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REVIEW

Cinacalcet for Infants and Young Children on Maintenance Dialysis: Determining the Right Time, the Right Dose and the Right Patients

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Chronic Kidney Disease - Mineral Bone Disorder (CKD-MBD) is a recognized complication of kidney failure, which can lead to short stature, bone deformity, slipped capital femoral epiphysis, and bone fracture in children. Despite the use of conventional therapies, a subgroup of patients receiving dialysis continues to experience secondary or even tertiary hyperparathyroidism. Cinacalcet, a calcimimetic agent, has been shown to be a promising therapeutic option to control hyperparathyroidism with reasonable safety profiles in adults and older children. Nevertheless, there is a paucity of data and guidance pertaining to its use among the younger children on dialysis, who are often the most challenging patients to manage with severe CKD-MBD. In this review, we summarize the available evidence on cinacalcet use among pediatric patients, especially infants and young children aged < 3 years. We also discuss the unique considerations in management and attempt to provide a pragmatic approach regarding the use of cinacalcet in this specific patient population.

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Kidney failure is a rare childhood condition associated with mortality and significant morbidities such as infection and a variety of noninfectious complications.[1-6] CKD-MBD is a recognized complication of kidney failure, characterized by abnormalities in minerals, parathyroid hormone (PTH), and vitamin D metabolism; with resultant disturbances in bone turnover, mineralization, bone volume, and cardiovascular abnormalities.[7,8] Recognition of and attention to this condition is highly relevant in growing children, because it can lead to short stature, bone deformity, slipped capital femoral epiphysis, and bone fracture. Infants and young children are particularly vulnerable to this complication, owing to their rapid growing stage which requires optimal mineral balance for bone ossification.[9-11]

Conventional treatment for CKD-MBD includes nutritional management such as adequate calcium intake and phosphate restriction, inactive and active vitamin D supplementation, as well as calcium-based and/or non–calcium-containing phosphate binder therapy. Despite the use of these therapies, a subgroup of patients continues to experience secondary or even tertiary hyperparathyroidism. Cinacalcet, a calcimimetic agent, has been shown to be a promising therapeutic option to control hyperparathyroidism with reasonable safety profiles in adults and older children.[12] It modulates and increases the sensitivity of the calcium-sensing receptor in the parathyroid gland, thus modifying PTH release and restoring desirable calcium and phosphate metabolism.[13] In 2017, the European Medicine Agency approved the use of cinacalcet in children aged ≥ 3 years with kidney failure requiring dialysis when CKD-MBD is inadequately controlled, despite standard therapy. Nevertheless, there is a paucity of data pertaining to the use of cinacalcet among the youngest children on dialysis, which is often the most challenging patient population

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with severe CKD-MBD to manage.[1] In this review, we summarize the available evidence on cinacalcet use among pediatric patients, especially infants and young children aged < 3 years. We also discuss the unique considerations in the management and attempt to provide a pragmatic approach regarding the use of cinacalcet in this specific patient population.

Current Evidence of Cinacalcet Use in Pediatric Patients Aged > 3 Years

The use of cinacalcet in adults on maintenance dialysis has been well-studied in the past decade.[14-16] The landmark EVOLVE trial, demonstrated that cinacalcet reduced the risk of reaching the primary composite outcome (cardiovascular events and death) by 12%, after adjusting for baseline characteristics.[17] Furthermore, the need for parathyroidectomy was reduced by 56%.[17] Consequently, the Kidney Disease: Improving Global Outcomes guidelines on CKD-MBD recognized calcimimetics as one of the recommended PTH-lowering therapies among adults receiving chronic dialysis.[18]

In contrast, data pertaining to the use of cinacalcet among pediatric patients remains limited.[19-30] In Table 1, we show the published studies on cinacalcet use among pediatric patients aged > 3 years with CKD. Among these studies, there was only 1 multicenter, randomized controlled trial, in which cinacalcet or placebo were assigned to patients who had PTH > 300 pg/ml (mean PTH = 776 pg/ml), despite receiving standard therapy.[26] The primary endpoint, which consisted of a ≥30% reduction in PTH level compared with baseline at randomization, was achieved in 12 of 22 and 4 of 21 patients in the intervention and placebo groups (55% vs. 19%; $P = 0.0017$), respectively. The most common adverse event was gastrointestinal symptoms, including vomiting and nausea. More patients in the cinacalcet group (32% vs. 14%) developed hypocalcemia (< 8.4 mg/dl). However, it was unclear whether these hypocalcemia episodes were symptomatic or not. Of note, 1 fatality was observed in a female adolescent subject with a prolonged QT interval before drug initiation, which led to early termination of the study. The patient succumbed after a fatal cardiopulmonary arrest. Although the cause of cardiopulmonary arrest was deemed to be multifactorial, hypocalcemia caused by cinacalcet use could not be excluded.

