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SPECIAL REPORT

Cinacalcet use in paediatric dialysis: a position statement from the European Society for Paediatric Nephrology and the Chronic Kidney Disease-Mineral and Bone Disorders Working Group of the ERA-EDTA

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ABSTRACT

Secondary hyperparathyroidism (SHPT) is an important complication of advanced chronic kidney disease (CKD) in children, which is often difficult to treat with conventional therapy. The calcimimetic cinacalcet is an allosteric modulator of the calcium-sensing receptor. It has proven to be effective and safe in adults to suppress parathyroid hormone (PTH), but data on its use in children are limited. To date, studies in children only consist of two randomized controlled trials, nine uncontrolled interventional or observational studies, and case reports that report the efficacy of cinacalcet as a PTH-lowering compound. In 2017, the European Medical Agency approved the use of cinacalcet for the treatment of SHPT in children on dialysis in whom SHPT is not adequately controlled with standard therapy. Since evidence-based guidelines are so far lacking, we present a position statement on the use of cinacalcet in paediatric dialysis patients based on the available evidence and opinion of experts from the European Society for Paediatric Nephrology, Chronic Kidney Disease-Mineral and Bone Disorder and Dialysis Working Groups, and the ERA-EDTA. Given the limited available evidence the strength of these statements are weak to moderate, and must be carefully considered by the treating physician and adapted to individual patient needs as appropriate. Audit and research recommendations to study key outcome measures in paediatric dialysis patients receiving cinacalcet are suggested.

Keywords: cinacalcet, CKD-MBD, consensus statement, dialysis, paediatrics

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Secondary hyperparathyroidism (SHPT) is an important complication of advanced chronic kidney disease (CKD) in children, characterized by high serum parathyroid hormone (PTH) concentration, parathyroid gland hyperplasia and disturbances in mineral metabolism. SHPT results from disturbances in serum

calcium (Ca), phosphate (P) and vitamin D homeostasis, and contributes to the complex of CKD-associated mineral and bone disorders (CKD-MBD) [1]. PTH is a uraemic toxin [2]; SHPT contributes to complications of CKD-MBD, including ectopic calcifications and renal osteodystrophy, but it has also been associated with impaired longitudinal growth, fractures, anaemia, left ventricular hypertrophy and increased mortality [3–10].

Cinacalcet is an allosteric modulator of the calcium-sensing receptor (CaSR) expressed in several tissues, including the parathyroid glands. It enhances the CaSR sensitivity for extracellular Ca, resulting in reduced serum PTH, Ca and P levels, allowing better control of SHPT [11]. The use of cinacalcet in adults undergoing chronic dialysis has been well described. A recent meta-analysis including 23 randomized controlled trials (RCTs) with a total of 8481 adult dialysis patients, showed a significant decrease in PTH and the incidence of parathyroidectomy, but failed to demonstrate significant effect for the risk of fractures, cardiovascular events and all-cause or cardiovascular mortality [12]. To a large extent, this meta-analysis rests on data derived from the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial. In this trial, 3883 adult patients on haemodialysis, with PTH at baseline of $\geq$300 pg/mL (31.8 pmol/L) and calcium concentration $\geq$8.4 mg/dL (2.1 mmol/L), were randomized to either cinacalcet or placebo [13]. The primary endpoint was time to a composite of death, myocardial infarction or hospitalization for a cardiovascular event. In the primary unadjusted analysis, the study was negative. After pre-specified adjustment for baseline imbalances, in particular age, the relative hazard ratio for those allocated to cinacalcet was 0.88 [95% confidence interval (95% CI) 0.79–0.97] for the primary endpoint [13]. Secondary analyses suggested benefit from cinacalcet for non-atherosclerotic cardiovascular events (like admission for heart failure) and a lower incidence rate of subsequent parathyroidectomy.

To date, studies in children consist of two RCTs, nine uncontrolled interventional or observational studies, and case reports, studying the PTH-lowering effects of cinacalcet. In 2017, the European Medicines Agency (EMA) approved the use of cinacalcet for the treatment of SHPT in children >3 years on dialysis in whom SHPT is not adequately controlled with standard therapy, whereas the US Food and Drug Administration (FDA) has not yet approved its use in children [14]. There are no evidence-based practice recommendations on the use of cinacalcet in paediatric dialysis patients.

