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Effects of Pump versus Twice-Daily Injection Delivery of Synthetic Parathyroid Hormone 1-34 in Children with Severe Congenital Hypoparathyroidism

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Abstract

Objective—To compare the response with synthetic human parathyroid hormone (PTH) 1-34 delivery via twice-daily injection vs insulin pump in children with severe congenital hypoparathyroidism due to calcium receptor mutation or autoimmune polyglandular syndrome type 1.

Study design—Children and young adults aged 7-20 years with congenital hypoparathyroidism (N = 12) were randomized to receive PTH 1-34, delivered either via twice-daily subcutaneous injection or insulin pump for 13 weeks, followed by crossover to the opposite delivery method. The principal outcome measures were serum and urine calcium levels. Secondary outcomes included serum and urine magnesium and phosphate levels and bone turnover markers.

Results—PTH 1-34 delivered via pump produced near normalization of mean serum calcium (2.02 ± 0.05 [pump] vs 1.88 ± 0.03 [injection] mmol/L, $P < .05$, normal 2.05-2.5 mmol/L), normalized mean urine calcium excretion (5.17 ± 1.10 [pump] vs 6.67 ± 0.76 mmol/24 h/1.73 m^2, $P = .3$), and significantly reduced markers of bone turnover ($P < .02$). Serum and urine calcium and magnesium showed a biphasic pattern during twice-daily injection vs minimal fluctuation during pump delivery. The PTH 1-34 dosage was markedly reduced during pump delivery (0.32 ± 0.04 vs 0.85 ± 0.11 μg/kg/d, $P < .001$), and magnesium supplements were also reduced ($P < .001$).

Conclusion—Compared with twice-daily delivery, pump delivery of PTH 1-34 provides more physiologic calcium homeostasis and bone turnover in children with severe congenital hypoparathyroidism.

Hypoparathyroidism remains among the few hormonal insufficiency states not treated by replacement of its missing hormone.[1,2] Conventional therapy with vitamin D analogs and calcium may lead to chronic kidney disease due to progressive nephrocalcinosis.[3,4] This is the case especially in congenital hypoparathyroidism due to activating calcium receptor (CaR) mutation, in which hypercalciuria may occur even when the serum calcium level is low-normal or below normal.[5] Furthermore, patients with autoimmune polyglandular

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syndrome type 1 (APS-1) may not respond to conventional vitamin D analog therapy due to chronic malabsorption.[6,7]

Because of the risks of conventional treatment and because some patients with APS-1 are refractory to conventional treatment, we hypothesized that parathyroid hormone (PTH) replacement, with its active N-terminal 1-34 fragment, might be safer and more effective than conventional therapy. Over the past 2 decades, we have evaluated 3 PTH 1-34 regimens —initially, once-daily PTH 1-34 replacement in adults[8]; subsequently, twice-daily PTH 1-34 replacement in adults[5] and children[9]; and most recently, insulin pump delivery of PTH 1-34 in adults with postsurgical hypoparathyroidism.[10] For each regimen, the subcutaneous PTH 1-34 injection dosage was individualized throughout treatment to maintain optimal calcium homeostasis, analogous to insulin dosage individualization in type 1 diabetes. The twice-daily PTH 1-34 regimen was shown to be safe and effective in maintaining stable calcium homeostasis for 3 years in both adults and children[11,12]; however, bone turnover markers remained above the normal range and serum calcium levels showed a biphasic fluctuation. In contrast, pump delivery of PTH 1-34 in postsurgical hypoparathyroid adults produced stable calcium levels and normalized bone turnover markers and markedly reduced the daily PTH dose.[10]

Other investigators showed the benefits of PTH 1-84, either in addition to or as replacement for conventional treatment.[13-15] In addition, pump delivery of rhPTH 1-34 was shown to control refractory hypoparathyroidism for periods of 1-3 years in 1 adult[16] and 3 children.[6]

In the current study, we compared pump delivery with twice-daily injections of PTH 1-34 in 12 children and young adults with hypoparathyroidism due to APS-1 or CaR.

Methods

Twelve children and young adults (7-20 years of age; 5 males [patients E, G, H, I, and J]) with chronic hypoparathyroidism due to APS-1 (n = 5) or CaR (n = 7) were studied (Table). All had a confirmed mutation in the autoimmune regulator or CaR genes except patient E, who had the classic APS-1 triad (mucocutaneous candidiasis, hypoparathyroidism, and Addison disease). Hypoparathyroidism was diagnosed in early childhood (age 1.5-5 y) in all patients with APS-1 and in infancy in all patients with CaR. All except patient K had severe tetany or seizures at diagnosis, and all except patient J had radiographic nephrocalcinosis at study baseline. Additionally, 7 patients (C, D, F, I, J, K, and L) had nephrolithiasis. Patients G and H were siblings with an affected father. The A840V CaR variant in patient K (and her hypoparathyroid father) is a novel mutation. Patients I and E, with APS-1, were Hispanic, from South America and Puerto Rico, respectively. Patient J was from a mixed African American (father) and white (mother) racial background. Two patients with APS-1 (A and F) were from northern European ancestry.

During the year before study entry, 5 patients (F, I, J, K, and L) had undergone 13 hospitalizations. Patient F, a 13-year-old girl with APS-1, had 3 hospitalizations for asthma, pneumonia, and adrenal insufficiency, respectively. Patients I and J, 2 teenage boys with APS-1, each had 4 hospitalizations requiring intravenous calcium treatment for severe

hypocalcemia that occurred while receiving conventional treatment with calcitriol and calcium. Two patients with CaR (K and L) underwent a single hospitalization for severe hypocalcemia and seizure (patient L) while receiving conventional treatment.

