2014

Cinacalcet Administration by Gastrostomy Tube in a Child Receiving Peritoneal Dialysis

Kristen R. Nichols
Butler University, knichols@butler.edu

Chad A. Knoderer
Butler University, cknodere@butler.edu

Bethanne Johnston

Amy C. Wilson

JPPT

Case Report

Cinacalcet Administration by Gastrostomy Tube in a Child Receiving Peritoneal Dialysis

Kristen R. Nichols, PharmD,[1,2] Chad A. Knoderer, PharmD,[1] Bethanne Johnston, MSN,[3] and Amy C. Wilson, MD[3]

[1]Department of Pharmacy Practice, College of Pharmacy and Health Sciences, Butler University, Indianapolis, Indiana, [2]Department of Pharmacy, Riley Hospital for Children, Indiana University Health, Indianapolis, Indiana, [3]Department of Pediatrics, Section of Pediatric Nephrology, Indiana University School of Medicine, Indianapolis, Indiana

A 2-year-old male with chronic kidney disease with secondary hyperparathyroidism developed hypercalcemia while receiving calcitriol, without achieving a serum parathyroid hormone concentration within the goal range. Cinacalcet 15 mg (1.2 mg/kg), crushed and administered via gastrostomy tube, was added to the patient's therapy. This therapy was effective in achieving targeted laboratory parameters in our patient despite instructions in the prescribing information that cinacalcet should always be taken whole.

INDEX TERMS: chronic kidney disease, cinacalcet, hypercalcemia, secondary hyperparathyroidism

J Pediatr Pharmacol Ther 2014;19(3):202–205

INTRODUCTION

Abnormal bone and mineral metabolism and secondary hyperparathyroidism are well-described consequences of chronic kidney disease (CKD), with progression to renal osteodystrophy, growth impairment, and vascular calcification if left untreated. Overcorrection is associated with adynamic bone disease.[1] In addition to dietary phosphate binders, active vitamin D sterols are recommended to prevent bone disorders. Calcitriol (Rocaltrol, Roche Pharmaceuticals, Nutley, NJ) is the most commonly used form of vitamin D replacement in children who require renal replacement therapy, though its use can be limited by hypercalcemia.[2] Alternatives associated with lower risk for hypercalcemia are available for adults, including doxercalciferol (Hectorol, Genzyme Corporation, Cambridge, MA), paricalcitol (Zemplar, Abbvie Inc, North Chicago, IL), and cinacalcet (Sensipar, Amgen, Thousand Oaks, CA), but optimal dosage regimens in children receiving peritoneal dialysis (PD) are lacking.[3] We aim to describe our use of an alternate administration method for cinacalcet in a child with CKD, hypercalcemia, and secondary hyperparathyroidism.

CASE REPORT

A 2-year-old, 10.3-kg, Caucasian male with a history of CKD presented to the pediatric clinic for evaluation for peritoneal dialysis after an emergency department admission for worsening vomiting and dehydration and was found to have stage 5 CKD. His past medical history was significant for bilateral renal dysplasia, vesicoureteral reflux, posterior urethral valves, chronic vomiting with failure to thrive, and CKD with anemia and secondary hyperparathyroidism.

At that time, he was receiving calcitriol 0.2 mcg (0.02 mcg/kg) per gastrostomy tube (GT) twice daily and cinacalcet 6 mg (0.6 mg/kg) by GT. The 30-mg cinacalcet tablet (Sensipar) was crushed and mixed with 10 mL of water. A 5-mL portion of the solution was then administered for treatment of secondary hyperparathyroidism. The cinacalcet product was prepared fresh each time it was administered and the remainder of the water/cinacalcet mixture was discarded. He was also receiving sodium and potassium phosphorous (2-mmoL phosphorus = ¼ packet 250 mg twice daily), but adherence to this regimen was uncertain.

Laboratory results on this regimen were as

Table. Patient Information and Laboratory Parameters

	Presentation	+ 3 Months	+ 5 Months	+ 6 Months
Patient information				
Height, cm	76.5	80	-	84.5
Weight, kg	10.3	12.4	12.7	13.9
Medication	Calcitriol 0.2 mcg BID Cinacalcet 6 mg (adherence uncertain)	Calcitriol 0.2 mcg	Calcitriol 0.15 mcg	Calcitriol 0.15 mcg Cinacalcet 15 mg
Laboratory value (institution normal for age)				
PTH, pg/mL (10-65 pg/mL)*	596	368	513	246
Phosphorus, mg/dL (3.5-6.5 mg/dL)	3.3	6.1	3.5	5.2
Calcium, mg/dL (8.5-10.5 mg/dL)	11	11	10	9.6
Albumin, g/dL (3.1-4.7 g/dL)	3.9	3.3	3.2	3.1
Serum creatine, mg/dL (0.2-0.7 mg/dL)	3.61	5.11	4.49	3.57

