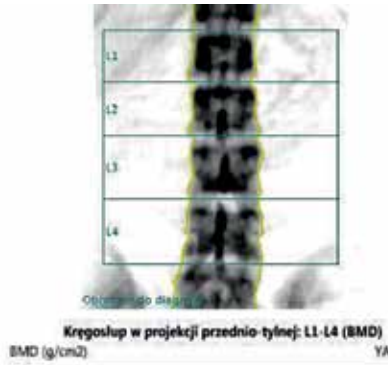
A. BMD of the spine in anterior-posterior projection; date: 09-May-2013



Densitometry: USA (Lunar)			
Region	**BMD [g/cm³]**	**T-score**	**Z-score**
L1	0.805	–2.7	–1.6
L2	0.866	–2.8	–1.6
L3	0.761	–3.7	–2.5
L4	0.779	–3.5	–2.4
L1-L4	0.799	–3.2	–2.0



B. Bone mineral density of the spine in anterior-posterior projection; date: 26 March 2014



Densitometry: USA (Lunar)			
Region	**BMD [g/cm³]**	**T-score**	**Z-score**
L1	1.428	2.5	3.3
L2	1.447	2.1	2.9
L3	1.369	1.6	2.5
L4	1.305	0.9	1.7
L1–L4	1.387	1.7	2.5

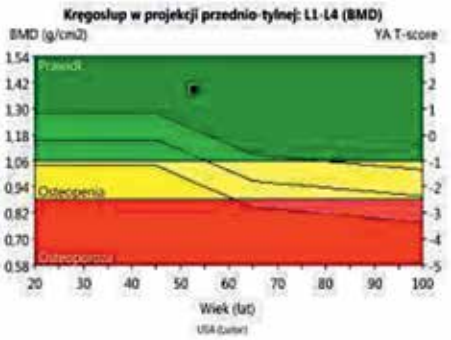


Figure 2. *Bone mineral density before and after 10 months of treatment for severe symptomatic hypoparathyroidism following the removal of parathyroid adenoma; Lunar bone densitometer*

Rycina 2. *Wynik badania gęstości mineralnej kości przed i po 10 miesiącach leczenia z powodu ciężkiej, objawowej niedoczynności przytarczyc po usunięciu gruczolaka przytarczyc, wykonane aparatem Lunar*

trointestinal tract was performed and the specimens of duodenum were sampled — malabsorption syndrome was excluded. DEXA densitometry revealed osteoporosis BMD L1-L4 0.799 g/cm², T-score — 3.4 (Fig. 2).

After 11 weeks of hospitalisation at the Department, the patient's physical and mental condition improved, her body weight increased by 7 kg (BMI — 18.4 kg/m²), and the continuous sensation of tingling and numbness in the limbs and face subsided, but each attempt to discontinue IV calcium treatment resulted in the recurrence of tetany symptoms, irrespective of oral calcium and magnesium dosing. The patient also suffered from generalised bone pain, although it was less severe. As the treatment used so far proved ineffective and it was

Table I. *Calcium-phosphate balance parameters in subsequent months of hospitalisation in a patient with symptomatic hypoparathyroidism after resection of parathyroid adenoma and teriparatide treatment*

Tabela I. *Stężenia parametrów gospodarki wapniowo-fosforanowej w trakcie kolejnych miesięcy hospitalizacji pacjentki z objawową niedoczynnością przytarczyc po usunięciu gruczolaka przytarczyc i po zastosowaniu teryparatydu*

Parameter/normal ranges	Baseline	V–VII 2013	VIII 2013	VIII 2013 — 3	VIII 2013 — 8	IX 2013	III 2014
Total Ca (2.1–2.54 mmol/L)	1.16	1.34–1.89	1.9	2.38	2.36	2.05	2.64
Ionised Ca (1.12–1.32 mmol/L)	0.6	0.56–1.08	0.92	1.23	1.26	1.02	1.3
P (0.81–1.45 mmol/L)	1.5	2.1–1.4	1.8	1.5	1.4	1.6	1.1
Vit. OHD (30– 80 ng/mL)	23	12.5–37.5	28.9	na	na	48.4	29.5
PTH (11–67 pg/mL)	4.3	5.8–9.44	3.36	na	na	< 3	< 3
Mg (0.66–1.07 mmol/L)	0.8	0.7–0.97	0.76	0.72	0.63	0.66	0.66
Ca in 24h urine collection (0.0–6.2 mmol/d)	0.86	1.62–2.04	6.98	6.24	2.71	3.59	6.3
P in 24h urine collection (12.9–42 mmol/d)	0.21	0.6–0.21	15.75	20.6	15.5	1.71	15.4
ALP (35–105 U/L)	304	268	112	na	105	na	77