Major eligibility criteria included children aged ≥7 years with the clinical diagnosis of APS-1- or CaR-related hypoparathyroidism with normal renal function (glomerular filtration rate [GFR] >25). Two children with APS-1 were excluded due to investigator concern regarding compliance, and 3 children who enrolled (2 with APS-1 and 1 with CaR) were excluded from data analysis because they withdrew after the initial inpatient admission due to school conflicts. Patients I-L were referred by their local physician because of difficulty managing their hypoparathyroidism with conventional therapy.

Patients A-H were recruited from protocol NCT00001304 (same principal investigator) while receiving long-term PTH 1-34 via twice-daily (patients A-C) or 3-times-daily injections (patients D-H). These 8 patients had experienced multiple hospitalizations or emergency department visits related to calcium fluctuations while on conventional therapy before entry into the preceding study (NCT00001304). PTH injections improved their metabolic control and thus decreased their need for emergency medical intervention. The 4 newly referred patients (I-L) were receiving calcitriol and calcium supplement at study baseline. Baseline calcitriol doses (patients I-L) ranged from 0.5 to 8 μg/d, and daily calcium supplement doses ranged from 2000 mg (patient K) to 4000 mg (patient L), with patients J and I receiving 3000 mg/d. Nine patients (all except patients I, J, and L) were also receiving cholecalciferol, and 10 (all except patients C and I) were receiving mean ± SD daily magnesium supplement of 804 ± 179 mg. All patients with CaR received past treatment with thiazide diuretics for the treatment of nephrocalcinosis that was diagnosed in infancy (16 months; patient B), early childhood (3-8 years; patients D, G, H, and L), or adolescence (patients C and K). There was no washout period before initiation of the study or between study arms.

All patients with APS-1 had chronic malabsorption. Other typical features included vitiligo (patients F and J), hypogonadism (patient A), or hypothyroidism (patient E). Three children with APS-1 had chronic active hepatitis (patients A, F, and I) that was diagnosed at 8, 3, and 1 years, respectively. Most patients with APS-1 had Addison disease except 1 adolescent male (patient J) who had positive 21-hydroxylase antibodies.

Late adolescent patients (patients A-D, G, H, J, and K) attained a final height that either reached or surpassed their genetic potential based on reported parental heights. Patient I, however, reached a final adult height of 160 cm (midparental height 174.5 cm) and a concurrent weight of 43 kg. Patient E reached a final height of 179 cm (midparental height 187 cm) and concurrent weight of 56 kg. In early childhood, 2 patients with CaR (C and D) and 2 with APS-1 (E and I) experienced failure to thrive and short stature, and 1 (E) had classic pituitary growth hormone (GH) deficiency. All 4 received GH therapy for varying periods (6 months-10 years). No patient received GH while participating in this study.

Protocol

The study was approved by the institutional review board, and all patients and parents of minors gave written informed consent. The study compared PTH 1-34 delivery via pump vs twice-daily injection in a randomized, crossover design. Patients underwent 2 study periods of 13 weeks, each consisting of a 1-week inpatient dose-adjustment phase, an outpatient phase with continued dose adjustment as needed, and a concluding 4-day inpatient evaluation with daily measurement of serum and 24-hour urine mineral levels and bone turnover markers for 3 days, followed by serial blood (every 2 hours) and urine (every 4 hours) measurements on the fourth day. During serial testing, a standard diet containing 1200 mg elemental calcium was provided (3 meals at 7:00 a.m., 1:00 p.m., and 6:00 p.m. with snacks at 10:00 a.m. and 10:00 p.m.). During the remainder of the study, calcium intake ranged from 800 to 1200 mg elemental calcium based on dietary history and a food frequency questionnaire.

Study Treatments

PTH 1-34 (Bachem Inc, Torrance, California) was prepared for human administration in 200 μg/mL multidose vials at the National Institutes of Health (NIH) Clinical Center as previously described. After baseline testing, study participants were randomized to receive PTH 1-34 delivered via an insulin pump (OmniPod, Insulet) or via twice-daily injection at 8:00 a.m. and 8:00 p.m. All patients received oral cholecalciferol 1000 IU daily, and calcitriol and calcium supplements were discontinued in patients who had been receiving them. No study participant received diuretics or phosphate binders. The PTH 1-34 dose during twice-daily injection was adjusted empirically in increments or decrements of 10%-20% to optimize serum and urine calcium. During pump delivery, smaller increments or decrements ranging from 2% to 10% were used empirically to optimize calcium levels.