The other retrospective and prospective studies that have been conducted have reported good drug efficacy in reducing PTH and reasonable side effect profiles in older children (Table 1).[19-25,30] The degree of reduction in PTH ranged from 10.8% to 86%. The considerable variations in treatment efficacy were due to heterogeneity in study design, duration of observation, patient population, and drug dosing. Hypocalcemia was not uncommon and occurred in up to 17% of patients aged > 3 years and receiving cinacalcet who were evaluated in the available studies ($n = 18/102$) (Table 1).[19-26,30] Importantly, all reported hypocalcemia episodes occurring in these older children were asymptomatic.[19-25,30] There is a European postauthorization study (EUPAS24954), which is a multicenter noninterventional observational registry sponsored by pharmaceuticals of pediatric patients on dialysis (aged 3–18 years) receiving cinacalcet for secondary hyperparathyroidism. The study has been completed and the results of this study will provide further insight pertaining to the use and safety of cinacalcet among older children and adolescents.

In 2019, the CKD-MBD workgroup of the European Society for Pediatric Nephrology subsequently issued a position statement on the use of cinacalcet in pediatric patients on dialysis.[31] In this statement, it is recommended to initiate cinacalcet in children aged > 3 years and receiving maintenance dialysis who exhibit persistent and severe hyperparathyroidism after the optimization of conventional treatments, including nutritional management and active vitamin D supplementation. Calcium levels should be closely monitored before and after drug initiation. PTH should be maintained within the desired range, with the lowest effective dose of cinacalcet prescribed. The recommended starting dose of cinacalcet is 0.2 mg/kg/d, whereas the maximum daily dose is 2.5 mg/kg/d (< 180 mg in absolute dose). The cinacalcet dose can be increased in increments of 0.2 mg/kg/d.

Current Evidence Pertaining to Cinacalcet Use Among Infants and Children Aged < 3 Years

Management of secondary and tertiary hyperparathyroidism among infants and young children receiving maintenance dialysis is challenging because these children are experiencing a period of rapid growth and require a positive mineral balance for proper skeletal development. Although cinacalcet has not yet been licensed for use in children aged < 3 years, the medication is prescribed occasionally in difficult-to-treat patients as off-label use as has been reported in 3 studies (Table 2).[27-29] Although these reports are limited by their retrospective study design, small patient number, and heterogeneous prescription practice, the data presented provide important insights regarding the use of this therapeutic option among the youngest children with CKD. To that end, the European Society for Pediatric Nephrology CKD-MBD and dialysis working groups recently (2023) published clinical practice points specific to infants with CKD-MBD.[32] Specifically, cinacalcet may be prescribed with extreme caution in infants, despite optimized conventional therapies,