Total Ca — total calcium; Ionized Ca — ionized calcium; P — phosphates; Vit. OHD — 25 hydroxyvitamin D; PTH — parathormone; Mg — magnesium; Ca in 24h urine collection — 24-hour calcium elimination; P in 24h urine collection — 24-hour phosphate elimination; ALP — alkaline phosphatase; VIII 2013 -3 — after starting teriparatide treatment on day 3; VIII 2013 -8 — after starting teriparatide treatment on day 8; na — not assayed

impossible to discontinue intravenous therapy, the decision was made to start teriparatide (Forsteo; Eli Lilly) 20 μg/0.08 mL in daily subcutaneous injections given for 28 days. Three days after the start of teriparatide therapy, clinical and laboratory features of normal calcium levels prevailed (Table I) despite the fact that the ions were supplemented by oral route only — and the substitution doses of the drugs were reduced on the next days. The patient was discharged from hospital and her outpatient treatment during the next four weeks included the following drugs in addition to teriparatide: calcium carbonate 5 g/day with dose reduction to 3 g/day, alphacalcidol 2 μg/day and cholecalcipherol 0.075 mg/day, magnesium citrate 3000 — 2000 mg/day, and hydrochlorothiazide 25 mg. While the patient was on this treatment, tetany symptoms were not observed, and calcium, magnesium, and phosphate levels remained within normal ranges. At follow-up visit one week after last teriparatide dose, the patient reported that the symptoms recurred — she had tingling and periodic cramps in the limbs, although less severe, and laboratory tests demonstrated slightly reduced calcium levels, hyperphosphataemia, low parathormone level, normal 24-hour calcium elimination with reduced phosphate elimination, and normal vitamin D levels (Table I). Oral doses were increased and the following drugs were used on an outpatient basis: calcium carbonate 6 g/day, alphacalcidol 2 μg/day, and cholecalcipherol 0.075 mg/day, while magnesium citrate 3000 mg/day and hydrochlorothiazide 25 mg were continued as before. Gradual relief and resolution of clinical symptoms were observed during the next few weeks, and two months later laboratory normocalcaemia was achieved, while the patient had oral-only ion substitution therapy. At the next visit five months later, laboratory findings included hypercalcaemia, low PTH levels, slightly elevated 24-hour calcium elimination, normal phosphate elimination, and normal ALP levels (Table I). The patient reported having no tetany symptoms for five months, no bone pain for three months and she did not take calcium preparation (it was discontinued eight months after surgery), and she continued treatment with vitamin D preparation (alphacalcidol and cholecalcipherol). Physical examination showed normal BMI (20.9 kg/m^2) and the patient's mental status was normal. Follow-up densitometry of the spine demonstrated high bone mineral density BMD L1-L4 = 1.387 g/cm^2, T-score + 1.37, T-score increased by 73% after 10 months (Fig. 2). At the time of writing, the patient requires treatment with low substitution doses of vitamin D3 and calcium (500 mg calcium carbonate per day and 1 ug alphacalcidol) despite persistent very low PTH levels.

Case no. 2

A female patient (33) with iatrogenic hypoparathyroidism, after total thyroidectomy in 1996 due to thyroid papillary carcinoma, with congenital tubulopathy associated with renal calcium and magnesium loss was referred to the Department of Endocrinology at the Medical University of Warsaw because of recurrent, severe, life-threatening tetany attacks. Uncontrolled, very painful muscle cramps with lockjaw and periodic breathless-

Table II. *Calcium-phosphate balance parameters on subsequent days of teriparatide treatment in a patient with symptomatic hypoparathyroidism, after thyroidectomy because of papillary thyroid cancer, with infection of vascular port*

Tabela II. *Stężenia parametrów gospodarki wapniowo-fosforanowej w trakcie kolejnych dni stosowania teryparatydu u pacjentki z objawową niedoczynnością przytarczyc, po tyreoidektomii z powodu raka brodawkowatego tarczycy, z zakażeniem portu naczyniowego*