During pump delivery, patients filled the pod device with 1.5 mL (300 μg) PTH 1-34; attached the device to the abdomen, lower back, or upper arm; and changed it every 72 hours. Seven basal rates and 7 bolus options were programmed into a wireless device that controlled pump delivery rate. Initial basal rates were estimated for each patient based on body weight (0.2 μg/kg/d) and prior calcitriol or PTH 1-34 dose requirements. Basal rates ranged from 3 to 14 pulses/h, with each pulse delivering 0.1 μg of PTH 1-34. Two of the 7 basal options included a 4-hour or 8-hour nighttime dosage step-up of 1 pulse/h from midnight to 4:00 a.m. or from midnight to 8:00 a.m., to mimic the known circadian variation in circulating PTH.[17,18]

The monitoring protocol for dose adjustment consisted of twice-daily serum calcium and daily 24-hour urine calcium measurements during the initial 1-week inpatient admission, twice-weekly serum calcium and a single 24-hour urine calcium measurements during the first outpatient week, and once- or twice-weekly serum calcium and biweekly 24-hour urine calcium measurements thereafter (up to 22 serum calcium measurements during the outpatient phase). During the pump phase, frequency of serum calcium monitoring was reduced for all patients except 1 teenager with CaR (patient G) to biweekly by the third month because of stable, normal serum and urine calcium levels that required no dose adjustments. During the injection phase, for patients who had been previously treated with

twice-daily PTH injections (A-C), the frequency of monitoring was initially the same as for the pump arm with reduction to biweekly serum and urine calcium levels within the first outpatient weeks. For those who had never received PTH injections (patients I-L) or who were receiving 3-times-daily PTH injections (patients D-H) at baseline, the monitoring frequency was identical to that for the pump arm with subsequent adjustments to the frequency based on clinical results. Dose adjustments for mild hypocalcemia or hypercalcemia involved a gradual incremental change in the basal rate of 1 pulse/h for 4 hours, then for 8 hours (at nighttime only), and finally, continuously for the entire 24 hours.

Study End Points

The principal outcome measures, determined daily for 3 days during the 4-day inpatient evaluation at conclusion of each treatment arm, were the fasting 8:00 a.m. serum (before PTH injection for those receiving twice-daily delivery) and 24-hour urine calcium levels. Secondary outcomes, measured during the same 3 days, included fasting 8:00 a.m. serum and 24-hour urine magnesium and phosphate levels, fasting 8:00 a.m. serum 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 levels, markers of bone turnover (fasting serum 8:00 a.m. bone-specific alkaline phosphatase, osteocalcin, and 24-hour urine N-terminal telopeptide of type 1 collagen), and daily PTH 1-34 dose. Additionally, on the fourth day, serum was collected every 2 hours for 24 hours beginning at 8:00 a.m. (before 8:00 a.m. PTH 1-34 dose for those receiving twice-daily PTH), and urine was collected at 4-hour intervals for 28 hours from 4:00 a.m. until 8:00 a.m. for the serial measurements shown in Figures 1-3 (Figure 3; available at www.jpeds.com).

Assays

Assay methods and their coefficients of variation have been described previously.[10] Serum and urine calcium, phosphorus, magnesium, creatinine, and serum total alkaline phosphatase and osteocalcin levels were measured at the NIH Clinical Center. Radioimmunoassays for intact PTH 1-34, cyclic adenosine monophosphate (cAMP), *N*-telopeptide, bone-specific alkaline phosphatase, 25-Hydroxyvitamin D3, and 1,25-dihydroxyvitamin D3 were measured at Mayo Clinic laboratories.

Statistical Analyses

Data are mean ± SE unless otherwise stated and were analyzed with custom R codes with SAS system software version 9.1 (SAS Institute, Cary, North Carolina). Daily serum and urine measurements during pump vs injection delivery were compared by paired *t* test. Because no statistically significant sequence effects were observed for the 2 delivery methods (P = .42-.99 [range for bone turnover markers], P = .08-.92 [other study end points]), data from the first and second periods for each delivery method were combined for analysis. Calcium excretion (Ca_E) was computed as $Ca_E = calcium_{urine} \times creatinine_{serum}/creatinine_{urine}$. All urine measures were corrected to body surface area of 1.73 m^2.

The 24-hour profiles of serum calcium, magnesium, phosphorus, and 1,25-dihydroxyvitamin D3 were analyzed by harmonic regression modeling with random effects.[20,22] Circadian pattern of serum profiles was assessed by a linear mixed model with 2 harmonic terms.[20] Correlation between repeated measurements was accounted for with a single random

intercept. Mean 24-hour levels and circadian pattern between pump and injection delivery were compared by the likelihood ratio test.

The 24-hour profiles of urine calcium excretion, tubular phosphate reabsorption, magnesium-to-creatinine ratio, and cAMP excretion were analyzed by a linear mixed model with random intercept.[22] For each urine measure, time of day, delivery method, and time × delivery method interaction effects were determined by the likelihood ratio test. For each 4-hour collection, tubular maximum phosphate reabsorption/GFR was computed as tubular maximum phosphate reabsorption/GFR = $P_{serum} - (P_{urine} \times creatinine_{serum}/creatinine_{urine})$, where P_{serum}, P_{urine}, $creatinine_{serum}$, and $creatinine_{urine}$ refer to the concentration of phosphate and creatinine in serum and urine, respectively.[23,24] *P* values ≤.05 were considered statistically significant.