BID, twice daily; ESRD, end-stage renal disease; PTH, parathyroid hormone
** ESRD goal, 200- 300 pg/mL*

follows (see Table): serum calcium 11 mg/dL (normal, 8.5-10.5 mg/dL), phosphorus 3.3 mg/dL (normal, 3.5-6.5 mg/dL), and parathyroid hormone (PTH) 596 pg/mL (goal, 200-300 pg/mL). In an attempt to improve his management and simplify his medication regimen, cinacalcet was discontinued and calcitriol (Rocaltrol) was changed to a dose of 0.2 mcg (0.02 mcg/kg once daily. In addition, his enteral formula was changed from Similac PM 60/40 to half Similac Advance (Abbott, Abbott Park, IL) with half Similac PM 60/40 (Abbott) to increase the amount of phosphorous supplementation. At that time, both his weight and length were lower than the third percentile for his age.

At a 3-month follow-up visit, his serum calcium concentration remained elevated at 11 mg/dL. At this time his phosphorus concentration was within the normal range at 6.1 mg/dL but his PTH concentration remained elevated at 368 pg/mL. Calcitriol was decreased to 0.15 mcg (0.012 mcg/kg) per GT once daily. Two months following the calcitriol dose reduction, the calcium concentration had normalized (10 mg/dL); unfortunately, the PTH concentration remained elevated (513 pg/mL). Phosphorous concentration remained in the low-normal range throughout this period (3.5 mg/dL). The patient was subsequently given 15 mg (approximately 1.2 mg/kg) of cinacalcet extemporaneously as prepared above.

One month following the addition of cinacalcet the PTH concentration was within the goal range of 200 to 300 pg/mL, at 246 pg/mL, as were his calcium (9.6 mg/dL) and phosphorus (5.2 mg/dL) concentrations. He subsequently required an increase in the dose of calcitriol to 0.2 mcg (0.015 mcg/kg) owing to increasing PTH concentrations. By this time the patient had demonstrated improvement in his growth, with a weight of 13.2 kg.

DISCUSSION

Active vitamin D therapy, namely with calcitriol, is recommended by the KDOQI (Kidney Disease Outcomes Quality Initiative) Clinical Practice Guidelines for Bone Metabolism and Disease in Children with Chronic Kidney Disease for children with PTH serum concentrations that are above the target range for CKD stage.[1] Our patient likely experienced calcitriol-associated hypercalcemia due to the increased gastrointestinal tract absorption of calcium and phosphorus.[2] The KDOQI guidelines recommend that for serum calcium concentrations greater than 10.2 mg/dL, the calcitriol should be held until the serum calcium concentration is less than 9.8 mg/dL and restarted at half of the previous dose. Unfortunately, this may not result in a serum PTH concentration within the goal range.[1]

For adults with CKD and secondary hyperparathyroidism, alternative options are available for active vitamin D therapy and PTH suppression. The vitamin D analogs paracalcitol and doxercalciferol have a lesser effect on the absorption of calcium in the gastrointestinal tract but still

reduce serum PTH concentrations.[3–5] These are not available in formulations for patients who are unable to swallow a solid dosage form (as with our patient). Both alternatives are available as soft gelatin capsules, and though the contents can be evacuated with a syringe for subsequent administration, this strategy may be difficult and inexact.[6,7] This technique does not allow lesser amounts than available dosage forms to be easily administered. While both paracalcitol and doxercalciferol are available as intravenous formulations, parenteral administration is not practical for PD patients, who are typically seen in clinic only 1 to 2 times per month.[6,7] No information was found to support the use of the intravenous formulations enterally, though this could be an alternative option to investigate.

Though vitamin D therapy (calcitriol) has been shown to be effective in suppressing hyperthyroidism in end-state renal disease (ESRD) patients, resulting hypercalcemia is undesirable owing to potential for adverse effects and cardiovascular disease.[8] Cinacalcet is a calcimimetic that increases the sensitivity of the calcium-sensing receptor on the parathyroid gland, leading to a decreased PTH concentration without a concomitant increase in serum calcium.[3] It also increases the expression of vitamin D receptors on the thyroid gland, potentially allowing for a lower effective calcitriol dose.[8] Cinacalcet has been studied in a small number of children and adolescents with ESRD and has been shown to result in decreased PTH without elevation in calcium or phosphorus.[9–11] These studies have added cinacalcet to calcitriol therapy. Therefore, cinacalcet may be an additive option in children and adolescents with ESRD when the dose of calcitriol is limited by hypercalcemia (serum calcium >10.2 mg/dL) and the PTH concentration is above the goal range. Combination therapy may also result in a decrease in phosphate binder requirement.[10] The dose used in our patient was chosen from a review of the experience as published by Platt and colleagues,[9] where a wide initial dosing range of 0.4 to 1.4 mg/kg was used, and for simplicity of preparation by the patient's caregiver.