Table 1. Summary table of cinacalcet use in children aged > 3 years

Study	Study design	Study population	Treatment duration	Cinacalcet dose (initial and titration)	Cinacalcet dose (maximum)	Cinacalcet dose (final)	Significant findings	Hypocalcemia	Other side effects
Warady *et al.* (2019)[26]	Randomized, double-blinded, placebo-controlled trial	Patients aged 6 to <18 yrs with CKD on dialysis ($N = 43$) with iPTH > 300 pg/ml were randomized to receive cinacalcet ($n = 22$) vs. placebo ($n = 21$) Dialysis modality: cinacalcet group (HD [$n = 15$, 68.2%], PD [$n = 7$, 31.8%]); placebo group (HD [$n = 12$, 57.1%], PD [$n = 9$, 42.9%])	Mean duration 110 d in double-blind phase and 119 d in open-label phase for cinacalcet	Initial: mean 0.18 mg/kg/d Dose titration: every 4 wks	1.54 mg/kg/d (or 50.4 mg/d)	0.77 mg/kg/d (or 34.6 mg/d)	iPTH reduction > 30% from baseline Mean PTH was 757.1 pg/ml (cinacalcet group) vs. 795.8 pg/ml (placebo group) at baseline Cinacalcet: 12/22 (54.5%) Placebo: 4/21 (19%) (OR: 4.26, 95% CI: 0.99–18.3) Growth Growth velocity from baseline to wk 30 (95% CI) 3.3 cm/yr (cinacalcet) vs. 3.1 cm/yr (placebo) No significant differences in growth velocity from baseline to end-of-study (95% CI: −3.1 to 3.6)	Hypocalcemia Total Ca < 8.4 mg/dl: 32% (cinacalcet) vs. 14% (placebo) Total Ca < 8 mg/dl: 23% (cinacalcet) vs. 19% (placebo); Total Ca < 7.5 mg/dl 14% (cinacalcet) vs. 0% (placebo) Potential symptoms of hypocalcemia Muscle spasms: (14%, 5%), myalgia (14%, 5%), and tremor (14%, 0)	The study was terminated after 14 mo because of a case of fatality. Gastrointestinal Vomiting (cinacalcet: 32% vs. placebo 24%) Nausea (cinacalcet: 18% vs. placebo 14%) Others Hypertension (cinacalcet 14% vs. placebo 24%)
Sohn *et al.* (2018)[25]	Open-label, single dose study	Children aged 28 d to <6 yrs with CKD receiving dialysis ($N = 12$) 4/12 (33%) patients were aged < 3 yrs	Single dose, followed-up until 72 h postdose	A single dose of 0.25 mg/kg Cinacalcet orally or by nasogastric or gastric tube	-	-	Cinacalcet exposure Mean plasma cinacalcet Cmax and AUC values were 1.6- to 2.3-fold higher in subjects aged ≥ 3 to < 6 yrs compared with subjects aged < 3 yrs PTH reduction Median 10.8% and 29.6% PTH reduction from baseline were observed at and 8 h postdose, respectively and returned to baseline by 12 to 72 h Median % reductions in PTH were greater at 8 h postdose in subjects aged ≥ 3 yrs to < 6 yrs (−42.2%) than in subjects aged < 3 yrs (−5.2%)	Asymptomatic hypocalcemia (1/12, 8.3%)	5 treatment-emergent AEs were reported for 3/12 (25%) subjects: vomiting, catheter site hemorrhage, catheter expulsion, increased body temperature, and asymptomatic hypocalcemia

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Table 1. (Continued) Summary table of cinacalcet use in children aged > 3 years

Study	Study design	Study population	Treatment duration	Cinacalcet dose (initial and titration)	Cinacalcet dose (maximum)	Cinacalcet dose (final)	Significant findings	Hypocalcemia	Other side effects
Alharthi *et al.* (2015)[24]	Prospective observation cohort analysis	Children aged 9 mo to 14 yrs with CKD 4–5, with mean baseline iPTH >300 pg/ml despite maximum conventional treatment for at least 3 mo ($N = 28$) Dialysis modality: HD ($n = 6$); PD ($n = 16$); conservative ($n = 6$)	24 mo	Initial: 0.5 mg/kg/d Dose titration: every 2 wks	1.5 mg/kg/d	Some patients who achieved target iPTH were maintained on ≤0.5 mg/kg/d on daily, alternate or twice weekly therapy	iPTH reduction Mean iPTH decreased from 1932 ± 795 pg/ml to 354 ± 274 pg/ml end of study ($P < 0.001$) All patients showed at least 60% reduction (range 60%–97%) in iPTH over 24 mo 80% of patients achieved iPTH ≤ 300 pg/ml within 6 mo Growth Growth parameters did not deteriorate by cinacalcet management.	Hypocalcemia There was no significant difference in serum calcium (2.45 ± 0.07 vs. 2.451 ± 0.13, $P = 0.157$)	Hypophosphatemia There was no significant difference in serum phosphate (1.47 ± 0.16 vs 1.39 ± 0.29, $P = 0.207$) Others No other adverse events reported.
Dotis *et al.* (2013)[23]	Case report	Children aged 3.5–12.5 yrs on PD ($N = 4$)	1–12 mo	Initial: 0.25 mg/kg/d Dose titration: every 15 d by 0.15 mg/kg	0.4 mg/kg/d ($N = 2$); 0.8 mg/kg/d ($N = 4$)	0.4 mg/kg/d ($N = 2$); 0.8 mg/kg/d ($N = 4$)	PTH reduction Baseline PTH ranged from 930 to 1350 pg/ml PTH reduced by > 70% at 4 wks and > 60% at 3 mo or > 6 mo in 2/4 (50%) patients. Another 2/4 (50%) patients had suboptimal response to cinacalcet and underwent surgical parathyroidectomy after 6 or 12 mo	Asymptomatic hypocalcemia Not reported Change in serum Ca from baseline ranged from −1.1 to +1.4 mg/dl posttreatment.	Hypophosphatemia 1/4 (25%) patient had reduced serum P from 8 to 6.7 mg/dl (16% reduction)
Padhi *et al.* (2012)[30]	Open-label, single dose study	Pediatric patients on dialysis aged 6–17 yrs (mean age 11.33 ± 3.68 yrs) ($N = 12$) Did not mention individual number of patients under each dialysis modality	Single dose, followed-up until 72 h postdose	A single dose of 15 mg with blood measurement up to 72 h postdose	-	-	iPTH reduction Mean (SD) % change in iPTH over the first 12 h postdose was 57.94% (71.82%) with a nadir of −35.65% (55.82%) at 2 h. Calcium change Mean (SD) % change in serum Ca over the first 12 h postdose was −2.93% (5.70%) with a nadir of −4.34% (6.04%) at 8 h. Serum Ca returned to baseline by 48 h postdose	Hypocalcemia Serum Ca < 2.23 mmol/l (range: 2.0–2.22 mmol/l) was reported in 6/12 (50%) of patients	One case of QT prolongation reported at 72 h postdose

