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Case Report

Initiation of Continuous rhPTH Infusion With Insulin Pump in an Inpatient Setting

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Abstract

Hypoparathyroidism is one of the few remaining hormonal insufficiencies not treated with replacement of its missing hormone. Conventional therapy involves multiple daily oral doses of calcium, active vitamin D, and magnesium, which is not only cumbersome for patients, but carries risk of nephrocalcinosis and is inadequate in patients with enteral malabsorption. Subcutaneous parathyroid hormone 1-34 (PTH[1-34]) has been tested as a hormonal replacement therapy for treatment of hypoparathyroidism. PTH(1-34) delivered by continuous infusion via insulin pump decreases or eliminates the need for oral medications, stabilizes serum and urine calcium at normal levels with minimal fluctuation, and significantly reduces PTH doses. In this case report, we describe the clinical application of PTH(1-34) via insulin pump in an adolescent with autoimmune polyendocrinopathy syndrome type 1 (APS1). Transition to a PTH pump reduced hospital admissions for calcium abnormalities and allowed our patient to discontinue all scheduled daily conventional therapy.

Key Words: hypoparathyroidism, continuous PTH delivered by pump, recombinant human parathyroid hormone, autoimmune polyglandular syndrome type 1, autoimmune polyendocrinopathy syndrome type 1

Abbreviations: APS1, autoimmune polyendocrinopathy syndrome type 1; PTH, parathyroid hormone; rhPTH, recombinant human parathyroid hormone.

Introduction

Autoimmune polyendocrinopathy syndrome type 1 (APS1) is due to alterations in the *AIRE* gene resulting in predisposition to the development of multiple autoimmune disorders. It classically manifests as chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency [1]. Hypoparathyroidism develops in 80% to 90% of individuals with APS1, and conventional therapy includes multiple daily doses of calcium, active vitamin D (calcitriol or alfacalcidol), and magnesium [2]. Conventional therapy does not replace the missing parathyroid hormone (PTH); therefore, renal calcium excretion is elevated, which necessitates permissive serum hypocalcemia to avoid nephrocalcinosis and renal insufficiency.

Initially developed as an osteoporosis treatment in the 1970s [3], synthetic human PTH(1-34) administered as multiple daily injections was first reported as a treatment for hypoparathyroidism in 1996 [4]. In later studies, 15 children with hypoparathyroidism were successfully treated with synthetic PTH(1-34) via an insulin pump resulting in near normalization of serum calcium, normalized urinary calcium excretion, and decreased need for oral supplements [5, 6]. PTH delivered by pump also provides a bolus option for acute hypocalcemia and the ability to adjust basal rates for gastrointestinal (GI) illnesses, increased activity level, or other intrinsic changes that could alter serum calcium levels.

We report our experience of continuous recombinant human parathyroid hormone rhPTH(1-34) (Forteo) via pump therapy in an adolescent female individual with APS1 to provide practical clinical considerations for the medical management of this rare disease.

Case Presentation

We present the case of a 14-year-old female patient with history of APS1 with confirmed *AIRE* mutation. She was diagnosed with hypoparathyroidism at 5 years old and started calcitriol and calcium supplementation. She also developed exocrine pancreatic insufficiency and enteropathy. Over the years, she had numerous admissions for both hypocalcemia and hypercalcemia, attributed to GI malabsorption and difficulty maintaining an arduous oral medication regimen. She started rhPTH(1-84) (Natpara) at age 12.5 years. Despite dosing every 12 hours, she had large fluctuations in serum calcium levels (Fig. 1), similar to previously described fluctuations in individuals with APS1 and *CASR* mutations taking twice-daily PTH(1-34) [7]. The decision was made to transition to continuous infusion of rhPTH by insulin pump per protocols previously described [5].

No studies have assessed the safety or efficacy of rhPTH(1-84) via insulin pump delivery; therefore, we sought approval for rhPTH(1-34). This was granted after appeal.