Calcium should be closely monitored during therapy, and consideration for cinacalcet discontinuation or dose reduction should be given if the serum calcium concentration decreases to less than 8.4 mg/dL. Though used for only a short time period in these studies, cinacalcet has been generally well tolerated until the report of the recent death of a 14-year-old adolescent during a cinacalcet clinical trial.[12] The US Food and Drug Administration stopped all pediatric clinical trials of cinacalcet and issued a drug safety communication until the cause of the death can be determined; causality has not been assigned.[12]

Liquid dosage forms of cinacalcet are not available. To administer 15 mg (approximately 1.2 mg/kg), we instructed the parents to crush a 30-mg tablet, mix it with 10 mL of water, and administer 5 mL. The tablet was not to be halved before crushing, as it is not scored. Prescribing information indicates that the available tablet dosage form should be swallowed whole and not divided, though there is no evidence to demonstrate that crushing the tablet would result in drug inactivation. Administration of weight-based cinacalcet to a group of 7 pediatric patients was described by Muscheites and colleagues,[10] whereby 30-mg tablets were ground into powder and re-pressed into tablets containing 2.5, 5, and 7.5 mg. The resultant diminished serum PTH, phosphorus, and calcium concentrations were reassuring and indicated that cinacalcet could be safely crushed for administration in our patient. An additional study that evaluated single-dose cinacalcet in pediatric patients used a 15-mg dose, achieved by splitting a 30-mg tablet.[13] The split tablet was weighed to confirm the appropriate dose and administered with 90 ml of water; unfortunately, it is not clear in this study whether the split tablet was subsequently crushed or was swallowed whole.

We believe that the GT administration of cinacalcet after crushing has no deleterious results on the medication's effectiveness. This is supported by the normalization of our patient's laboratory parameters (serum PTH and calcium within goal range). The normalization was temporally associated with cinacalcet administration via GT in the absence of other interventions. More data are needed to determine the role of cinacalcet therapy in children with CKD and if GT administration results in outcomes similar to administration of the solid tablet form. Our experience with this case supports the use of cinacalcet when crushed for GT administration.

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the

manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Abbreviations CKD, chronic kidney disease; ESRD, end-state renal disease; GT, gastrostomy tube; KDOQI, Kidney Disease Outcomes Quality Initiative; PD, peritoneal dialysis; PTH, parathyroid hormone

Correspondence Kristen R. Nichols, PharmD, Riley Hospital for Children, 705 Riley Hospital Dr, Room W6111, Indianapolis, IN 46202, email: knichol4@iuhealth.org or knichols@butler.edu

REFERENCES

1. National Kidney Foundation. KDOQI clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. *Am J Kidney Dis.* 2005;46:S1-S121.
2. Salusky IB. Are new vitamin D analogues in renal bone disease superior to calcitriol? *Pediatr Nephrol*. 2005;20(3):393-398.
3. Cannata-Andia JB, Rodriguez-Garcia M, Roman-Garcia P, et al. New therapies: calcimimetics, phosphate binders and vitamin D receptor activators. *Pediatr Nephrol*. 2010;25(4):609-616.
4. Greenbaum LA, Benador N, Goldstein SL, et al. Intravenous paricalcitol for treatment of secondary hyperparathyroidism in children on hemodialysis. *Am J Kidney Dis.* 2007;49(6):814-823.
5. Greenbaum LA, Grenda R, Qiu P, et al. Intravenous calcitriol for treatment of hyperparathyroidism in children on hemodialysis. *Pediatr Nephrol.* 2005;20(5):622-630.
6. Zemplar (paricalcitol) [package insert]. Lake Forest, IL: Hospira Inc; April 2011.
7. Hectorol (doxercalciferol) [package insert]. Cambridge, MA: Genzyme Corporation; February 2011.
8. Lee YT, Ng HY, Kuo CC, et al. Comparison between calcitriol and calcitriol plus low-dose cinacalcet for the treatment of moderate to severe secondary hyperparathyroidism in chronic dialysis patients. *Nutrients*. 2013;5(4):1336-1348.
9. Platt C, Inward C, McGraw M, et al. Middle-term use of cinacalcet in paediatric dialysis patients. *Pediatr Nephrol.* 2010;25(1):143-148.
10. Muscheites J, Wigger M, Drueckler E, et al. Cinacalcet for secondary hyperparathyroidism in children with end-stage renal disease. *Pediatr Nephrol*. 2008;23(10):1823-1829.
11. Silverstein DM, Kher KK, Moudgil A, et al. Cinacalcet is efficacious in pediatric dialysis patients. *Pediatr Nephrol.* 2008;23(10):1817-1822.
12. Sensipar (cinacalcet hydrochloride): drug safety communication—FDA suspends pediatric clinical trials after report of death. US Food and Drug Administration Web site. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm341255.htm. February 2011. Accessed August 12, 2013.
13. Padhi D, Langman CB, Fathallah S, et al. An open-label study to evaluate a single-dose of cinacalcet in pediatric dialysis subjects. *Pediatr Nephrol*. 2012;27(10):1953-1959.