Parameter/normal ranges	Baseline	V–VII 2013	VIII 2013	VIII 2013 — 3	VIII 2013 — 8	IX 2013	III 2014
Total Ca (2.1–2.54 mmol/L)	1,53	1.51	1.58	1.72	1.71	2.4	2.3
Ionized Ca (1.12–1.32 mol/L)	0,8	0.76	0.77	0.83	0.83	1.21	1.13
P (0.81–1.45 mmol/L)	1,84	1.85	0.87	1.03	1.07	1.00	1.28
Vit. OHD (30– 80 ng/mL)	27.96	na	na	24.18	na	19.96	na
PTH (11–67 pg/mL)	1.32	na	na	na	na	na	na
Mg (0.66–1.07 mmol/L)	0.63	0.71	0.71	0.75	0.71	0.76	0.72
Ca in 24h urine collection (0.0–6.2 mmol/d)	5.03	na	10.4	na	na	9.2	12.9
ALP (35–105 U/L)	69	131	na	na	na	115	na

Total Ca — total calcium; Ionized Ca — ionised calcium; P — phosphates; Vit. OHD — 25 hydroxyvitamin D; PTH — parathormone; Mg — magnesium; Ca in 24-hour urine collection — 24-hour calcium elimination; ALP — alkaline phosphatase; na — not assayed

ness were observed on the first days following thyroidectomy. Despite treatment with high doses of active vitamin D (alphacalcidol up to 10 μg), calcium carbonate (up to 12g/day), and hydrochlorothiazide 25 mg/day, the attacks recurred every 2–3 days and required intravenous calcium infusion at Hospital Emergency Departments. As a consequence, the patient's peripheral veins were damaged, narrowed, and obstructed, and eventually a venous port was inserted into the vein. Four attempts were made to transplant the homogenate of parathyroid cells, but all of them were unsuccessful. In 2008, the port placed in the right subclavian vein was infected and damaged permanently. Since then, every effort was made to maintain the port placed in left subclavian vein. Currently, after another admission to the Department, infection of the venous port — the only venous access — has been observed, which made intravenous therapy impossible. Laboratory findings included hypocalcaemia, hyperphosphataemia, and low PTH levels (Table II). Because of the life-threatening condition of the patient, teriparatide bridging therapy was prepared (Forsteo; Eli Lilly) with subcutaneous injections of 20 μg/0.08 mL dose started immediately after admission to the Department. There was a complete resolution of clinical symptoms of hypocalcaemia, but teriparatide dose was administered every 8–12 hours. Normocalcaemia was obtained on day 16 of teriparatide treatment (Table II), which triggered a once daily dose reduction. The dose reduction did not result in the onset of clinical symptoms of hypocalcaemia. Hypercalciuria persisted as a result of congenital renal defect. Treatment with rhPTH made it possible to restore the venous port. At the same time, during teriparatide treatment, the patient has not suffered from any tetany symptoms for the first time since 1996. Once the infection was cured, rhPTH was discontinued and substitution treatment with oral calcium, magnesium, and vitamin D preparations was administered as before. Unfortunately, tetany attacks recurred. Currently, the patient is being treated with vitamin D (alphacalcidol 10 mg) and calcium carbonate (up to 9 g/day), and she requires calcium infusions every 2–3 days because of tetany symptoms.

Case no. 3

Female patient (52) with a history of laryngo-pharyngo-oesophagectomy with lymphadenectomy due to relapsed cancer of laryngopharynx and cervical oesophagus, after strumectomy, after alimentary tract reconstruction with free autograft of small intestine (20 August 2012) complicated with enterocutaneous fistula, fed through percutaneous endoscopic gastrostomy (PEG), and treated with clonazepam for epilepsy, was referred to the Department of Internal Diseases and Endocrinology at the Medical University of Warsaw in December 2012 because of severe symptomatic postoperative hypoparathyroidism, resistant to calcium and vitamin D_3 treatment.

On the day of admission to the Department, the patient complained about recurrent, paroxysmal muscle cramps in the face and limbs, and severe abdominal pain. Laboratory tests revealed hypocalcaemia, hyperphosphataemia, and low PTH levels (Table III). Despite intensification of PEG-administered drugs: 16 g/day cal-

Table III. *Calcium-phosphate balance parameters on subsequent days of teriparatide treatment in a patient with symptomatic hypoparathyroidism, after resection of laryngopharynx and cervical oesophagus due to cancer*

Tabela III. *Stężenia parametrów gospodarki wapniowo-fosforanowej w trakcie kolejnych dni stosowania teryparatydu u pacjentki z objawową niedoczynnością przytarczyc po resekcji gardła dolnego i szyjnej części przełyku z powodu raka*