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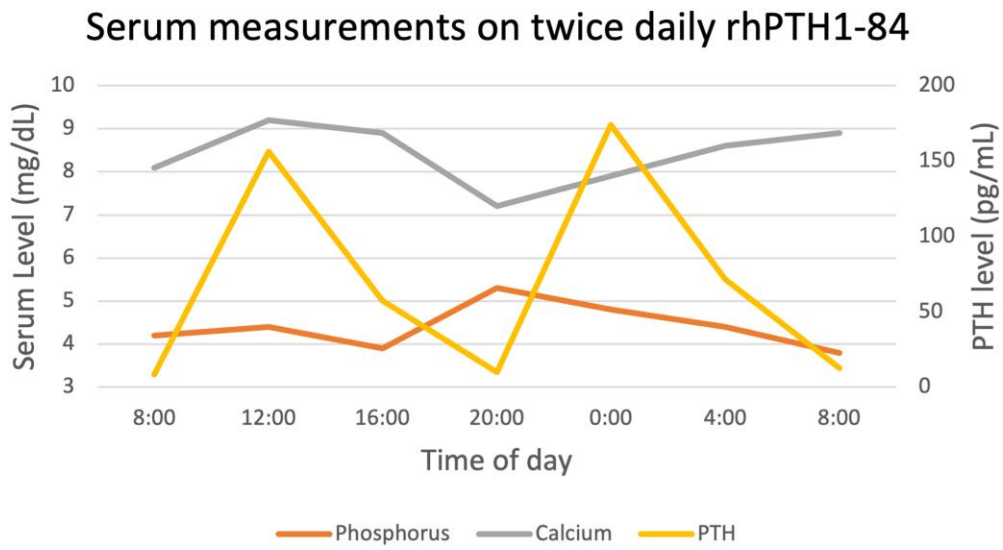

Figure 1. Pharmacokinetic study evaluating serum calcium, phosphorus, and magnesium levels every 4 hours over a 24-hour period while on rhPTH(1-84) 25 mcg twice daily. Reference ranges: calcium 8.7-10.8 mg/dL; phosphorus 3.4-5.9 mg/dL; magnesium 1.6-2.6 mg/dL; PTH 15.0-62.0 pg/mL.

Medtronic pumps have the lowest minimum fill requirement; however, insurance approved the Omnipod system. Once supplies and medication were approved, multiple meetings to coordinate the logistics were held between the endocrine team, pharmacy, and hospital risk management. The inpatient pharmacy prepared prefilled rhPTH(1-34) syringes to fill the insulin pump. Per user manual, rhPTH(1-34) can be at room temperature for only 36 hours; thus, during hospitalization, the pump was refilled on this interval despite prior data demonstrating stability for 72 hours (K.K.W. communication). Another study used diluted rhPTH(1-34) prepared at their institutions to minimize waste [6]. We taught the family to fill the Omnipod reservoir directly with undiluted rhPTH(1-34) retrieved from its pen injector via syringe, since the stability of the hormone solution mixed with normal saline has not been validated. The Omnipod system was not changed in any way for delivery of rhPTH(1-34). The family was taught pump operations per instructions in the user guide.

Treatment

Upon admission, the patient's home regimen for hypoparathyroidism management was rhPTH(1-84) 50 mcg twice daily, calcitriol 0.25 mcg twice daily, calcium carbonate 1000 mg (salt) three times daily, and magnesium 200 mg three times daily. Baseline serum levels were as follows: calcium 7.1 mg/dL (1.7 mmol/L) (range, 8.7-10.8 mg/dL; 2.2-2.7 mmol/L), phosphorus 6.3 mg/dL (2.0 mmol/L) (range, 3.4-5.9 mg/dL; 1.1-1.9 mmol/L), and albumin 3.3 gm/dL (33 g/L) (range, 3.3-4.8 mg/dL; 33-48 g/L). Renal ultrasound shortly after initiation of the PTH pump showed medullary nephrocalcinosis. Prior to admission, she started cholecalciferol 50 000 IU twice weekly due to a low 25-OH vitamin D level of 17 ng/mL (42.4 nmol/L [range, 30-100 ng/mL; 75-250 nmol/L]) for 3 months and has continued once-weekly dosing in the setting of malabsorption.