Here, we present 22 statements on the use of cinacalcet in paediatric dialysis patients, and include practical suggestions for its administration and safety aspects related to its use. This consensus document is based on the available evidence and the opinion of experts from the European Society for Paediatric Nephrology (ESPN) CKD-MBD and Dialysis Working Groups (WGs), and the ERA-EDTA, and clearly graded as such (Table 1). Given that there are very few high-quality studies to guide evidence-based practice, these statements must be carefully considered by the treating physician and adapted to individual patient needs as appropriate. Audit and research recommendations to further improve our knowledge on cinacalcet use in paediatric dialysis patients are also suggested.

MATERIALS AND METHODS

This consensus document was developed to provide guidance to healthcare professionals on the use of cinacalcet in paediatric dialysis patients. This is a field where there is little evidence, but approval has been granted by the EMA. These recommendations reflect the available evidence from clinical studies, opinion of experts in paediatric CKD-MBD and extrapolation from adult studies, where appropriate. The methodology we used to develop this consensus document on the indications, dosing and monitoring of cinacalcet therapy in children on dialysis is described below.

The consensus development group

Two groups were assembled: a core WG and a voting panel. The core group comprised peadiatric nephrologists, a representative from the ERA-EDTA CKD-MBD WG (M.V.) and a paediatric pharmacist (M.W.), who were together responsible for defining the scope of the project, formulating the key questions, performing a literature review, rating the quality of evidence, grading recommendations, conducting the voting panel, and drafting the initial and final version of the manuscript. The voting group included members of ESPN CKD-MBD and Dialysis WGs and of the EDTA CKD-MBD WG, and patients' representatives. All conflicts of interest are declared. The individual expertise and responsibilities of the core group members are summarized in Supplementary Table S1.

Developing PICO questions

In order to give specific actionable advice, we developed clinical questions to be addressed under the following categories: the Patient (or Population) to whom the recommendation will apply; the Intervention being considered; the Comparison (which may be 'no action', placebo or an alternative intervention); and the Outcomes affected by the intervention (PICO) [15]. These PICO elements were arranged into the questions to be addressed in the literature searches. Each PICO question then formed the basis for a statement.

The population covered consisted of children undergoing chronic dialysis since RCTs, and an EMA licence is only available for this subgroup. There are only isolated reports of cinacalcet use in children with pre-dialysis CKD and after renal transplantation: these groups were therefore not included. The intervention was cinacalcet use, and the comparator placebo, standard of care (i.e. vitamin D analogues) or intra-patient comparison using the status at baseline, before starting cinacalcet therapy. The outcomes addressed were change in PTH from baseline, and the difference between groups at the end of study period. Important safety outcomes, including change in serum calcium levels, are presented. The paediatric studies available did not investigate key patient level outcomes, such as bone pain, parathyroidectomy, cardiovascular events, bone fractures or mortality, and we are unable to discuss these further, but have included them as important topics for future research. We addressed statements for indications, contra-indications, treatment schedule, monitoring and discontinuation of cinacalcet in paediatric dialysis patients.

Table 1. Summary of the consensus statement for the use of cinacalcet in paediatric dialysis