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Table 1. (Continued) Summary table of cinacalcet use in children aged > 3 years

Study	Study design	Study population	Treatment duration	Cinacalcet dose (initial and titration)	Cinacalcet dose (maximum)	Cinacalcet dose (final)	Significant findings	Hypocalcemia	Other side effects
Youssef (2012)[22]	Case report	Patients aged 11–13.5 yrs ($N = 2$) on HD	8 wks	Fixed dose of 30 mg/d	-	-	PTH reduction Case 1: PTH reduced from 901 to 666.3 (4 wks, reduced by 26%) and to 546 (8 wks, reduced by 39.4%) Case 2: PTH reduced from 1230 to 918.3 (4 wks, reduced by 25.3%) and to 733 (8 wks, reduced by 40.1%)	-	No adverse reactions reported
Platt *et al.* (2010)[21]	Retrospective review	Children aged 11 mo to 14 yrs with CKD on dialysis ($N = 6$) 3/6 (50%) were aged < 3 yrs Dialysis modality: HD ($n = 4$); PD ($n = 2$)	5 mo to 3 yrs	Initial: 0.4–1.4 mg/kg/d	Only dose range reported, final/maximum dose not specified	0.4–2.6 mg/kg/d	PTH reduction Mean PTH decreased from 102.9 pmol/l to 7.9 pmol/l at 1 mo ($P = 0.002$) 6/6 (100%) showed at least 86% PTH reduction over the treatment period	Asymptomatic hypocalcemia 2/6 (33.3%); Cinacalcet was discontinued in 1 case for a 5-mo period because of refractory hypocalcemia despite treatment	Hypophosphatemia 3/6 (50%), fall of serum P by 39%–61%, all cases were aged < 3 yrs at initiation Gastrointestinal No significant problems reported
Muscheites *et al.* (2008)[20]	Prospective clinical study	Children aged 1.1–19 yrs with CKD 5, with PTH > 500 pg/ml in previous 2 mo despite standard treatment with calcitriol and phosphate binders ($N = 7$) Dialysis modality: HD ($n = 3$); PD ($n = 3$); conservative ($n = 1$)	4 wks	Fixed dose of 0.25 mg/kg/d	-	-	PTH reduction After first dose: Median serum PTH values decreased rapidly after 4 h and 12 h by 43% (−7% to 83%) and 39% (−15% to 76%), respectively After 4 wks: Initial PTH 932 pg/ml (range: 511–1938) vs. final 199 pg/ml (range: 121–940) ($P < 0.05$), median decrease 74% (range: −59% to −89%) Calcium After first dose: Median decrease from 2.69 to 2.38 mmol/l (at 4 h postdose) ($P < 0.05$) and to 2.58 mmol/l (at 24 h postdose) ($P < 0.05$). Phosphate level Median decrease in phosphate was from 2.13 to 1.42 mmol/l by 0.71 mmol/l (−0.27 to 1.34 mmol/l) ($P = 0.091$)	Asymptomatic hypocalcemia Total Ca < 2.2 mmol/l: 2/7 (28.6%) Symptomatic hypocalcemia None	Gastrointestinal None

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Table 1. (Continued) Summary table of cinacalcet use in children aged > 3 years