The evening dose of rhPTH(1-84) was held and continuous rhPTH infusion via pump using rhPTH(1-34) was started the following morning. Basal rates were estimated based on body weight (0.2 mcg/kg/day) and prior calcitriol or PTH dose requirements [5]. The rhPTH(1-34) dose was converted from mcg/mL to units (1 mcg rhPTH = 0.4 units rhPTH(1-34) using 600 mcg/2.4 mL solution). She started at a rate of 0.15 units/hour with the same rate each hour (9 mcg rhPTH(1-34) daily; 0.26 mcg/kg/day). This was substantially less than her 50-mcg twice-daily dose of rhPTH(1-84) (although no direct conversion between the 2 forms of rhPTH exists). Programmed bolus doses used for acute hypocalcemia equaled the unit/hour basal rate dose, that is, 0.15-unit boluses. During admission, calcium, phosphorus, albumin, and magnesium were obtained every 6 to 12 hours along with monitoring urine calcium excretion. Medications were adjusted based on serial serum calcium and phosphorus levels (Fig. 2). Ultimately, all scheduled oral hypoparathyroid medications, except for cholecalciferol, were discontinued. She was discharged with a basal rate of 0.25 units/hour (0.43 mcg/kg/day). A 24-hour urine calcium was elevated at 465.5 mg/day (11.6 mmol/day) (range, 100-300 mg/day; 2.5-7.5 mmol/day).

Outcome and Follow-Up

Since discharge, the pump rate for rhPTH(1-34) has remained between 0.25 and 0.4 units/hour, most recently at 0.35 units/hour (0600-2100) and 0.3 units/hour (2100-0600). Serum calcium levels were initially checked weekly and now at least monthly. Pump rates are adjusted by 0.05 unit/hour (smallest increment change possible with Omnipod) to target serum calcium levels between 8.5 and 9.5 mg/dL. Omnipod was replaced every 72 hours as previously reported with rhPTH(1-34) continuous pump therapy [5]. Renal ultrasound after 2 years of PTH pump therapy showed stable medullary nephrocalcinosis. Urine calcium to creatinine ratios have normalized since starting the PTH pump, most recently at 0.03 mg/mg (0.17 mmol/mmol) (normal: <0.2 mg/mg; <0.56 mmol/mmol). Her most recent serum calcium levels range from 7.8 to 10.8 mg/dL (mean of 9.3 mg/dL) and serum phosphorus values range from 3.8 to 4.8 mg/dL (mean of 4.3 mg/dL). We have not formally assessed for a downtrend of calcium levels nearing the time of pump change, but this