Results

Effect of Delivery Method on Mineral Levels and Bone Turnover Markers

Compared with twice-daily injection, pump delivery of PTH 1-34 normalized the mean 24-hour urine calcium excretion (5.17 ± 1.10 [pump] vs 6.67 ± 0.76 mmol/24 h/1.73 m^2, *P* = .31, normal reference 1.25-6.25) and produced near normalization of mean serum calcium (2.02 ± 0.05 [pump] vs 1.88 ± 0.03 mmol/L, *P* < .02, normal 2.05-2.5; Figure 4). Similarly, pump delivery reduced magnesium excretion (6.06 ± 1.28 [pump] vs 7.38 ± 1.33 mmol/24 h/ 1.73 m^2, *P* < .001, normal 3.04-4.25) and normalized mean serum magnesium (0.74 ± 0.02 [pump] vs 0.65 ± 0.02 mmol/L, *P* < .001, normal 0.75-1.00; Figure 4). Pump delivery produced higher serum phosphate (1.78 ± 0.08 [pump] vs 1.58 ± 0.07 mmol/L, *P* < .01, normal 0.8-1.5), and urine phosphate excretion was similar and within the normal range for both delivery methods (Figure 4). Pump delivery did not affect 25-Hydroxyvitamin D3 levels (38 ± 3 [pump] vs 33 ± 4 ng/ mL, *P* = .09 [data not shown]). Pump delivery was associated with higher mean ± SEM 8:00 a.m. fasting 1,25-hydroxyvitamin D3 levels vs those during injection delivery, which corresponded to nadir levels 12 hours after the previous PTH 1-34 injection (75.2 ± 8 [pump] vs 55.6 ± 5 pg/mL, *P* < .02, normal 18-78 [data not shown]). However, this difference was not apparent on the day of serial testing, when there were no significant differences in pattern or mean 1,25-hydroxyvitamin D3 levels between the 2 delivery methods (Figure 1, D).

Pump delivery reduced all 3 bone turnover markers significantly, by 37%-63%, compared with twice-daily delivery (*P* < .02; Figure 4, C). For the 2 turnover markers with established pediatric norms, the mean values during pump delivery were in the mid-normal range but were high-normal or slightly above normal during twice-daily delivery.

Effect of Delivery Method on 24-Hour Profiles

Serial testing during twice-daily injections revealed a biphasic pattern for both serum and urine calcium and magnesium, and for urine cAMP excretion, compared with minimal fluctuation during pump delivery (Figures 1, A and B, and 2, A, B, and D). The circadian pattern of sequential 2-hour measurements of serum calcium and magnesium differed significantly between pump vs injection delivery (*P* < .001). Similarly, serial 4-hour urine

measurements of calcium ($P < .01$), magnesium ($P < .001$), and cAMP ($P < .01$) excretion yielded significantly different circadian patterns for pump vs injection delivery (Figure 2, A, B, and D).

Effect of CaR vs APS-1 Diagnosis on Response to PTH 1-34

Serial 24-hour measurements showed lower serum calcium and higher urine calcium levels in CaR compared with patients with APS-1 for both delivery methods, but these differences did not achieve statistical significance for the small number of patients with each diagnosis (Figure 3). The urine calcium excretion–to–serum calcium ratio was lower during pump delivery of PTH for the patients with APS-1 but also was not significant. In contrast, patients with CaR demonstrated no difference in the urine calcium excretion– to–serum calcium ratio between delivery methods (3.07 for both pump and injection, $P = 1.0$).

Patients with CaR also tended to have lower creatinine clearance (103 ± 6 [CaR] vs 129 ± 11 mL/min/1.73 m^2, $P < .05$) and serum 1,25-dihydroxyvitamin D3 levels (57 ± 7 vs 77 ± 6 pg/mL, $P < .05$) and higher serum phosphorus levels (1.78 ± 0.05 [CaR] vs 1.55 ± 0.09 mmol/L, $P < .05$). PTH 1-34 dosage was similar between diagnostic groups for each delivery method: during pump delivery, 0.34 ± 0.06 (CaR) vs 0.29 ± 0.03 (APS-1) μg/kg/d, P = NS; and during injection delivery, 0.73 ± 0.15 (CaR) vs 1.03 ± 0.12 (APS-1) μg/kg/d, P = NS.

Effect of Delivery Method on PTH 1-34 Dosage

At the conclusion of 13 weeks of PTH treatment with a pump, 6 patients remained on a continuous basal rate throughout the day, 3 received a continuous rate through the day with a 4-hour dosage increase from midnight to 4:00 a.m. (patients G, I, and L), and 3 received a continuous basal rate with an 8-hour dosage increase from midnight to 8:00 a.m. (patients A, E, and J). Although bolus options had been programmed into the wireless controlling device in event of severe hypocalcemic symptoms, only adjustments in basal dose rate were actually made during the study, with a mean of 5 changes during the outpatient phase (range 0-17). Compared with twice-daily injection, pump delivery was associated with a 62% reduction in the daily PTH 1-34 dose (0.32 ± 0.04 vs 0.85 ± 0.11 μ/kg/d, $P < .001$). Additionally, pump delivery, by raising serum magnesium, permitted reduction in mean ± SEM magnesium supplement (532 ± 105 [pump] vs 944 ± 158 mg/d, $P < .001$).

Adverse Events

There were no episodes of severe tetany or seizures and no severe hypocalcemia (or hypercalcemia) requiring emergency treatment during the study, including the 2 patients with APS-1 (I and J) who had each had 4 hospitalizations for severe hypocalcemia during the year before the study. One patient with APS-1 (F) was hospitalized for bronchitis and asthma during pump delivery. Two patients from a warm climate (D and E) reported that the pod fell off before the prescribed 72-hour time period, which required more frequent device changes. At the conclusion of the study, patients A, B, D, F-H, and J-L reported preference for pump delivery because of reduced symptoms associated with calcium fluctuations, ease of use, and the potential long-term health benefits. Patients C, E, and I preferred twice-daily injections because they did not like having a device attached to their body continuously.