Study	Study design	Study population	Treatment duration	Cinacalcet dose (initial and titration)	Cinacalcet dose (maximum)	Cinacalcet dose (final)	Significant findings	Hypocalcemia	Other side effects
Silverstein *et al.* (2008)[19]	Prospective clinical study	Children aged 14.5 ± 1.0 (range: 7.5–17.5) yrs on dialysis, with an average of iPTH 400 pg/ml for 3 consecutive mo ($N = 9$) Dialysis modality: HD ($n = 6$); PD ($n = 3$)	3 mo	Initial: 30 mg/d Dose titration: every month	120 mg/d	53.3 ± 13 mg/d (1.27 ± 0.3mg/kg/d)	iPTH reduction 51.5% of reduction in iPTH from 1070 ± 171.5 (baseline) to 417.6 ± 97.8 pg/ml after 3 mo ($P = 0.005$)	Hypocalcemia There was no significant difference in serum calcium (9.4 ± 0.2 vs. 9.5 ± 0.4, $P = 0.9$)	Hypophosphatemia There was no significant difference in serum P (5.1 ± 0.4 vs. 5.2 ± 0.6) ($P = 0.9$) Gastrointestinal Nausea: 3/9 (33.3%) patients Others There was 1 patient (of the 9 patients) who developed generalized tonic-clonic seizure after 1 dose of cinacalcet) with normal serum calcium and ionized calcium levels, leading to immediate treatment discontinuation.

AE, adverse event; AUC, area under the curve; Ca, calcium; CI, confidence interval; CKD, chronic kidney disease; HD, hemodialysis; IQR, interquartile range; iPTH, intact parathyroid hormone; OR, odds ratio; P, phosphate; PD, peritoneal dialysis; PTH, parathyroid hormone.
Combined prevalence of hypocalcemia: 18 in 102 patients (17%)

including active vitamin D. There are, however, no recommendations regarding the dosing regimen of cinacalcet in the clinical practice points because of a lack of evidence in the infant population upon which to base any recommendations.

In the 3 aforementioned studies, Bernardor *et al.*,[29] Morales *et al.*,[28] and Joseph *et al.*[27] describe median cinacalcet doses of 0.4 mg/kg/d, 0.7 mg/kg/d, and 0.55 mg/kg/d at drug initiation, respectively. However, the initial dosing in these 3 studies ranged from 0.1 up to 1.2 mg/kg/d.[27–29] The maximum cinacalcet dose prescribed in these studies were also highly variable, between 0.2 and 2.1 mg/kg/d.[27–29] This dose corresponds to the maximal tolerable dose, or the dose at which hyperparathyroidism was adequately controlled. Importantly, there was a steady decline of PTH that took place gradually over a period of 6 to 12 months.[29]

As noted above, hypocalcemia is a recognized, and potentially lethal complication of cinacalcet use. Bernardor *et al.*[29] reported that hypocalcemia episodes occurred in 27% of the infant subjects, which was greater than the rate of 17% among older children.[19–26,30] Of note, this prevalence could well be underreported, because the nadir of serum calcium typically occurs within 24 hours following cinacalcet administration and might not be captured by a random schedule of blood monitoring.[31] Indeed, Morales *et al.*[28] found that 6 of 10 patients (60%) had a serum calcium < 8.5 mg/dl (or 2.05 mmol/l), whereas Joseph *et al.*[27] reported that just 3 of 18 patients developed hypocalcemia, with the lowest calcium level being 7.7 mg/dl (or 1.92 mmol/l).[27,28] All but 1 of the hypocalcemia episodes described in the 3 studies were asymptomatic, and were adequately managed with calcium supplementation. Bernardor *et al.*[29] did identify the cinacalcet dose as the only significant risk factor for developing hypocalcemia, and patients who experienced a hypocalcemia episode received a significantly higher dose of cinacalcet (1.5 vs. 0.8 mg/kg/d; $P = 0.03$). The only subject who developed a hypocalcemic seizure is illustrative.[29] This was a child with congenital nephrotic syndrome who was hypocalcemic (2.09 mmol/l) and exhibited severe hyperparathyroidism (19.5× UNL) at baseline. The initial cinacalcet dose was high, 1.4 mg/kg/d, and poor adherence to calcium supplementation was documented. The seizure occurred 2.5 months after drug initiation. These findings highlight the importance of optimizing serum calcium and vitamin D levels before cinacalcet treatment initiation and possibly maintaining the serum calcium levels of cinacalcet-treated patients in the high to high-normal range.

Bernardor *et al.*[29] also described largely stable growth with the use of cinacalcet.[29] This observation was partly confounded by the use of growth hormone (GH) in 7 of 26