		Statements	Grade/strength
Factors to consider before starting cinacalcet	1	We recommend that serum calcium, phosphate, PTH and 25OH vitamin D levels are regularly monitored, and treatment decisions based on trends in these levels are considered together.	Grade B Moderate recommendation
	2	We recommend that albumin-corrected calcium levels are used. Ionized calcium levels are a more accurate measure of free (bioavailable) calcium, and should be used where available.	Grade C Weak recommendation
	3	We recommend that serum calcium and phosphate levels are kept within the age-appropriate normal range. Calcium intake from diet, medications and dialysate should be taken into account when evaluating calcium and phosphate levels.	Grade B Moderate recommendation
Which patients may benefit from cinacalcet therapy and what are the contraindications for its use?	4	We suggest that cinacalcet is used in children >3 years of age on dialysis who have persistent and severe hyperparathyroidism in the presence of high or high-normal calcium levels, despite optimized conventional management, including active vitamin D.	Grade B Moderate recommendation
	5	There is no clear threshold level of PTH above which cinacalcet therapy should be started.	Ungraded
	6	Do not start cinacalcet in patients with albumin-corrected calcium levels <2.40 mmol/L.	Grade X Strong recommendation
	7	Do not start cinacalcet in patients with prolonged QT interval.	Grade X Strong recommendation
	8	We recommend that cinacalcet is used with caution in patients with history of seizures, cardiac arrhythmia, significant liver disease or poor adherence to medications.	Grade X Moderate recommendation
	9	We suggest that drugs that prolong the QTc interval or interact with cinacalcet are used with caution; the relative benefit of the drug or withholding cinacalcet must be considered on an individual patient basis.	Grade X Moderate recommendation
What is the treatment schedule?	10	We recommend a starting dose of cinacalcet of ≤0.2 mg/kg/day based on dry weight rounded to the nearest whole dose unit.	Grade B Moderate recommendation
	11	The cinacalcet dose may be increased in increments of 0.2 mg/kg/day to a maximum daily dose of 2.5 mg/kg (not exceeding 180 mg) based on PTH levels provided that albumin-corrected calcium serum levels remain >2.2 mmol/L. Dose titration intervals should be at least 4 weeks.	Grade B Moderate recommendation
	12	Cinacalcet can be given orally or by nasogastric/gastric tube, once daily.	Ungraded
	13	We suggest that the minimal effective cinacalcet dose is used to maintain PTH levels in the desired PTH target range, taking into account its effects on calcium and phosphate concentrations.	Grade B Moderate recommendation
	14	We suggest to decrease cinacalcet dose when PTH levels are in the lower target range between 100 and 150 pg/mL, low for the individual patient or declining too rapidly, and to discontinue cinacalcet when PTH concentrations are below the target range.	Grade B Moderate recommendation
	15	We recommend that serum calcium levels are maintained within the normal range for age, by titrating conventional therapy including nutritional calcium intake, calcium-based phosphate binders, vitamin D analogues and dialysate calcium, and by titrating cinacalcet dose.	Grade B Moderate recommendation
	16	We suggest decreasing or withdrawing cinacalcet when albumin-corrected serum calcium levels fall <2.2 mmol/L.	Grade X Moderate recommendation
How should a child on cinacalcet therapy be monitored?	17	We suggest that serum calcium levels are monitored within 1 week of starting cinacalcet therapy, weekly during the titration phase, and at least monthly when maintenance dose has been established in a patient.	Grade C Moderate recommendation
	18	We suggest that PTH serum levels are checked on a monthly basis.	Grade B Moderate recommendation
	19	We recommend that children and their caregivers are informed of symptoms of hypocalcaemia, the importance of adherence to taking all medications regularly as well as instructions regarding serum calcium monitoring and caution about other medications which may prolong QTc interval or interact with cinacalcet.	Grade X Moderate recommendation
	20	We recommend that cinacalcet is withhold when albumin-corrected serum calcium levels are <2.0 mmol/L and/or ionized calcium levels are <1.0 mmol/L. Cinacalcet may be restarted in a lower dose when serum calcium levels return to the higher end of the normal range.	Grade X Moderate recommendation

Continued

Table 1. Continued

		Statements	Grade/strength
	21	Withdraw cinacalcet in case of symptomatic hypocalcaemia, including paraesthesia, myalgia, cramps, tetany and convulsions, long QT interval or severe side effects.	Grade X Strong recommendation
How should a pediatric patient with persistent severe SHPT despite conventional therapy and cinacalcet be treated?	22	We suggest that parathyroidectomy is considered in case of severe and persistent SHPT despite optimized cinacalcet and conventional therapy, including active vitamin D.	Grade C Weak recommendation

Literature review and studies included

The PubMed database was searched until 18 February 2019: articles included were RCTs, prospective uncontrolled or observational studies irrespective of number of patients, registry data, retrospectives studies and case reports with more than five paediatric patients, restricted to human studies in English (Tables 2–4).