Parameter/normal ranges	Baseline	06.02.12	08.02.12	27.12.12	30.12.12	19.01.13	07.02.13
Total Ca (2.15–2.60 mmol/L)	1.23	1.30	1.96	1.86	2,03	1,96	2.20
Ionized Ca (1.15–1.29 mol/L)	0.65	0.73	1,03	1,00	1.12	0.97	1.12
P (0.81–1.45mmol/)	2.19	2,04	1.24	1.64	1.36	1.89	1.11
PTH (11–67 pg/mL)	2.8	na	na	4,15	na	na	na
Mg (0.66–1.07 mmol/L)	na	na	na	0,60	na	0.66	0.70

Total Ca — total calcium; Ionised Ca — ionised calcium; P — phosphates; PTH — parathormone; Mg — magnesium; na — not assayed

cium carbonate, 4 μg/day alphacalcidol, and 2000 mg/day magnesium hydroaspartate, tetany cramps recurred every 1–2 days and laboratory features of hypoparathyroidism persisted. During hospitalisation, the patient experienced a hypocalcaemic crisis. Intravenous calcium and magnesium formulations were started, resulting in the relief of symptoms, but these failed to bring the expected effects. A decision was made to start teriparatide treatment (Forsteo; Eli Lilly) at 20 μg/0.08 mL administered twice daily as subcutaneous injections. After the first teriparatide dose, the patient had nausea and vomiting, but these occurred once and no further adverse reactions were observed as the treatment continued. After starting teriparatide therapy, the patient did not present any clinical signs of hypocalcaemia, and the parameters of calcium-phosphate balance gradually returned to normal (Table III). Six weeks after the beginning of teriparatide therapy, its dose was reduced to 2 × 20 μg every second day. Treatment lasting two months resulted in the correction of laboratory parameters of calcium-phosphate balance (Table III). On the following weeks, the patient did not report any open tetany symptoms or its equivalents.

Discussion

The three cases presented in our article have one common feature: the presence of severe, life-threatening hypocalcaemia resistant to standard treatment. Each of them, however, presents a different clinical problem underlying the postoperative hypoparathyroidism. In case no. 1, the underlying cause of the surgery is hyperparathyroidism associated with adenoma of the lower left parathyroid gland. In case no. 2, the damage of parathyroid glands was the consequence of total thyroidectomy due to papillary thyroid cancer. In case no. 3, parathyroid glands were removed during major oncology surgery because of cancer of the lower pharynx and cervical oesophagus.

Hypocalcaemia following the surgery of parathyroid adenoma is a relatively frequent phenomenon and may be of temporary nature (transient suppression of function and impaired blood supply to other parathyroid glands and hungry bone syndrome) — or it may be permanent as a result of intraoperative damage or resection of all parathyroid glands [3, 27, 28]. Treatment effects are usually obtained with standard doses of oral calcium and vitamin D preparations, sometimes combined with a thiazide diuretic [4]. However, in rare cases, prolonged symptomatic hypocalcaemia is observed despite oral and intravenous therapies.

In patient no. 1, who was operated for parathyroid adenoma, even long-term supplementation with high doses of calcium carbonate at 11 g/day and alphacalcidol at 6 μg/day proved ineffective and required constant intravenous infusions of calcium ions. The patient was also treated with thiazide diuretics in order to enhance renal calcium reabsorption [4, 29] and received supplementation of magnesium ions because their deficiency is a well-known cause of hypocalcaemia [30], but this also proved ineffective. Based on endoscopy with the sampling of duodenal specimens and the determination of anti-transglutaminase antibodies, malabsorption syndrome was ruled out as a potential cause of impaired calcium absorption in the digestive tract. A frequent complication following surgical treatment of primary hyperparathyroidism is hungry bone syndrome (HBS), especially in patients with advanced bone changes associated with this disease [31]. Our patient suffered from generalised bone pain, low mineral density of lumbar spine (BMD L1-L4 T-score — 3.4), and elevated serum levels of alkaline phosphatase (ALP), which could indicate enhanced bone remodelling with intensive re-calcification of bone tissue. Hungry bone syndrome is observed in 13–30% of cases following parathyroid surgery [32]; in patients with bone changes caused by hyperparathyroidism the incidence of HBS is increased to 25–90%, while the absence of bone changes is as-