Table 2. Summary table of cinacalcet use in infants and children aged < 3 years

Study	Study design	Study population	Treatment duration	Cinacalcet dose (Initial and titration)	Cinacalcet dose (Max)	Cinacalcet dose (Final)	Significant findings	Hypocalcemia	Other side effects
Bernardor *et al.* (2024)[29]	Retrospective, multicenter analysis	Children aged < 3 yrs ($N = 26$) with CKD and on dialysis Dialysis modality: HD ($n = 1$); PD ($n = 25$)	Median 1.2 yrs (IQR: 0.7–2)	Initial: 0.4 mg/kg/d (IQR: 0.2–0.8) Dose titration: Frequency not mentioned	Median: 1.1 mg/kg/d (IQR: 0.6–1.2)	Median: 1 mg/kg/d (IQR: 0.4–1.2)	PTH reduction Median PTH was 792 (IQR: 411–1397) pg/ml at baseline PTH reduced from 11.6 times of ULN to 4.3 (IQR 2.2–7.8), 2.0 (IQR 1.0–5.3) and 1.6 (IQR 0.5–3.4) times ULN after 6 mo, 12 mo, and last follow-up, respectively ($P = 0.017$, 0.003, and < 0.0001, log-transformed PTH). Growth Body length SDS was stable over treatment −1.7 (baseline) vs. −1.2 (mo 12) vs. −1.5 (last follow-up)	Asymptomatic hypocalcemia 7/26 (27%) patients developed 9 episodes (Ca < 2.1 mmol/l) after median 8 mo (IQR: 2–14) at median dose 1.5 mg/kg/d (IQR: 0.9–3.2) Symptomatic hypocalcemia 1/26 (3.8%) patient had symptomatic hypocalcemia because of nonadherence to calcium supplements	Hypophosphatemia There was no significant change in serum P (median: 1.47) (IQR: 1.16–1.71) at baseline vs. 1.34 (IQR: 1.13–1.74) at mo 12 77% of children had hypophosphatemia at cinacalcet initiation and remained stable for 1 yr follow-up Gastrointestinal No additional GI symptoms reported 7/26 (26.9%) patients developed 10 hypocalcemia episodes (9 were asymptomatic) after 8 mo at dose 1.5mg/kg/d. Others Precocious puberty occurred in 3/26 (11.5%) patients
Joseph *et al.* (2019)[27]	Retrospective chart review	Patients aged < 5 yrs on chronic HD or PD for at least 3 mo ($N = 18$) Mean age: 2.3 yrs (range: 8 mo to 4.5 yrs)	6 mo	Initial: Mean 6.2 ± 2.8 mg (0.55 mg/kg/d) Dose titration: Frequency not mentioned Maximum: Not specified Final: Mean 8.6 ± 5.3 mg (0.75 mg/kg/d)			PTH reduction Decreased from 929 pg/ml (IQR: 572–1056) to 427 pg/ml (IQR: 256−778) within 1 mo ($P = 0.009$) and to 385 pg/ml (IQR: 140−710) at 6 mo ($P = 0.1$) Growth Significant improvement in growth were observed in the 9/18 (50%) patients who received GH at cinacalcet initiation (median height z-score, −2.32 at baseline vs. −1.83 at 6 mo, $P = 0.04$)	Asymptomatic hypocalcemia 3/18 (16.7%) patients developed asymptomatic hypocalcemia (< 9.4 mg/dl) with lowest serum Ca 7.7 mg/dl (1.89 mmol/l) There was no significant change in serum Ca at 1 mo and 6 mo after starting cinacalcet therapy ($P = 0.13$ and $P = 0.14$, respectively). Symptomatic hypocalcemia None	Hypophosphatemia Decreased from 5.6 (IQR: 4.8–6.4) to 4.8 (IQR: 4.5–5.9) at 1 mo ($P < 0.05$) and to 4.6 (IQR: 4–5.6) at 6 mo ($P < 0.05$) Gastrointestinal Not reported

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Table 2. (Continued) Summary table of cinacalcet use in infants and children aged < 3 years

Study	Study design	Study population	Treatment duration	Cinacalcet dose (Initial and titration)	Cinacalcet dose (Max)	Cinacalcet dose (Final)	Significant findings	Hypocalcemia	Other side effects
Arenas Morales *et al.* (2018)[28]	Retrospective chart review	Children with CKD 5, with iPTH > 500 pg/ml and refractory to standard therapy with phosphate binders and active vitamin D analogs at high doses for > 30 d ($N = 10$, 11 courses of therapy) Median age at cinacalcet initiation 18 mo (IQR: 6–36) ($N = 10$); 8/10 (80%) patients aged < 3 yrs Dialysis modality HD ($n = 3$); PD ($n = 3$); conservative ($n = 5$)	Mean duration 11 mo (range 8–46)	Initial: 0.7 ± 0.2 mg/kg/d (range: 0.4–1.1) Dose titration: Increased by 50% every 2–4 wks Effective dose: Median 2.8 mg/kg/d (IQR: 2.0–3.1) Final: Not specified			iPTH reduction Median iPTH was 943 pg/ml (IQR: 741–1144) at baseline Time to goal (iPTH 150–300 pg/ml) was 112 d (IQR: 56–259) with median overall decline in iPTH of 82% from baseline by 6 mo ($P < 0.0001$) Growth Significant improvement in linear growth was observed during cinacalcet therapy (SDS change −0.62 ± 1.2 versus +0.91 ± 1.4 at 6 mo; $P < 0.005$).	Asymptomatic hypocalcemia 6/10 (60%) Symptomatic hypocalcemia None	Hypercalcemia Hypercalcemia was notable occurrence in each patient with a peak calcium averaging 11.6 ± 1.0 mg/dl during cinacalcet treatment, attributed to the high concurrent doses of active vitamin D analogs (median dose of calcitriol 0.15 ug/kg/d or 2 ± 1.4 ug/d); median dose of paricalcitol 0.36 ± 0.07 ug/kg/d or 5.1 ± 3.8 ug/d before start of cinacalcet) Gastrointestinal Nausea, vomiting, and loss of appetite were the predominant adverse events, especially at high doses and taken orally instead of via G-tube. PTH oversuppression Transient oversuppression of PTH below 150 pg/ml occurred in 10 of 11 treatment courses, with nadir 93 pg/ml (IQR: 63–98).