Grading system

We applied the grading system from the American Academy of Pediatrics (Figure 1) [24]. The quality of evidence is graded high (A), moderate (B), low (C) and very low (D). Grading (X) refers to exceptional situations, where validating studies cannot be performed and benefit or harm clearly predominates: in that case, a moderate or a strong recommendation may be given. This letter was used to grade contraindications for cinacalcet use and safety parameters. The strength of a statement was graded strong, moderate, weak or discretionary (when no recommendation can be made).

Voting group members were asked by using an e-questionnaire to provide a level of agreement for all the 22 statements included in this manuscript on a five-point scale (strongly disagree, disagree, neither agree/disagree, agree and strongly agree) (Delphi method) and to suggest re-wording if appropriate. A consensus level of at least 70% was achieved for all the 22 points.

CONSENSUS STATEMENTS

Factors to consider before starting cinacalcet

1. We recommend that serum calcium, phosphate, PTH and 25OH vitamin D levels are regularly monitored, and treatment decisions based on trends in these levels are considered together (grade B, moderate recommendation).

2. We recommend that albumin-corrected calcium levels are used. Ionized calcium levels are a more accurate measure of free (bioavailable) calcium, and should be used where available (grade C, weak recommendation).

3. We recommend that serum calcium and phosphate levels are kept within the age-appropriate normal ranges. Calcium intake from diet, medications and dialysate should be taken into account when evaluating calcium and phosphate levels (grade B, moderate recommendation).

Evidence and rationale. When evaluating a child as a candidate for cinacalcet treatment, the complexity and interdependency of all CKD-MBD laboratory parameters need to be emphasized. Treatments of CKD-MBD should be based on serial assessment of phosphate, calcium and PTH levels altogether for clinical decision-making [25]. Normal phosphate and calcium levels depend on age, as summarized in Table 5 for calcium and ionized calcium [26, 27]. In the setting of cinacalcet use, both the trends and absolute values in serum calcium levels before initiating cinacalcet therapy must be carefully evaluated, because of the risk of cinacalcet-related hypocalcaemia. Clinical symptoms of hypocalcaemia include paresthesia, myalgia, cramps, tetany and convulsions, but importantly, even severe hypocalcaemia may be asymptomatic until severe complications occur as presenting symptom.

The extracellular calcium fraction is tightly regulated and can be measured in serum, where approximately half is bound to albumin and proteins; the remainder corresponds to 'free' or ionized calcium, the latter form being biologically active and responsible for most of its physiological functions [28, 29]. Compared with total calcium levels, ionized calcium is not influenced by alterations in serum albumin levels that are common in dialysis patients, but can be influenced by acidosis [30]. We suggest that ionized calcium levels be used where available, but given that albumin-corrected serum calcium levels are more readily available, and have been used in all cinacalcet trials, unless detailed otherwise, in the following paragraphs of this manuscript, 'calcium levels' refer to albumin-corrected calcium; the calculation is detailed in Table 5.

The standard of care of CKD-MBD in paediatrics relies on a combination of different measures. All metabolic and clinical abnormalities (i.e. metabolic acidosis, anaemia and low nutritional calcium intake) should be corrected as well as possible [31]. We suggest that vitamin D deficiency be corrected, aiming for a target of circulating 25OH vitamin D levels ranging between 75 and 120 nmol/L [32]. In addition, nutritional control of phosphate intake, calcium-based and non-calcium/non-aluminum-based phosphate binders can be used [23]. The KDOQI 2008 nutrition guidelines in pediatric CKD suggests that the total calcium intake from nutritional sources and medications be in the range of 100–200% of the daily recommended intake (DRI) for calcium for age, as summarized in Table 5 [27].