Discussion

In this randomized, crossover study, insulin pump delivery of synthetic PTH 1-34 showed clear advantages over delivery via twice-daily injection in difficult-to-manage children with hypoparathyroidism due to APS-1 or CaR. These results represent the closest approach to date to physiologic replacement therapy in these patients and confirm previous evidence of the ready adaptability of insulin pump technology to the treatment of hypoparathyroidism.[6,10,16]

Compared with previous pump delivery of PTH 1-34 in adults with postsurgical hypoparathyroidism, children with APS-1 or CaR required nearly twice the per-kilogram PTH 1-34 dosage (0.32 ± 0.11 vs 0.17 ± 0.03 μg/kg/d). Potential explanations include greater residual PTH production in the postsurgical adults and age- or disease-related differences in PTH requirement. Current evidence does not permit distinction among these. Additionally, we have no explanation for the unexpectedly higher serum phosphate levels during pump compared with injection delivery. A more in-depth analysis of phosphorus response, including additional measures such as serum FGF-23 level, might provide further insight in future studies.

During the pump arm, we introduced a nighttime step-up in PTH dosage that mimics the known circadian pattern of PTH secretion[17,18] and eliminated the slight nighttime downward drift in serum calcium that was observed in some patients in the earlier adult study.[10]

For reasons of technical feasibility, we could not precisely mimic the physiologic pattern of PTH secretion by superimposing, on the underlying circadian profile, intermittent small boluses at randomly varying intervals. Theoretically, such boluses could simulate the stochastic pulsatility that is superimposed on the basal circadian pattern of PTH release.[17,18] Additionally, although no statistically significant sequence effects were detected for any study end point for either delivery method, the possibility of small carry-over effects cannot be excluded because of the lack of washout periods at baseline and between crossover arms.

Our results confirm the benefits of PTH replacement that have been observed with varied PTH regimens in other studies of with hypoparathyroid.[8-15] In all of these studies, a key difference between PTH replacement for hypoparathyroidism and insulin replacement for type 1 diabetes is the absence of a device for self-monitored blood calcium that would be analogous to the devices for self-monitored blood glucose. This is an important unmet need that would simplify monitoring and dose adjustment.

Based on the current and previous studies, we conclude that pump delivery of PTH 1-34 is an important advance in the treatment of difficult-to-manage children with congenital hypoparathyroidism who need lifetime treatment. Because pump delivery is more physiologic than twice-daily delivery, we hypothesize that it holds the greatest prospect of avoiding both the acute hypocalcemic crises and the chronic renal insufficiency that have remained a challenge with conventional treatment.[25] Testing this hypothesis will require long-term study.

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References

1. Horwitz MJ, Stewart AF. Hypoparathyroidism: is it time for replacement therapy? J Clin Endocrinol Metab. 2008; 93:3307–9. [PubMed: 18772463]
2. Rejnmark L, Sikjaer T, Underbjerg L, Mosekilde L. PTH replacement therapy of hypoparathyroidism. Osteoporos Int. 2013; 24:1529–36. [PubMed: 23184178]
3. Weber G, Cazzuffi MA, Frisone F, De Angelis M, Pasolini D, Tomaselli V, et al. Nephrocalcinosis in children and adolescents: sonographic evaluation during long-term treatment with 1,25-dihydrocholecalciferol. Child Nephrol Urol. 1998:273–6.
4. Santos F, Smith MJ, Chan JC. Hypercalciuria associated with long term administration of calcitriol (1,25-dihydroxyvitamin D). Am J Dis Child. 1986; 140:139–42. [PubMed: 3753816]
5. Winer KK, Yanovski JA, Sarani B, Cutler GB Jr. A randomized, crossover trial of once-daily vs twice-daily human parathyroid hormone 1-34 in the treatment of hypoparathyroidism. J Clin Endocrinol Metab. 1998; 83:3480–6. [PubMed: 9768650]
6. Linglart A, Rothernbuhler A, Gueorgieva I, Lucchini P, Silve C, Bougneres P. Long-term results of continuous subcutaneous recombinant PTH 1-34 infusion in children with refractory hypoparathyroidism. J Clin Endocrinol Metab. 2011; 96:3308–12. [PubMed: 21865375]
7. Strogmann W, Bohrn E, Woloszczuk W. First experiences in the substitution treatment of hypoparathyroidism with synthetic human parathyroid hormone. Monatsschr Kinderheilkd. 1990; 138:141–6. [PubMed: 2162006]
8. Winer KK, Yanovski JA, Cutler GB Jr. Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism: results of a randomized crossover trial. JAMA. 1996; 276:631–6. [PubMed: 8773636]
9. Winer KK, Sinaii N, Peterson D, Sainz B Jr, Cutler GB Jr. Effects of once-daily versus twice-daily parathyroid hormone 1-34 in children with hypoparathyroidism. J Clin Endocrinol Metab. 2008; 93:3389–95. [PubMed: 18492754]
10. Winer KK, Zhang B, Shrader JA, Peterson D, Smith M, Albert PS, et al. Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism. J Clin Endocrinol Metab. 2012; 97:391–9. [PubMed: 22090268]
11. Winer K, Ko CW, Reynolds J, Dowdy K, Keil M, Peterson D, et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone 1-34 and calcitriol and calcium. J Clin Endocrinol Metab. 2003; 88:4214–20. [PubMed: 12970289]
12. Winer KK, Sinaii N, Reynolds J, Peterson D, Dowdy K, Cutler GB Jr. Long-term treatment of 12 children with chronic hypoparathyroidism: a randomized trial comparing synthetic human parathyroid hormone 1-34 versus calcitriol and calcium. J Clin Endocrinol Metab. 2010; 95:2680–8. [PubMed: 20392870]
13. Sikjaer T, Rejnmark L. The effect of adding PTH 1-84 to conventional treatment of hypoparathyrodism. J Bone Miner Res. 2011; 26:2358–70. [PubMed: 21773992]
14. Cusano NE, Rubin MR, McMahon DJ, Zhang C, Ives R, Tulley A, et al. Therapy of hypoparathyroidism with intact parathyroid hormone 1-84: a prospective four year investigation of efficacy and safety. J Clin Endocrinol Metab. 2013; 1:137–44. [PubMed: 23162103]