Ca, calcium; CKD, chronic kidney disease; GH, growth hormone; HD, hemodialysis; iPTH, intact parathyroid hormone; IQR, interquartile range; P, phosphate; PD, peritoneal dialysis; SDS, standard deviation score; PTH, parathyroid hormone; ULN, upper limit of normal.
Combined prevalence of hypocalcemia: 16 in 54 patients (30%).

Table 3. Age-specific and CKD stage-based reference ranges[10]

Age	iCa mmol/l	Ca mg/dl or mmol/l	Phosphate mg/dl or mmol/L
0–5 mo	1.22–1.4	8.7–11.3 mg/dl or 2.17–2.82 mmol/l	5.2–8.4 mg/dl or 1.68–2.71 mmol/l
6–12 mo	1.20–1.4	8.7–11.0 mg/dl or 2.17–2.74 mmol/l	5.0–7.8 mg/dl or 1.61–2.52 mmol/l
1–5 yrs	1.22–1.32	9.4–10.8 mg/dl or 2.35–2.69 mmol/l	4.5–6.5 mg/dl or 1.45–2.1 mmol/l
6–12 yrs	1.15–1.32	9.4–10.3 mg/dl or 2.35–2.57 mmol/l	3.6–5.8 mg/dl or 1.16–1.87 mmol/l
13–20 yrs	1.21–1.30	8.8–10.2 mg/dl or 2.2–2.54 mmol/l	2.3–4.5 mg/dl or 0.74–1.45 mmol/l

Ca, calcium; CKD, chronic kidney disease; iCa, ionized calcium.

subjects (26.9%). In contrast, Morales *et al.*[28] and Joseph *et al.*[27] both reported an improvement in linear growth after the use of cinacalcet.[27,28] Half of the subjects experienced "catch-up" growth, and 3 of 10 patients reported a comparable growth velocity before and after cinacalcet initiation.[28] Favorable factors associated with improved growth included younger age (< 2 years), concomitant use of GH treatment, and a shorter time to reach the target PTH level.[28] The use of GH may also be confounded by efforts to control hyperparathyroidism, because GH is often temporarily withheld if PTH is > 500 pg/ml.[33] Thus, achievement of stable and adequate control of hyperparathyroidism by cinacalcet allows continuous GH use without disruption of growth promotion.

One concerning finding on the drug's side effect profile observed in children aged < 3 years has been the reported development of premature thelarche.[29] This observation was not previously observed in larger cohorts of older children treated with cinacalcet.[12,34] The authors hypothesized that this might be linked to underlying *HNF1B* variants, but a causal relationship could not be substantiated. Furthermore, premature thelarche is rather common and is different from precocious puberty which is characterized by progressive secondary sexual development, an enhanced growth spurt, hormonal changes, and skeletal maturation. If identified, collaborative management of premature thelarche with pediatric endocrinology is recommended. Finally, in contrast to previous reports where gastrointestinal disorders occurred in 40% of patients,[12] none of the children in the study by Bernardor *et al.*[29] reported such symptoms apart from the presumed dialysis-related nausea and vomiting.