sociated with a risk reduction to 0–6% [28]. Most HBS definitions include the presence of hypocalcaemia in a patient subjected to surgery for hyperparathyroidism, as well as hypophosphatemia and hypomagnesaemia as an effect of bone remineralisation [28, 33]. Some authors define HBS-related hypocalcaemia as the values < 8.5 mg/dL and hypophosphatemia as the values < 3.0 mg/dL [27] with hypocalcaemia persisting for over four days despite calcium ion supplementation, with normal vitamin D levels in serum [31]. Parathormone serum levels are normal or elevated [27, 28, 34]. It is believed that severe hypocalcaemia observed in HBS is a consequence of increased calcium ion inflow to bones as a result of rapid compensation for earlier effects of high PTH levels on the resorption of osteoclasts, leading to decreased activation rate of new sites of bone remodelling, inhibition of resorption, and continued bone formation [28]. It is commonly believed that the factors predisposing for HBS include old age, the size of removed parathyroid glands, high preoperative calcium, ALP and PTH levels, changes in bone system (bone cysts, brown tumours, subperiosteal bone resorption, osteopaenia, osteoporosis), vitamin D deficiency [27, 28, 35], or parathyroid cancer [36]. On the other hand, Latus et al. [31], having analysed 84 patients after surgery for secondary hyperparathyroidism, found that the risk of HBS is higher in younger patients and in patients with low preoperative calcium levels. These authors also observed that preoperative vitamin D therapy did not prevent HBS and had no impact on the duration of postoperative intravenous calcium supplementation [31]. Literature reports consistently claim that preoperative bisphosphonate treatment may prevent hungry bone syndrome after parathyroidectomy, both in primary and secondary hyperparathyroidism, although in the long perspective, this treatment may potentially delay bone remodelling [37–39]. HBS treatment is long-lasting and usually requires high doses of calcium and vitamin D preparations [33, 35]. Prolonged hypocalcaemia despite treatment is the reasons for long hospitalisations. Araya et al. [40] reported that mean duration of hospital treatment was 19 days. On the other hand, Juarez-Leon et al. [33] described a female patient with HBS, who required oral and intravenous supplementation of calcium for up to three months. Our patient no. 1 presented high preoperative PTH and calcium levels and severe osteoporosis with persistent postoperative hypocalcaemia but also with hyperphosphataemia, and low vitamin D and PTH levels, which corresponds to the diagnosis of postoperative hypoparathyroidism with coexistent hungry bone syndrome being responsible for the symptoms reported by the patients [34].

In our patients no. 2 and 3, severe hypocalcaemia was not only the consequence of postoperative hypoparathyroidism but also a result of underlying disease making the hypocalcaemia even more severe. In patient no. 2 this underlying disease was congenital tubulopathy associated with renal loss of calcium and magnesium, while in case no. 3, calcium absorption might have been impaired as a result of alimentary tract reconstruction. Literature data indicate that severe hypocalcaemia may develop as a consequence of enhanced renal loss of calcium in patients after kidney transplantation with coexistent postoperative hypoparathyroidism [8] as well as in patients with postoperative hypoparathyroidism undergoing Roux-en-Y gastric bypass (RYGB) bariatric surgery with subsequent impairment of calcium gastrointestinal absorption [7].

Like other authors [5, 9], we also observed severe postoperative hypoparathyroidism in our patients, which was resistant to treatment and which coexisted with low PTH levels, requiring many weeks of intravenous ion substitution. Although necessary, in the long run this treatment may trigger symptoms associated with hypercalciuria and ectopic calcification of soft tissues [4, 41]. Attempts have been made for several years to treat such cases with recombinant human PTH (rhPTH) using the full length PTH molecule (1-84), as well as with active short PTH (1-34) [7–9, 11, 42–47]. Daily subcutaneous injections of rhPTH (1-34) resulted in rapid resolution of clinical features of hypocalcaemia in all our patients, while laboratory features of normocalcaemia was achieved on day 3 in patient no. 1, on day 16 in patient no. 2, and after 2 months in patient no. 3 (Tables I–III). Like other authors [8, 9, 43, 45, 48], we also demonstrated the efficacy of teriparatide in reducing urine elimination of calcium. Rapid effect of normocalcaemia, observed after one or more days of subcutaneous rhPTH added to standard treatment with calcium and vitamin D preparations, has been also emphasised by other authors [11, 47]. On the other hand, Puig-Domingo et al. [9] described a female patient who failed to obtain normocalcaemia with subcutaneous injections of teriparatide as frequently as 4–6 times a day — it was only after using a teriparatide infusion pump that the parameters of calcium-phosphate balance were effectively corrected and the symptoms subsided; the treatment lasted one year. Because of the high cost of teriparatide treatment, we used a short-term therapy lasting 4 to 12 weeks, which proved sufficient to control serum calcium levels with oral calcium and vitamin D formulations in patients no. 1 and 3, and additionally in patient no. 1 the symptoms of hypocalcaemia subsided completely during the next few days. We also observed reduced use of calcium and vitamin D preparations in the following months, which was described in earlier reports [11, 45, 49]. During the four-year rhPTH (1-84) therapy in patients with hypoparathyroidism, Cusano

