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ORIGINAL ARTICLE

Cinacalcet is efficacious in pediatric dialysis patients

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Abstract Secondary hyperparathyroidism (high-turnover bone disease, or HTBD) is manifested by elevated parathyroid hormone (PTH) levels. Control of HTBD may be achieved by maintaining low serum phosphorous levels and administering vitamin D therapy, although some patients continue to exhibit high PTH levels. We report the results of the efficacy of the calcimimetic cinacalcet in six hemodialysis (HD) and three peritoneal dialysis (PD) pediatric patients with HTBD, age 14.5±1.0 (range 7.5–17.5) years. Six patients received 30 mg/day, one required 60 mg/day, and two received 120 mg/day. Treatment with cinacalcet resulted in a 61% decline in intact PTH (iPTH) levels (1,070±171.5 pretreatment to 417.6±97.8 posttreatment pg/ml, p=0.005). Serum alkaline phosphatase also declined (561.8±169.6 U/L pretreatment to 390.3±110.3 U/L posttreatment pg/ml). During therapy, serum calcium (p=0.9) and phosphorous (p=0.9) levels, calcium-phosphorous product (p=0.8), systolic blood pressure (BP) (p=1.0), diastolic BP (p=0.8), and hemoglobin (p=0.9) remained unchanged. The dose of oral calcitriol for the three patients on PD while receiving cinacalcet trended downward (0.8±0.2 pretreatment vs. 0.5±0.0 μg/day posttreatment pg/ml), as did the dose of paracalcitol for those receiving HD (6.6±2.3 pretreatment vs. 4.3±1.7 micrograms/day posttreatment pg/ml). We conclude that short-term treatment with the calcimimetic cinacalcet is efficacious in adolescent dialysis patients.

Keywords Secondary hyperparathyroidism · Calcimimetic · Parathyroid hormone · Calcium · Phosphorous

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Introduction

Renal osteodystrophy remains one of the most perplexing problems for pediatric nephrologists. Although the mechanisms involved in the pathogenesis of renal osteodystrophy have been elegantly outlined and reviewed over the past few decades [1–6], management remains difficult. There are three main types of renal osteodystrophy: high-turnover bone disease (HTBD), mixed lesion, and adynamic or low-turnover bone disease. The proportion of patients with these three subtypes varies with each study and patient population. The most common form of renal osteodystrophy in our pediatric end-stage renal disease (ESRD) population is HTBD, due in part to the frequent inability of our patients to adhere to the required low phosphorous diet and to maintain adequate compliance with medication regimens. We routinely prescribe a vitamin D analog, either oral calcitriol to our patients on chronic peritoneal dialysis (PD) or paracalcitol to our hemodialysis (HD) patients. Despite aggressive and concerted efforts to control HTBD with these measures, we continue to observe hyperparathyroidism with markedly elevated intact parathyroid hormone (iPTH) levels.

Therapy with an analog of 1,25 vitamin D_3 [7] and maintenance of low serum phosphorous levels via dietary restriction of phosphorous intake and use of phosphate binders [8] suppress PTH secretion by the parathyroid glands. High serum calcium can also suppress PTH secretion [9]. When the parathyroid gland senses high

serum calcium, the calcium-sensing receptor is activated, stimulating a cascade of intracellular reactions resulting in the reduction of PTH production by the parathyroid glands. Unfortunately, maintaining high serum calcium levels is not an option, as this may contribute to metastatic calcifications [10–14], including calcium deposits in coronary vessels leading to a high rate of cardiovascular complications in young adults.

The advent of calcimimetics provided a mechanism whereby PTH can be suppressed in the absence of high serum calcium levels. Like other calcimimetics, cinacalcet binds to the calcium-sensing receptor; this simulates calcium binding, leading to a decrease in PTH release. There is a growing body of literature providing evidence that cinacalcet suppresses PTH without significantly altering serum calcium or phosphate levels in adult ESRD patients [15–26], although studies show that serum calcium may increase [27] or decrease in some patients on cinacalcet [26, 28, 29]. There has been some concern that calcimimetics in children may alter bone growth. However, although cinacalcet localizes in the parathyroid glands and chondrocytes [30], activation of the calcium-sensing receptor in the growth plate induces rather than inhibits longitudinal bone growth [31]. Regardless, pediatric nephrologists have faced a daunting dilemma: accept dangerously high PTH levels and risk the development of fibrotic bone disease, refer for subtotal parathyroidectomy, or use calcimimetics without adequate study data in the pediatric population.