Nutritional intake of calcium should be recorded; calcium intake may come from diet, but also from medications (direct calcium intake through calcium supplementation or calcium-

Table 2. Summary of the two RCTs reporting cinacalcet use in pediatric dialysis

References	Type and duration	Patients	Indications and contra-indications for use	Treatment schedule	Efficacy	Adverse events (AE)/ discontinuation	Comments
Warady *et al.* [16]	Amgen study: Phase 3 randomized, double-blind, placebo-controlled study of 30 weeks, followed by a 30-week open-label extension phase In the double-blind phase: mean exposure time 110 versus 123 days in control group In the open-label extension phase, mean exposure time 119 days	$N = 22$ cinacalcet, 21 placebo, children aged 6–18 years, mean 12.6 years, 51% boys	PTH >300 pg/mL, Ca ≥2.2 mmol/L (8.8 mg/dL) and P ≥1.29 mmol/L (6 to <12 years) or P ≥1.13 mmol/L (12 to <18 years) For subjects already receiving vitamin D sterols or growth hormone, stable dose within the preceding 2 months Exclusion criteria: parathyroidectomy within 6 months before or anticipated within 6 months after randomization; treatment with cinacalcet within 1 month before randomization	Starting dose 0.18 mg/kg/day Mean average dose 1.54 mg/kg/day Highest dose 60 mg, mean (min–max) maximal weight-adjusted daily dose: 0.7 (0.2–1.9) mg/kg	Overall 54.5% of subjects achieved the primary endpoint (namely decrease in iPTH >30%) in the cinacalcet group, versus 19% in the placebo group ($P < 0.05$)	Vomiting (32% cinacalcet, 24% placebo), hypocalcaemia (23%, 19%), nausea (18%, 14%), hypertension (14%, 24%) Thirty-two per cent of patients in the cinacalcet group and 48% in the placebo group had grade ≥3 treatment-emergent AEs; 41 and 43% experienced serious AEs. The most common serious AE was hypertension (9%; $n = 2$) in the cinacalcet group and diarrhoea, pyrexia and dehydration (10% each; $n = 2$ each) in the placebo group Seven patients (32%) in the cinacalcet group and three (14%) in the placebo group had calcium <2.1 mmol/L at any time during the double-blind phase. Five patients (23%) in the cinacalcet group and one (5%) in the placebo group had corrected total serum calcium concentration <2 mmol/L and three patients (14%) in the cinacalcet group and no patients in the placebo group had corrected total serum calcium concentration <1.87 mmol/L. Potential symptoms of hypocalcaemia included muscle spasms (14%, 5%), myalgia (14%, 5%) and tremor (14%, 0%); AEs of interest that were identified risks were hypocalcaemia (23%, 19%), convulsions/seizures (0%, 10%), hypotension (9%, 5%), cardiac failure (5%, 0%) and hypersensitivity (9%, 14%) A fatal AE occurred during the double-blind period in a female adolescent with prolonged QT interval at baseline receiving	Study terminated early because of a fatality

Continued

Table 2. Continued

References	Type and duration	Patients	Indications and contra-indications for use	Treatment schedule	Efficacy	Adverse events (AE)/ discontinuation	Comments
						PD, cinacalcet (90 mg at time of death), and multiple concomitant medications. During study week 23, she acutely developed severe nausea, vomiting, diarrhoea, dehydration and fever (102.4°F) and was treated with acetaminophen and odansetron. Later the same day, she went into fatal cardiopulmonary arrest. On the day of death, she had a PTH of 439 pg/dL, and a laboratory report that became available after the fatality showed a total calcium of 1.12 mmol/L and a corrected calcium of 1.33 mmol/L on the morning of the patient's death. Although the fatality was determined to be multifactorial, a causal role for hypocalcaemia as a result of treatment with cinacalcet could not be excluded	
Schaefer (2017)[a] ASN FR-PO292	Amgen study: Phase 3 multicenter randomized open label controlled (SOC), cinacalcet exposure time 113 (41) days	$N = 27$ cinacalcet (28 SOC) children aged 6–18 years; stratification by age 27/28 enrolled (22/25 randomized)	Eligible subjects had two consecutive iPTH levels $\geq$300 pg/mL at entry and Ca $\geq$8.8 mg/dL	Starting dose 0.2 mg/kg Adjusted once monthly up to 2.5 mg/kg/d (max 180 mg)	The proportion of subjects who achieved iPTH reduction >30% was not significantly different: 32% with C + SOC, 22% with SOC (p = NS)	Infections in 14 patients in cinacalcet and 6 in SOC group. Frequent AEs in cinacalcet group: hypocalcaemia (24%), muscle spasms (12%), nausea (12%), headache (4%). Four serious AEs in the cinacalcet group, unrelated to cinacalcet. Dose reduction and interruptions occurred even in situations, where the Ca value would have allowed dose maintenance or increase	Withrawal of cinacalcet if iPTH <100 pg/mL, Ca <2 mmol/L or iCa <1 mmol/L Dosing rules based on weekly assessment of Ca with specific iCa threshold ⇒ resulted in a high rate of dose interruption and dose reduction