et al. [45] observed decreased use of calcium supplementation by 37%, vitamin D use decline by 45%, while 26% of analysed patients did not require further vitamin D treatment. In all cases of rhPTH (1-34) use in severe postoperative hypocalcaemia after renal transplantation and previous parathyroidectomy, Nogueira et al. [11] obtained normal calcium levels and decreased need for vitamin D and calcium doses, and after several months of treatment (treatment duration ranging from 1 month to 32 months), teriparatide was no longer required. Among the three patients described in our report, only patient no. 2 experienced the recurrence of severe hypocalcaemia following the discontinuation of teriparatide, which may be related to short duration of treatment and the presence of congenital tubulopathy with considerable loss of calcium and magnesium ions with urine.

Another effect of rh PTH (1-34) and rhPTH (1-84) treatment is the improvement of bone remodelling dynamics and the restoration of normal bone metabolism [50]. The anabolic effect of teriparatide on bone tissue is the consequence of restoring pulses of PTH secretion and increased osteoblast activity with the predominance of bone formation process, which has been used so far in the treatment of osteoporosis [51]. The considerable 73% increase in bone mineral density (BMD) of lumbar spine obtained in our patient no. 1 was many times higher than the BMD increase observed by Puig-Domingo et al. after one-year teriparatide treatment (7%) [9] or BMD reported by Cusano after four-year follow-up (5.5 ± 9%) [45]. Contrary to our findings, Sikjaer et al. [49] demonstrated a slight but significant decrease in lumbar vertebral BMD (-1.76 ± 1.0%) with rh PTH (1-84) treatment, but these results are difficult to compare as the study lasted for six months. However, this high BMD increase observed in our patient was similar to that reported by other authors in patients with hungry bone syndrome (27–65%) [28] and was probably the result of initial low bone mass and very intense recalcification of bone tissue after treatment. The potential coexistence of hypoparathyroidism and hungry bone syndrome as complications of parathyroidectomy requires further studies.

The safety of recombinant human parathormone (rhPTH) is highlighted in available literature, and, just like other authors [9, 11, 47], we did not observe any significant adverse reactions — the same observation was also confirmed by Cusano [45] in the follow-up of longest duration published so far for rhPTH. There is also a hypothesis that a correlation exists between the quality of life deterioration and the absence of parathyroid hormone, which is attributed to the beneficial effect of parathormone on the central nervous system [52]. A positive effect on quality of life is another aspect reported during rhPTH treatment for hypoparathyroidism [50, 52]. Until recently, hypoparathyroidism — *i.e.* PTH deficiency — was the only hormone deficiency disease without approved substitution therapy. Since 2015, full-length recombinant human parathormone [rhPTH (1-84); Natpara] has been approved in the USA as an adjunct to calcium and vitamin D to control hypocalcaemia in patients with hypoparathyroidism [53]. The onset and duration of treatment has not been specified and the most dangerous potential complication observed in rat studies is osteosarcoma of bones [54]. In Europe, rhPTH has not been approved yet for the treatment of severe hypocalcaemia associated with postoperative hypoparathyroidism.

Subcutaneous daily injections of rhPTH (1-84) and rhPTH (1-34) seem a very promising therapeutic option in postoperative hypoparathyroidism, not only for the control of hypocalcaemia, but also in relation to other aspects of the disease such as skeletal dysfunction and quality of life deterioration [50, 52]. Our studies also support the justified use, efficacy, and safety of such treatment. It should be pointed out that short teriparatide treatment prescribed by our team in severe hypocalcaemia associated with postoperative hypoparathyroidism, in 2 out of 3 presented patients, proved sufficient for further control of calcium levels with oral calcium and vitamin D products and for complete correction of calcium levels in the next months in one patient. This argument is of particular interest when discussing the expected costs of rh PTH treatment.

Conclusions

The use of recombinant human teriparatide results in the control of severe hypocalcaemia requiring intravenous calcium infusions in patients with postoperative hypoparathyroidism.

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