We observed unusually high iPTH levels in many of our adolescent patients due to admitted dietary and/or medication noncompliance. With no other options available, we decided to prescribe cinacalcet to some of the patients with long-standing, severe, secondary hyperparathyroidism. We report herein the results of this retrospective analysis.

Methods

Inclusion and exclusion criteria Patients aged 2–21 years on chronic HD or PD for at least 6 months, with iPTH levels of at least an average of 400 pg/ml for 3 consecutive months were eligible for treatment with cinacalcet. For high iPTH, all patients and their caretakers were provided with consistent and comprehensive dietary guidance, and all were on phosphate binders and receiving either oral or intravenous analog of 1,25 vitamin D_3. The study was approved by the Children's National Medical Center Institutional Review Board.

Dietary recommendations Dietary recommendations for calcium and phosphorous intake were according to standard guidelines: Kidney Disease Quality Initiative (K/DOQI) Clinical Practice Guidelines (Guidelines 4–7) for Bone Metabolism and Disease in Children With Chronic Kidney Disease [32]. Specifically, the total dose of elemental calcium provided by the calcium-based phosphate binders and the dietary calcium was prescribed to not exceed twice the dietary reference intake (DRI) for calcium based on age and not to exceed 2,500 mg/day. Dietary phosphorous intake was reduced to DRI for age if the iPTH was above target range and the serum phosphorous within target range. It was reduced to 80% of DRI in patients with elevated iPTH but high serum phosphorous.

Medications All patients were receiving a phosphate binder and an oral or intravenous analog of 1,25 vitamin D_3 prior to and during cinacalcet therapy. The choice of phosphate binder was individualized and according to each patient's serum calcium level and tolerance of the medication. Accordingly, patients received either calcium carbonate, calcium acetate, sevelemar chloride, or lanthanum carbonate. Patients maintained on hemodialysis received intravenous paracalcitol, with the following dosing guidelines: for iPTH 200–500 initiate at 0.04 μg/kg per treatment; for iPTH 500–800 initiate at 0.07 μg/kg per treatment; for iPTH > 800 initiate at 0.10 μg/kg per treatment. Changes in paracalcitol dose were made according to established guidelines [33, 34].

Cinacalcet use Initial dosing was 30 mg once each evening with food. The dose was increasedon a monthly basis by 30 mg to a maximum of 120 mg for persistent elevation of iPTH greater than 500 pg/ml, as tolerated by the patient.

Assessment of laboratory indices Our dialysis protocol includes monthly assessment of serum calcium and phosphate, alkaline phosphatase (ALK), and hemoglobin. Our usual protocol is to measure iPTH by immunoradiometric assay (IRMA) every 3 months; in patients (including all of those in the study) with very high or low iPTH levels, monthly evaluation was performed. After cinacalcet initiation, serum calcium and phosphorus levels were measured every 2–4 weeks, as clinically indicated.

Assessment of blood pressure Blood pressure (BP) values represent causal BP measured by oscillometry on validated and calibrated devices (Dinamap ProSeries, General Electric Technologies) using a appropriately sized cuff on the right arm at the level of the heart in a calm atmosphere and in the presence of a nurse. For HD patients, pre- and postcinacalcet readings represent five consecutive predialysis treatment recordings. For peritoneal dialysis patients, pre- and postcinacalcet readings represent three consecutive monthly measurements recorded at monthly visits. Abnormal BP values were immediately verified by repeat measurements.

BP values were compared with those as defined by the Fourth Report of Blood Pressure in Children [35].

Hemodialysis adequacy The HD prescription was individualized to maximize solute and solvent clearance. HD small-solute clearance (adequacy) was assessed monthly during a midweek dialysis treatment. Single-pool Kt/V (spKt/V) was calculated by the second-generation Daugirdas equation, which has been validated in children [36].

Statistical analysis Comparison between pre- and posttreatment groups was assessed by the paired or unpaired Student's *t* test. The relationship between pre- and posttreatment groups was assessed by univariate regression analysis. The determination of significance was defined as $p<0.05$.