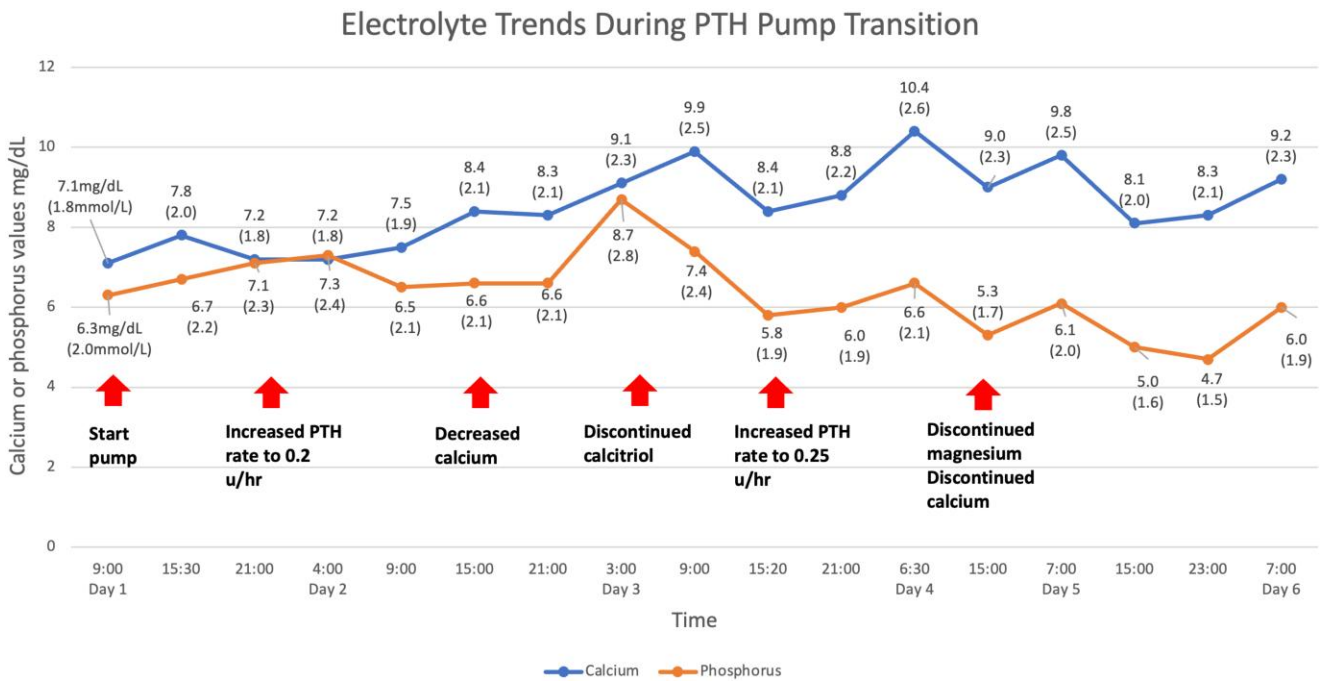

Figure 2. Trend of serum calcium and phosphorus levels during transition to rhPTH(1-34) delivered by pump.

could be considered. Lower serum calcium levels were frequently noted after days of increased activity; therefore, the patient now increases basal rates temporarily when strenuous activity is anticipated. Bolus doses are adjusted to match the current basal rate, which patient self-administers if experiencing symptoms or serum calcium is <7.5 mg/dL. If symptoms of hypocalcemia are not improved in 15 minutes, a second bolus is given with instructions to change the pod site and seek medical care if no improvement. Despite recent diagnosis of autoimmune hepatitis requiring high-dose steroids, rhPTH(1-34) via pump therapy has significantly improved her management of hypoparathyroidism. She has had only 2 admissions for hypocalcemia (lowest serum calcium 5.6 mg/dL; 1.4 mmol/L) over a 2-year period while on the PTH pump. These events occurred when: (i) shipment of Omnipod was delayed and (ii) Omnipod leakage occurred. We subsequently developed emergency care plans to give rhPTH(1-34) by intermittent injection should these scenarios recur.

Discussion

Hypoparathyroidism is one of the remaining hormone deficiencies not treated with hormone replacement therapy. Instead, multiple daily doses of calcium, calcitriol, and magnesium are administered, causing peaks and troughs of calcium influenced by numerous factors such as concurrent oral medications, gut absorption, dietary calcium intake, hydration status, and activity level. This conventional treatment approach is inadequate as calcitriol does not improve PTH-dependent renal calcium reabsorption, leaving patients at increased risk of progressive nephrocalcinosis.

While the initial approval for rhPTH(1-34) was as an anabolic agent to treat osteoporosis, it has been used off-label for treatment of patients with hypoparathyroidism. PTH(1-34) analog injections have resulted in improvement of serum calcium level fluctuations when used in patients with *CASR* mutations [8] and adults with postsurgical hypoparathyroidism [7]. However, in our patient with APS1, a biphasic pattern was seen with twice-daily rhPTH(1-84) injections (Fig. 1), attributed to her underlying etiology of hypoparathyroidism as well as enteral malabsorption. This prompted the decision to transition to a PTH pump.