Suggested Approach and Unique Considerations Regarding the Use of Cinacalcet in Infants and Young Children

Current studies provide important real-world data on the use of cinacalcet in infants and young children. Nevertheless, its use should be balanced against the potential risk of hypocalcemia and the lack of long-term safety data. More confirmatory data is also required among the youngest patients, infants aged < 1 year. For this reason, we support cautious use of cinacalcet in severe secondary or tertiary hyperparathyroidism that persists despite the provision of the full spectrum of conventional therapy. Optimization of nutrition and mineral intake, supplementation of native and active vitamin D, and compliance management should remain the priority.[31,32] Reliable and accurate assessment of calcium intake is crucial. Specifically, calcium intake from nutrition, medications, and dialysate, as well as medication adherence should all be taken into account. In addition, the use of cinacalcet should be accompanied with judicious and gradual dose adjustment, close monitoring of serum calcium levels, and timely withholding of cinacalcet should hypocalcemia occur.

Based on currently available evidence, cinacalcet should be initiated at a dose (0.2 mg/kg/d), in keeping with the guidance provided by the European Society for Pediatric Nephrology.[31] It should be made clear, however, that there is limited data to support this starting dose as being safe and effective in infants and young children.[25] Whereas a higher dose per kg may be clinically sound because dosing by body weight for other medications may be inadequate in young children compared with body surface area (m^2)–based dosing,[35,36] further data on this issue, as it relates to safety and efficacy, are needed. A baseline electrocardiogram should be performed because of the risk associated with cinacalcet usage combined with other medications that can prolong the QT interval.

The median peak effective dose of cinacalcet from available studies was 1.2 mg/kg/d (interquartile range: 0.75–1.38)[28,29] and this could be used as a reference target for cinacalcet dosage in clinical practice. Most reported cases in this specific patient population received a maximal dose of < 2 mg/kg/d.[27–29] We therefore suggest that the maximum dose of cinacalcet should likely be kept below this dosing level to prioritize patient safety, although dosing up to 7 mg/kg/d has been reported.[27–29]

The effect of cinacalcet takes time and a gradual, incremental increase in the dose of cinacalcet is necessary in search of the individualized threshold dose for both treatment efficacy and tolerability. Thus, dose adjustments should not occur earlier than 4 weeks after treatment initiation or modification. PTH should be regularly monitored and a PTH level between 100 and 300 pg/ml is a reasonable target for pediatric patients on

dialysis,[37] although different recommendations exist. Of note, accurate assessment of PTH level depends on an appropriate and consistent timing of blood sampling. The nadir of PTH following cinacalcet administration occurs 2 hours postdose, and gradually returns to baseline level between 8 and 48 hours.[25,38] We therefore suggest cinacalcet to be taken at night, with blood sampling the following morning to avoid picking up the transient nadir of PTH, which is not reflective of the overall control of hyperparathyroidism.

Identification and timely management of hypocalcemia are of paramount importance to prevent complications. However, symptoms and signs of hypocalcemia are often nonspecific among young children, including irritability, jitteriness, and gastrointestinal symptoms. Physicians should remain vigilant and consider these presentations as early and potential signs of hypocalcemia. Consequently, calcium and phosphate should be monitored regularly in accordance with the European Society for Pediatric Nephrology's recommendation. It is reasonable to check serum calcium levels within a week after dose adjustment. It should be noted that the normal range for serum calcium level is age-specific and continues to decrease after infancy and throughout early childhood until the age of 5 years (Table 3). For this reason, the general recommendation that cinacalcet should not be started in patients with an albumin-corrected calcium < 2.4 mmol/l and a target calcium > 2.2 mmol/l at any time may not be directly applicable to young children.[31] In addition to the albumin-corrected calcium level, we suggest that ionized calcium, if available, should be checked in these vulnerable patients and maintained above 1.2 mmol/l. Hypophosphatemia is also common, occurs in 77% of young children receiving cinacalcet,[29] and can further impair bone mineralization and building. Both serum calcium and phosphate levels should be kept within the age-appropriate normal range (Table 3), and ideally at the 50th centile to account for potential time-to-time fluctuation in their levels.[10]

Finally, the use of this potent medication, particularly among young children, should be limited to centers and health care providers with expertise in pediatric dialysis and CKD-MBD care. Adequate counseling and education should also be provided to caregivers for correct medication administration and early identification of complications.

Conclusion

Secondary and tertiary hyperparathyroidism remain challenging complications of CKD-MBD among infants and young children during the unique period of rapid skeletal growth and mineral requirement. Despite a promising safety and efficacy profile of cinacalcet, the use of this agent should be well-balanced against potential side effects, notably hypocalcemia, which can be fatal. Long-term data following cinacalcet use, pertaining to fracture risk, growth, and cardiovascular risk should be examined. To that end, additional data contributed through international collaborations, such as the International Pediatric Peritoneal Dialysis Network, should be leveraged to clarify the optimal indication, dosage, and duration of treatment in this unique patient population.

DISCLOSURE

BAW is a consultant for Amgen, Inc.

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