Results

Patient demographics A total of 13 patients were originally prescribed cinacalcet. Three admitted noncompliance shortly after starting the drug, and their data were excluded from the analysis. One patient experienced a seizure after receiving one dose of cinacalcet, prompting discontinuation of therapy. Data for the remaining nine patients (six on HD and three on PD) were included in the analysis. Patient age at the start of therapy was 14.5±1.0 (range 7.5–17.5) years. Eight were of African American descent; one was Latino. There were six male and three female patients. Dialysis vintage was 47.6± 9.9 (range 17–84) months. Pretreatment iPTH levels did not correlate with dialysis vintage ($r=0.18$, $p=0.6$).

Etiologies of ESRD were congenital urinary tract malformation (posterior urethral valves, dysplasia, cystic dysplasia, hydronephrosis) 3/9 (33.3%); glomerular disease (focal segmental glomerulosclerosis, antineutrophil cytoplasmic antibody-mediated rapidly progressive glomerulonephritis (RPGN), lupus nephritis/RPGN, hepatitis-C-mediated nephrotic syndrome) 5/9 (55.5%); chronic tubulointerstitial nephritis 1/9 (11.1%).

Dosing of cinacalcet All patients were started initially on 30 mg/day. Six patients remained on that dose, one required an increase to 60 mg/day, and two required 120 mg/day. The mean final dose/day was 53.3±13.0 mg/day, and the dose per kilogram per day was 1.27±0.30 mg/day.

Serum intact parathyroid hormone and alkaline phosphatase levels We assessed iPTH and ALK for 3 months prior to and after initiating cinacalcet therapy. As shown in Table 1, serum iPTH levels were markedly elevated prior to starting cinacalcet; treatment resulted in a mean 61% decline in iPTH levels from the 1-month pretreatment to 3-month posttreatment time periods. Comparing the 1-month pretreatment to the 1-, 2-, and 3-month posttreatment levels, there was a significant decrease in iPTH at all three test points. The change in iPTH level for each patient from the 1-month pretreatment value to that obtained after 3 months of therapy is shown in Fig. 1. Only one patient failed to exhibit a decline in iPTH while receiving cinacalcet. ALK changed from 561.8±169.6 (1 month pretreatment) to 390.3± 110.3 U/L (3 months posttreatment) pg/ml, and the trend revealed a decline at all posttreatment test points ($p=0.05$, $p=0.08$, and $p=0.06$ at 1, 2, and 3 months posttreatment, respectively, compared with pretreatment) (Table 1).

In HD patients ($n=6$) cinacalcet induced a 41.7% decline in iPTH level (845.73±145.2 1 month pretreatment to 493.0±133.4 3 months posttreatment pg/ml, $p=0.03$); in PD ($n=3$) patients, cinacalcet induced a 82.4% decline in iPTH level (1518.0±309.5 1 month pretreatment to 266.7± 93.6 3 months posttreatment pg/ml, $p=0.08$). This was not statistically significant, primarily due to the fewer number of PD compared with HD patients.

Serum calcium and phosphate levels while on cinacalcet Despite reductions in iPTH and ALK levels, compared with 1-month pretreatment values, serum calcium and phosphorous levels, and calcium-phosphorous (Ca-Pi) product were unchanged after 3 months of cinacalcet therapy. The Ca-Pi product increased in five patients and declined in four (Table 2).

Table 1 Effect of cinacalcet therapy on serum intact parathyroid hormone (iPTH) and alkaline phosphatase (ALK) levels

Parameter	Pretreatment			Posttreatment		
	3 months	2 months	1 month	1 month	2 months	3 months
iPTH	854.4±177.3	854.4±174.9	1070.0±171.5	519.3±125.0* (↓ 61.0%)	476.9±76.9** (↓ 55.4%)	417.6±97.8*** (↓ 51.5%)
ALK	429.4±105.6	476.9±124.8	561.8±169.6	360.2±97.7 (↓ 35.9%)	400.2±99.2 (↓ 28.8%)	390.3±110.3 (↓ 30.5%)

Serum iPTH levels were at least fourfold higher than the target values prior to cinacalcet therapy. There was a steady decline in iPTH levels after cinacalcet was started. Percent changes in iPTH and ALK values from the 1-month pretreatment value. All posttreatment iPTH levels were significantly lower than the 1-month pretreatment values (*$p=0.03$; **$p=0.006$; ***$p=0.004$)