While direct dose comparisons between rhPTH(1-84) and rhPTH(1-34) are unavailable, our patient required 2.9 mcg/kg/day of rhPTH(1-84) and at discharge, required 0.43 mcg/kg/day of rhPTH(1-34), suggesting a substantial decrease in medication dosage with use of a pump. Medical costs, including pump supplies, should be considered on an individual basis when deciding if PTH pump therapy is appropriate for a given patient. Normalization of urinary calcium excretion with use of a PTH pump has been described [5, 6], but our patient's spot samples may not accurately reflect urinary calcium excretion. It is difficult to interpret her 24-hour urine calcium, as it was collected before all oral medications had been discontinued. Given the presence of stable, though persistent, medullary nephrocalcinosis, this should continue to be monitored. Anecdotally, there has been significant improvement in quality of life for our patient as she is able to carry on her normal daily activities, attend in-person school, and work part-time. There are tools to capture patient-reported outcomes in individuals with hypoparathyroidism in development [9] and, if validated, these could be helpful to further personalize treatment regimens.

With the removal of the black box warning regarding development of osteosarcoma from current rhPTH(1-34) and the ongoing development of a long-acting prodrug of PTH(1-34) [10], endocrinologists have additional tools for replacement therapy for hypoparathyroidism. Although the principle behind the long-acting PTH analog is similar to the pump delivery of PTH(1-34), a comparison of the two would be required to confirm similar benefits. There are also

additional advantages of a pump. In the setting of GI illnesses or increased activity level, small adjustments to basal rate dosing may better address acute changes in calcium levels. A previous study noted benefits from increased basal rates overnight, mimicking circadian variation in PTH secretion [5]. Our patient has benefited from an increased basal rate during days of increased physical activity. During symptoms of acute hypocalcemia (cramping and tetany), PTH boluses via pump can be given. Our patient normalized her serum calcium using an rhPTH(1-34) bolus via pump during a preoperative admission, allowing her to continue with the planned procedure.

In conclusion, treatment of hypoparathyroidism with continuous rhPTH via insulin pump is clinically effective to stabilize serum calcium, phosphorus, and magnesium levels, to reduce or eliminate the need for active vitamin D and enteral calcium supplementation, and to provide titration of medication in response to varying environmental factors. There is also a lower urinary calcium excretion, thereby presumably reducing the risk of nephrocalcinosis progression and chronic renal insufficiency. Our patient has had a decrease in hospital admissions for hypocalcemia. As our knowledge of rhPTH for management of hypoparathyroidism continues to expand, this should be considered as a potential option for children with hypoparathyroidism who are refractory to conventional therapy. Ongoing studies are necessary to investigate the long-term safety and efficacy as well as assess quality of life outcomes in children with nonsurgical hypoparathyroidism.

Learning Points

- Conventional therapy for hypoparathyroidism, which includes multiple daily doses of oral medications, is burdensome for patients. Continuous PTH delivered by pump has been shown to decrease or even eliminate the need for conventional therapy.
- When compared with rhPTH(1-84) injections, continuous rhPTH(1-34) provides more stable serum calcium levels, thereby presumably decreasing risk of hypocalcemic crises and seizures, hypercalcemia, long-term risk of progressive nephrocalcinosis, renal failure, and soft tissue calcifications.
- Continuous rhPTH through an insulin pump allows for rhPTH boluses to be given as needed for acute hypocalcemia. Basal dose adjustments during times of GI illness, dehydration, increased activity, or other intrinsic changes assure maintenance of normal serum calcium levels with minimal fluctuation.

Contributors

All authors made individual contributions to authorship. F.L.M., H.W., and K.J. were involved in the diagnosis and management of this patient and manuscript submission. K.W. provided medical advice and recommendations throughout the management of this patient and was involved in manuscript submission. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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