15. Rubin MR, Sliney J Jr, McMahon DJ, Silverberg SJ, Bilezikian JP. Therapy of hypoparathyroidism with intact parathyroid hormone. Osteoporos Int. 2010; 21:1927–34. [PubMed: 20094706]
16. Puig-Domingo M, Diaz G, Nicolau J, Fernandez C, Rueda S, Halperin I. Successful treatment of vitamin D unresponsive hypoparathyroidism with multipulse subcutaneous infusion of teriperatide. Eur J Endocrinol. 2008; 159:653–7. [PubMed: 18703565]
17. Samuels MH, Veldhuis JD, Cawley C, Urban RJ, Luther M, Bauer R, et al. Pulsatile secretion of parathyroid hormone in normal young subjects: assessment by deconvolution analysis. J Clin Endocrinol Metab. 1993; 77:399–403. [PubMed: 8345044]
18. Harms HS, Kaptiana U, Kulpmann WR, Brabant G, Hesch RD. Pulse amplitude and frequency modulation of parathyroid hormone in plasma. J Clin Endocrinol Metab. 1989; 69:843–51. [PubMed: 2778038]
19. Peacock M, Nordin BE. Tubular reabsorption of calcium in normal and hypercalciuric subjects. J Clin Pathol. 1968; 221:353–8. [PubMed: 5699075]
20. Stroebel AM, Bergner M, Reulbach U, Biermann T, Groemer TW, Klein I, et al. Statistical methods for detecting and comparing periodic data and their application to the nycthemeral rhythm of bodily harm: a population based study. J Circadian Rhythms. 2010; 8:10. [PubMed: 21059197]
21. Albert PS, Hunsberger S. On analyzing circadian rhythms data using nonlinear mixed modes with harmonic terms. Biometrics. 2005; 61:1115–22. [PubMed: 16401286]
22. Pinheiro, JC.; Bates, DM. Mixed-effects models in S and S-Plus. New York: Springer Verlag; 2000.
23. Alon U, Hellerstein S. Assessment and interpretation of the tubular threshold for phosphate in infants and children. Pediatr Nephrol. 1994; 8:250–1. [PubMed: 8018507]
24. Brodehl J, Krause A, Hoyer P. Assessment of maximal tubular phosphate reabsorption: comparison of direct measurement with the nomogram of Bijvoet. Pediatr Nephrol. 1988; 2:183–9. [PubMed: 3153009]
25. Michell DM, Regan S, Cooley MR, Lauter KB, Vrla MC, Becker CB, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 2012; 97:4507–12. [PubMed: 23043192]

Glossary

APS-1	Autoimmune polyglandular syndrome type 1
cAMP	Cyclic adenosine monophosphate
CaR	Calcium receptor
GFR	Glomerular filtration rate
GH	Growth hormone
NIH	National Institutes of Health
PTH	Parathyroid hormone

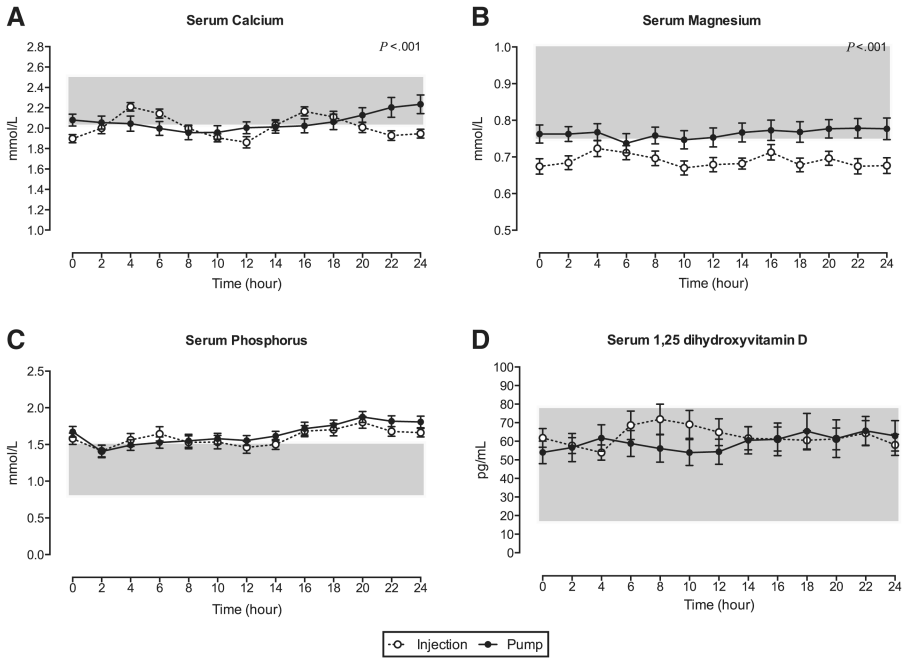

Figure 1.