For calcium and phosphate, the conversion factors from mmol/L to mg/dL are to multiply by 4 and 3.1, respectively.
[a]The data were presented only as abstract forms during an international conference and never completely published.
Ca, calcium levels; iCa, ionized calcium; PD, peritoneal dialysis; SOC, standard of care.

Table 3. Summary of the six prospective studies reporting cinacalcet use in pediatric dialysis

References	Type/duration	Patients	Indications and contra-indications for use	Treatment schedule	Efficacy	Adverse events/ discontinuation	Comments
Muscheites *et al.* [17]	Prospective clinical study, 4 weeks	$N = 7$ children (3 PD, 3 HD, 1 CKD5), between 1.1 and 19 years	Inadequately controlled SHPT despite conventional management All patients had PTH levels >500 pg/mL from at least two consecutive measurements during the previous 2 months, despite standard treatment with calcitriol and calcium-free/calcium-containing phosphate binders No contra-indications stated Pre-treatment serum Ca levels 2.54 (2.4–2.66) mmol/L	0.25 mg/kg/day	PTH before cinacalcet: 932 (511–1938) pg/mL; PTH 4 weeks after: 199 (121–940) pg/mL, $P < 0.05$	In 2/7 patients non-symptomatic hypocalcaemia (<2.20 mmol/L), successfully managed by calcium acetate/calcitriol, started on day 7 Ca decreased to a nadir after 4 h of 2.18–2.89 mmol/L after first dose No significant AE	No significant modification in the total number of drugs used for CKD-MBD control In two of the seven patients, calcitriol had been withdrawn 3 weeks prior to the onset of cinacalcet due to hypercalcemia (>2.79 mmol/L) and/or hyperphosphataemia (>2 SDs above the normal range). The dialysate calcium concentration in HD and PD patients was 1.25 mmol/L
Silverstein *et al.* [18]	Prospective clinical study, 3 months	$N = 13$ children included initially, results presented for 9 (6 HD, 3 PD) because of non-compliance, between 7.5 and 17.5 years	iPTH levels of at least an average of 400 pg/ml for 3 consecutive months No contra-indications stated, mean Ca 1 month prior to inclusion was 2.35 ± 0.05 mmol/L	30–120 mg/day; mean final cinacalcet dose: 1.27 ± 0.3 mg/kg/day	Sixty-one per cent decrease in PTH levels, from 1070 ± 172 pg/mL to 418 ± 98 pg/mL ($P = 0.005$) after 3 months. Similar decrease in total ALP levels	Three patients excluded for non-compliance, in one cinacalcet discontinued because of seizure episode (Na 132, otherwise normal electrolytes, CT scan normal). Three patients nausea. No episodes of hypocalcaemia, no further AEs	No significant modification in the dose of vitamin D analogs. Dietary recommendations for Ca and phosphorous intake were according to K/DOQI guidelines. Specifically, the total dose of elemental Ca provided by the calcium-based phosphate binders and the dietary calcium was prescribed to not exceed twice the DRI for Ca based on age and not to exceed 2500 mg/day All patients receiving P-binder ($CaCO_3$, Ca acetate, sevelemer or lanthanum) and oral or IV vitamin D3 prior to and during cinacalcet therapy
Padhi *et al.* [19]	Open-label study (single-dose) Amgen study, 72 h	$N = 12$ children HD/PD, 6–17 years, with Ca >2.1 mmol/L at inclusion	No PTH value defined for inclusion Pre-treatment serum Ca ≥ 2.1 mmol/L at baseline visit No contra-indications stated	15 mg in all children (38 ± 16 kg)	Mean percentage change in iPTH: nadir at 2 h (−36%)	Ca <2.23 mmol/L in 6/12 children (2.00–2.22 mmol/L), all asymptomatic. Return to baseline within 48 h 1/12 prolonged QT interval post-cinacalcet (investigator related it to a	ECG before cinacalcet in the child with unrelated increased QT interval?