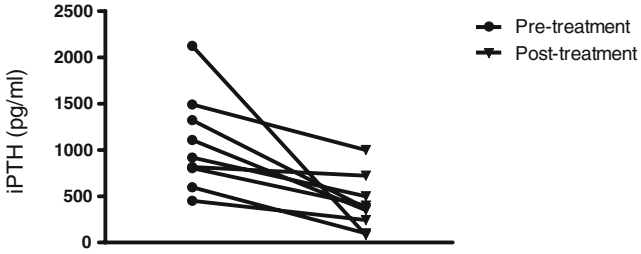

Fig. 1 Intact parathyroid hormone (iPTH) levels prior to and after initiation of cinacalcet therapy in individual patients. Compared with immediate (1-month) pretreatment iPTH levels, serum iPTH levels declined in all patients 3 months after therapy was started

Doses of phosphate binders One month prior to and 3 months after starting cinacalcet, all patients were receiving phosphate binders. The overall dose and dose per kilogram per day were virtually unchanged (p=0.3, 0.3, respectively). The doses and forms of phosphate binders are displayed in Table 3.

Dialysis adequacy before and after cinacalcet therapy Kt/V remained constant in HD and PD patients. For HD patients, spKt/V was1.48±0.11 1 month pretreatment vs. 1.54±0.03 3 months posttreatment pg/ml, p=0.6. One month pretreatment, spKt/V did not correlate with 3-month pretreatment iPTH levels in HD patients (r=0.2, p=0.6). For PD patients, Kt/V was 2.42±0.10 1 month pretreatment vs. 2.64±0.19 3 months posttreatment pg/ml, p=0.5. Due to the small number of patients, we could not assess the correlation between pretreatment Kt/V and pretreatment iPTH levels in PD patients.

Monitoring of potential adverse effects to cinacalcet therapy A variety of potential adverse effects of cinacalcet have been described, and these were reviewed [37]. Three HD patients reported mild nausea after starting cinacalcet, but this did not result in the need to discontinue the drug. Other potential adverse symptoms due to cinacalcet including myalgias, dizziness, or diarrhea were not reported. Since a decrease in hemoglobin level and elevation in BP may occur while receiving cinacalcet, we monitored for changes after initiating cinacalcet therapy. As shown in Table 1, BP and hemoglobin levels were unaffected by cinacalcet treatment.

Table 2 Assessment of laboratory and clinical values 1 month prior to (baseline) and 3 months after treatment with cinacalcet

Parameter	Baseline	Cinacalcet	*P* value
Serum calcium (mg/dl)	9.4±0.2	9.5±0.4	0.9
Serum phosphorous (mg/dl)	5.1±0.4	5.2±0.6	0.9
Calcium-phosphorous product	48.2±3.7	49.5±5.9	0.8
Hemoglobin (g/dl)	12.1±0.5	12.1±0.4	1.0
Systolic blood pressure (mmHg)	119.0±7.2	116.6±5.4	0.8
Diastolic blood pressure (mmHg)	62.0±4.7	62.9±4.1	0.9

There were no changes from baseline in any of the laboratory or clinical values while the patients were receiving cinacalcet

Table 3 Doses and forms of phosphate binders

Patient	One month precinacalcet	Three months cinacalcet
1	Calcium carbonate 3,750 mg/day	Same
2	Calcium carbonate 8,000 mg/day	Same
3	Lanthanum carbonate 2,000 mg/day	Same
4	Calcium acetate 5,336 mg/day	Same
5	Calcium carbonate 8,250 mg/day	Same
6	Calcium acetate 2,001 mg/day	Same
7	Calcium carbonate 300 mg/day	Same
8	Lanthanum carbonate 1,625 mg/day	Lanthanum carbonate 1,250 mg/day
9	Calcium acetate 6,670 mg/day	Same

The doses and forms of phosphate binders used 1 month prior to and after 3 months of cinacalcet treatment were almost identical at the two time points

One patient developed a generalized tonic-clonic seizure after receiving one dose of cinacalcet. The results of all investigations were normal, including serum calcium (9.0–10.3 mg/dl) and ionized calcium levels. The patient had one slightly low (132 mmol/L) serum sodium level, but the serum sodium levels were otherwise normal; serum potassium (4.5–5.5 mmol/L) and glucose (92–100 mg/dl) levels were also normal. There were no changes in white or red blood cell counts compared with baseline. Computerized tomography of the head was also normal. Cinacalcet was immediately discontinued, and the patient had no further seizures.