Serum levels of calcium, magnesium, phosphorus, and 1,25-dihydroxyvitamin D measured every 2 hours for 24 hours starting at 8:00 a.m. at the conclusion of each 3-month treatment arm comparing pump with twice-daily injection delivery of PTH 1-34 in children with hypoparathyroidism. The circadian patterns for serum calcium and magnesium differed significantly between delivery methods ($P < .001$).

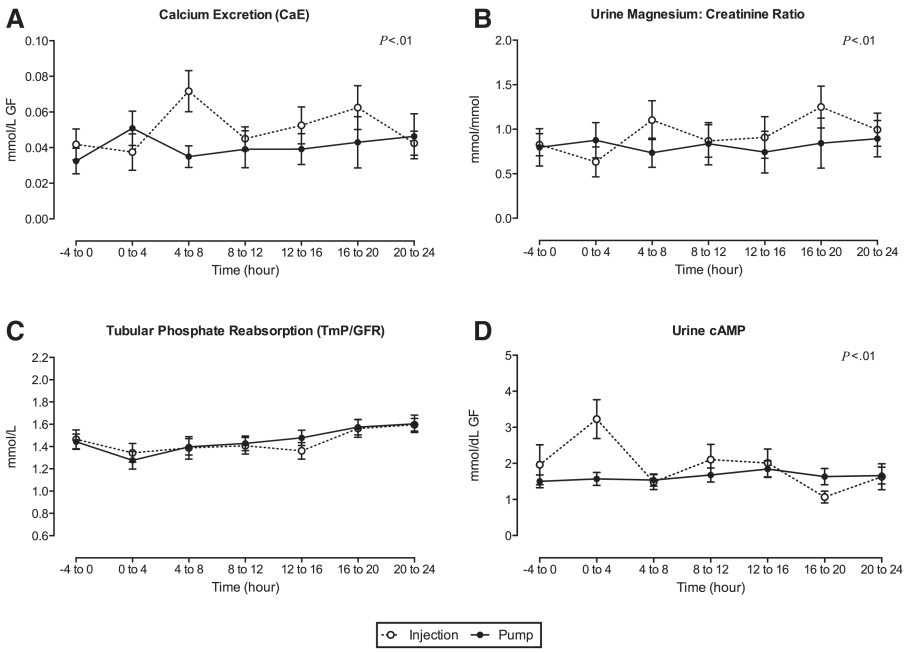

Figure 2.

Urine calcium, magnesium, phosphate, and cAMP excretion per unit of glomerular filtrate, measured every 4 hours for 28 hours starting at 4:00 a.m. at the conclusion of each 3-month treatment arm comparing pump with twice-daily injection delivery of PTH 1-34 in children with hypoparathyroidism. The circadian patterns for urine calcium, magnesium, and cAMP excretion differed significantly between delivery methods ($P < .01$).

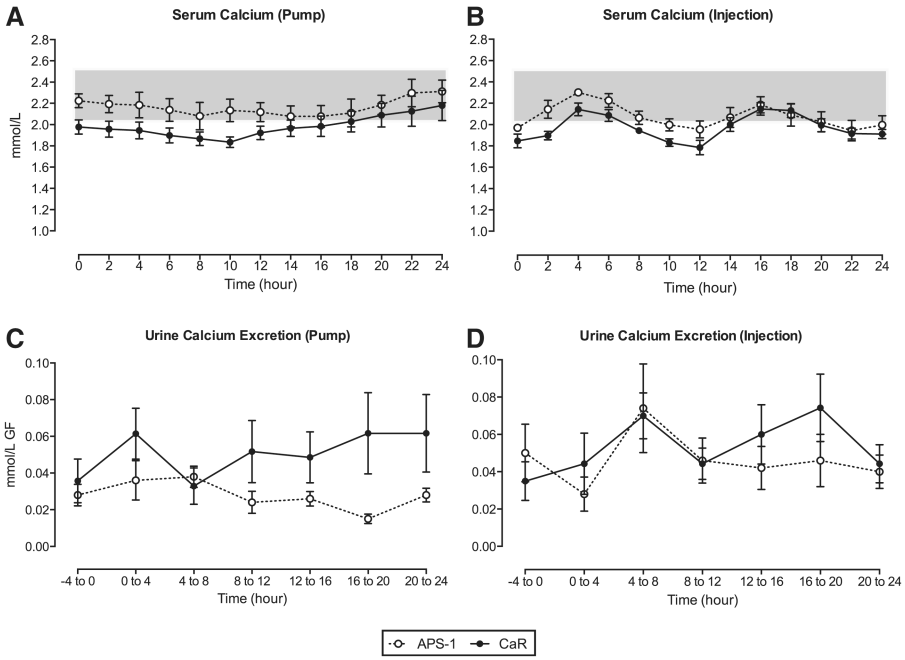

Figure 3.

Circadian patterns of serum and urine calcium for patients with hypoparathyroid with APS-1 vs those with CaR during pump vs injection delivery of PTH 1-34.