Continued

Table 3. Continued

References	Type/duration	Patients	Indications and contra-indications for use	Treatment schedule	Efficacy	Adverse events/ discontinuation	Comments
						prior trauma; persisted 6 but not 12 weeks later)	
Alharthi *et al.* [20]	Prospective cohort analysis in Egypt; monthly biochemistry for 2 years	28 children between 9 months and 18 years), 6 CKD4, 22 HD/PD	Uncontrolled SHPT (iPTH >300 pg/mL) despite maximum conventional treatment for at least 3 months Actual PTH levels much higher: 776–4350 pg/mL pre-cinacalcet Mean baseline corrected serum Ca >2.1 mmol/L Contra-indications: Serum Ca <2.1 mmol/L Patient with seizure disorder maintained on anti-convulsant treatment as hypocalcaemia, which might be caused by cinacalcet, lower the threshold for seizures Patients with hepatic impairment Patients with hypersensitivity to cinacalcet	Starting dose 0.5 mg/kg/day, titration every 2/4 weeks up to 1.5 mg/kg/day: 0.5 mg/kg/day in predialysis patients, 0.5–1 mg/kg/day in PD patients and 1–1.5 mg/kg/day in HD patients	Severe HPT: 776–4347 pg/mL before cinacalcet. PTH at the end of the study 39–1363 pg/mL. Little impact on reducing the total number of medications	No episodes of (symptomatic) hypocalcaemia, hypophosphataemia. No adverse events Six deaths during follow-up; 10 withdrawal of cinacalcet at the end of the study (duration 3–24 months); decrease of cinacalcet dose: daily/alternate and then twice-weekly dose	In association with vitamin D analogues Discrepancies between methods and results for the titration protocol
Sohn *et al.* [21]	Amgen study: open-label single-dose, follow-up 72 h	$N = 12$ children, aged 28 days to 6 years	CKD and SHPT Body weight ≥6 kg at screening and at Day 1 Serum calcium within age-appropriate normal ranges per NKF-K/DOQI guidelines at screening and at Day 1 Normal or clinically acceptable ECGs at screening and at Day 1 Contra-indications: A new onset of seizure or worsening of a pre-existing seizure Clinical lab signs of hepatic impairment Medications: use of grapefruit juice, herbal medications or potent CYP 3A4 inhibitors within 14 days prior to enrollment and during study	0.25 mg/kg	Reductions in serum PTH levels: −11% at 2 h and −30% at 8 h, return to baseline at 72 h	3/12 AEs: one asymptomatic hypocalcaemia, one body temperature increase and one subject with vomiting, catheter site haemorrhage and device expulsion	

			Concurrent or within 28 days prior to enrollment use of medications that are predominantly metabolized by the enzyme CYP 2D6 with a narrow therapeutic index Use of medications that prolong QT interval				
Goodman (2017)[a] ASN FR-PO291	Amgen study: 26-week, single-arm, open-label, safety study	$N = 18$ children aged 28 days to 6 years. All received cinacalcet + SOC	SHPT on dialysis with PTH levels ≥300 pg/mL and serum corrected Ca ≥2.35 mmol/L (28 days to <2 years) or ≥2.2 mmol/L (2 to <6 years)	Due to fatality in another trial, 14-month clinical hold/protocol changes: starting/max daily dose of cinacalcet 0.25/4.2 mg/kg prior to hold ($n = 8$); and 0.20/2.5 mg/kg (or 60 mg, whichever was lower, after hold ($n = 10$)	Overall 70.6% of subjects showed >30% reductions in PTH from baseline; 52.9% of subjects achieved PTH <300 pg/mL during the study	No Ca <2.25 mmol/L in subjects 28 days to <2 years No Ca <2.10 mmol/L in subjects 2 to <6 years, 2 had a Ca <2.2 mmol/L Overall 94.1% of subjects had ≥1 treatment-emergent AE 10 infections/infestations (58.8%; mostly upper respiratory tract infection, bronchitis and viral infection) Other AEs cough, hypertension, [4]. Nine serious AEs (none treatment-related). Neither fatal AE nor AE leading to cinacalcet discontinuation. One AE episode of hypocalcaemia	14-month clinical hold/protocol changes