Dose of calcitriol or paracalcitol while on cinacalcet The dose of paracalcitol (6.6±2.3 1 month pretreatment vs. 4.3±1.7 μg/dialysis treatment 3 months posttreatment pg/ml, p=0.1) in HD patients trended downward with cinacalcet treatment. The dose of oral calcitriol for the three patients maintained on PD while receiving cinacalcet trended downward, but the change was insignificant (0.8±0.2 1 month pretreatment vs. 0.5±0.0 μg/day 3 months posttreatment pg/ml, p=0.2).

Discussion

HTBD is a common type of renal osteodystrophy in pediatric HD patients [1–6] and by far the most common observed in our patient cohort. Despite exhaustive efforts to provide information and guidance regarding dietary control with reduction of phosphorous intake and after maximizing therapy with phosphate binders and vitamin D, we discovered that serum intact parathyroid hormone (iPTH) remained unacceptably elevated. We deemed that the only option available for our patients aside from subtotal parathyroidectomy was the use of a calcimimetic.

We had some reservations about the use of calcimimetics in pediatric patients due to their potential adverse effect on bone growth because of localization of calcimimetics in chondrocytes [30] and the fact that activation of the calcium-sensing receptor in the growth plate induces longitudinal bone growth [31]. We concluded that a trial of short-term therapy with cinacalcet in patients with recalcitrant secondary hyperparathyroidism/HTBD at risk for severe osteitis fibrosa was warranted and that the short-term benefits of therapy outweighed the risks.

Our preliminary results are certainly encouraging. Among all patients, we observed a mean 61% reduction in iPTH levels and a marked decrease in ALK. The decline in iPTH was far more pronounced in PD compared with HD patients, although admittedly, the numbers were too small to make any definite conclusions on this comparison. Despite the overall success, several patients continued to demonstrate elevated iPTH levels regardless of increases in cinacalcet dosing in some. There are several plausible causes for this. First, medication compliance may have been incomplete in some of the nonresponsive patients. Indeed, three patients originally prescribed cinacalcet admitted noncompliance and were eventually taken off the drug. Another potential contributing factor in some patients may have been due to long-standing secondary hyperparathyroidism.

The decreases in iPTH occurred in the absence of changes in serum calcium and phosphorous levels, as seen in several studies of adult dialysis patients treated with calcimimetic therapy (e.g. Quarles et al. [20]) but in contrast to other studies (as summarized by Strippoli et al. [26]) in which serum calcium and phosphorous levels declined with calcimimetic therapy. Moreover, we observed no change in the Ca-Pi product, similar to Moe et al. [27] but in contrast to several adult studies (also summarized by Strippoli et al. [26]). Finally, the doses of calcitriol or paracalcitol were able to be reduced or kept stable while the patients were receiving cinacalcet.

The most common adverse effect we observed was transient nausea that occurred immediately after the drug was introduced. This did not preclude continuation of the drug in any patient. Other reported adverse effects including hypertension and decrease in hemoglobin level did not occur in our patients. One patient did develop a seizure after receiving one dose of cinacalcet, although we cannot affirm that this was related to the drug.

There are several limitations to our study. Since the observation period was short, we did not assess for changes in bone histology or growth. This is a significant limitation, since inhibition of bone growth is a prominent concern among pediatric nephrologists caring for dialysis patients. Second, the number of patients was small, and we cannot extrapolate what our results may signify for a larger group of patients. Third, at the time of the study, we measured iPTH exclusively and did not assess the 1–84 and 7–84 PTH fragments (e.g. biointact PTH). Information on fragment concentration may be helpful to determine the effect of calcimimetics on the stimulating (1–84) and inhibiting (7–84) forms of PTH, although one recent study showed that calcimimetics do not differentially alter the 1–84/7–84 ratio [27].

In summary, our data provides encouraging results for the use of calcimimetics in adolescent dialysis patients. Although we observed reduction in iPTH in our patients, the time period was too brief to assess the effect of cinacalcet on bone growth. Our future studies are designed to assess the affects of calcimimetics on bone histology and growth in pediatric ESRD patients.

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