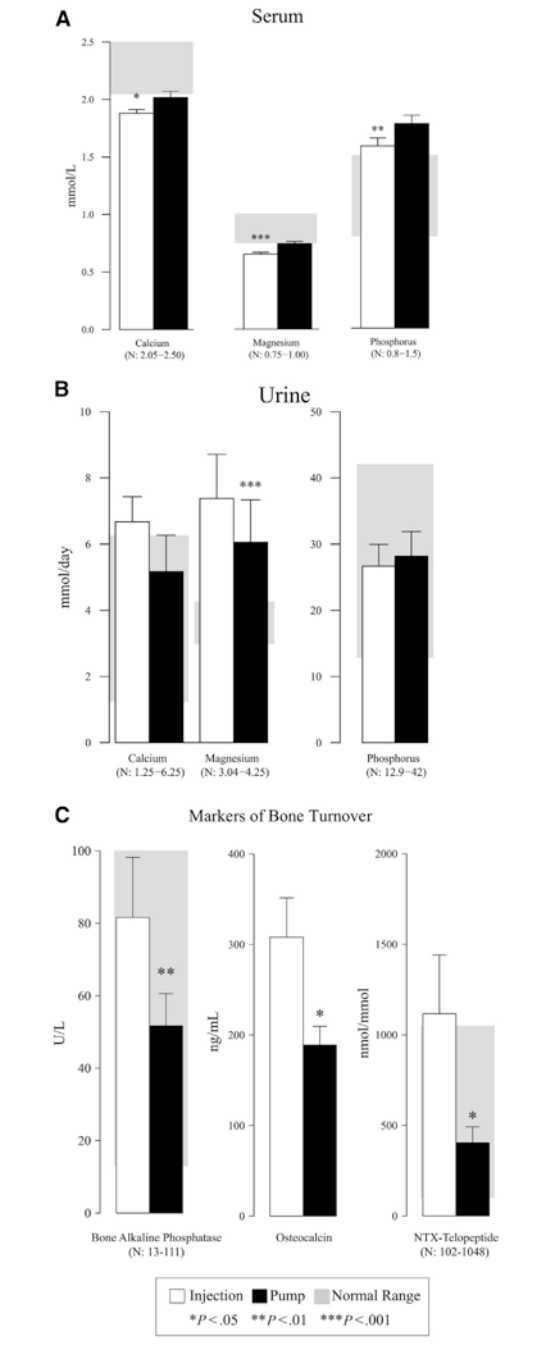

Figure 4.

A, Mean serum, **B**, 24-hour urine, and **C**, calcium, magnesium, and phosphorus levels and bone turnover markers obtained daily for 4 days at the end of each 3-month treatment arm comparing pump with twice-daily injection delivery of PTH 1-34 in children with hypoparathyroidism. **P* < .05, ***P* < .01, ****P* < .001. Urine measures were corrected to a body surface area of 1.73 m^2.

Table

Baseline subject characteristics

Patient	Age(y)	Diagnosis	Baseline treatment*	Baseline dose (μg)	Duration of disease (y)	Calcium (mmol/L [2.05-2.5])†	Phosphorus (mmol/L [0.8-1.5])†	Magnesium (mmol/L [0.75-1.0])†	Bone alkaline phosphatase (U/L [13-111])†	25-Hydroxyvitamin D (ng/mL [10-80])†	Urinary calcium§ (mmol/24 h [1.25-6.25])†	Urinary phosphorus§ (mmol/24 h [12.9-42])†	Urinary magnesium§ (mmol/24 h [3.0-4.25])†	Creatinine clearance§ (mL/min [90-125])†	Genetic mutation
A	17	APS-1	PTH	28	14.5	2.05	1.39	0.56	59	65	4.52	15.31	5.36	98	R257X
B	16	CAR	PTH	24	15	2.05	1.57	0.68	47	39	5.81	24.4	11.75	87	E127K
C	18	CAR	PTH	28	17.5	1.89	1.84	0.84	31	25	7.17	32.3	3.92	94	N802I
D	14	CAR	PTH	36	14	1.85	1.70	0.68	41	76	10.67	33.2	7.19	71	F832S
E	20	APS-1	PTH	72	15	2.26	1.19	0.71	38	39	3.82	16.6	4.79	102	-
F	13	APS-1	PTH	27	11.5	1.99	1.58	0.70	117	33	6.74	10.0	5.35	160	c.967 979del13
G	17	CAR	PTH	72	17	1.93	1.51	0.70	83	30	8.23	31.1	6.48	110	E604K
H	18	CAR	PTH	72	17.5	1.94	1.49	0.67	70	30	4.98	23.1	5.88	119	E604K
L	16	APS-1	Vitamin D	4.5	13	1.95	1.94	0.70	46	45	9.10	28.1	3.75	154	c.328delC
J	17	APS-1	Vitamin D	8	12.5	1.98	1.73	0.78	188	30	6.12	16.3	4.71	110	R257X
K	15	CAR	Vitamin D	0.5	14.5	2.04	1.50	0.69	10	39	8.55	28.8	5.99	119	A840V*
L	7	CAR	Vitamin D	2	7	1.71	2.51	0.71	72	35	10.39	30.3	18.53	124	F788C
Mean ± SEM	15.7 ±0.96				14.1 ±0.85	1.97 ±0.04	1.66 ±0.1	0.7 ± 0.02	66.8 ±13.6	40.5 ± 4.39	7.18 ±0.65	24.13 ±2.25	6.97 ±1.21	112.34 ±7.38	

*Normal range in parentheses.

†Baseline treatment included twice daily (A-C) or 3 times daily (D-H) PTH 1 -34 (PTH) or calcitriol (vitamin D).

‡Novel CaR mutation.

§Urine excretion measures were corrected to 1.73 m^2 body surface area.