For calcium and phosphate, the conversion factors from mmol/L to mg/dL are to multiply by 4 and 3.1, respectively.

[a]The data were presented only as abstract forms during an international conference and never completely published.

ALP, alkaline phosphatase; Ca, calcium levels; CT, computed tomography; HD, haemodialysis; K/DOQI, Kidney Disease Outcomes Quality Initiative; NKF, National Kidney Foundation; P-binder, phosphate binder; PD, peritoneal dialysis; SDS, standard deviation score; SOC, standard of care.

Table 4. Summary of the retrospective observational studies and registry data reporting cinacalcet use in pediatric CKD

References	Type	Patients	Duration	Indications and contra-indications for use	Treatment schedule	Efficacy	Adverse events/ discontinuation	Comments
Borzych *et al.* [5]	IPPN registry	$N = 25$ children (out of 890 on PD), mainly from North America. Gives age and regional distribution of cinacalcet use	Not defined	Not defined	Not defined	Not defined	Not defined	% cinacalcet usage in PD patients with persistent, *de novo*, resolved and absent clinical/ radiological signs of MBD: 0, 7.3, 3.1 and 0.9% of observation time
Platt *et al.* [22]	Retrospective case series	$N = 6$ children, (HD/ PD), 11 months to 14 years	5–36 months	Uncontrolled SHPT—defined as an elevation in PTH, despite optimization of serum Ca and phosphate levels PTH consistently >31.8 pmol/L (=300 pg/mL) at inclusion No contra-indications, pre-treatment Ca levels 2.47 ± 0.05 mmol/L	Starting dose 0.4–1.1 mg/kg/day; then 0.4–2.6 mg/kg/day	All six cases: at least an 86% reduction in PTH levels (range 86–98%). Treatment with cinacalcet had little impact on reducing the total number of drugs used for CKD-MBD control	Asymptomatic hypocalcaemia in 2/6, in one cinacalcet discontinued (for 5 months), the other solved by increase in calcium supplementation, and alfacalcidol 3/6 hypophosphataemia by month 3, corrected by cinacalcet dose reduction, reduction in P-binder and increase in alfacalcidol, respectively	Treatment ongoing in five patients at the end of the study (the sixth patient underwent renal transplantation)
Arenas Morales *et al.* [23]	Retrospective case series	$N = 10$ pediatric patients, median age 18 months (IQR 6–36)	6 months	Uncontrolled SHPT with iPTH >500 pg/mL	Starting dose 0.7 ± 0.2 mg/kg/day, increments every 2–4 weeks	Target PTH levels: 150–300 pg/mL Median effective dose to reach the iPTH target: 2.8 (IQR 2–3.1) mg/kg/day Time to reach the iPTH target: 112 (IQR 56–259 days) Overall decline in iPTH of 82% from baseline	Four asymptomatic hypocalcaemia, no severe AE	End-point on linear growth: improved linear growth after 6 months of cinacalcet from −0.62 ± 1.2 to 0.91 ± 1.4 SDS

For calcium and phosphate, the conversion factors from mmol/L to mg/dL are to multiply by 4 and 3.1, respectively.
Ca, calcium levels; HD, haemodialysis; IPPN, International Pediatric Peritoneal dialysis Network; IQR, interquartile range; P-binder, phosphate binder; PD, peritoneal dialysis.

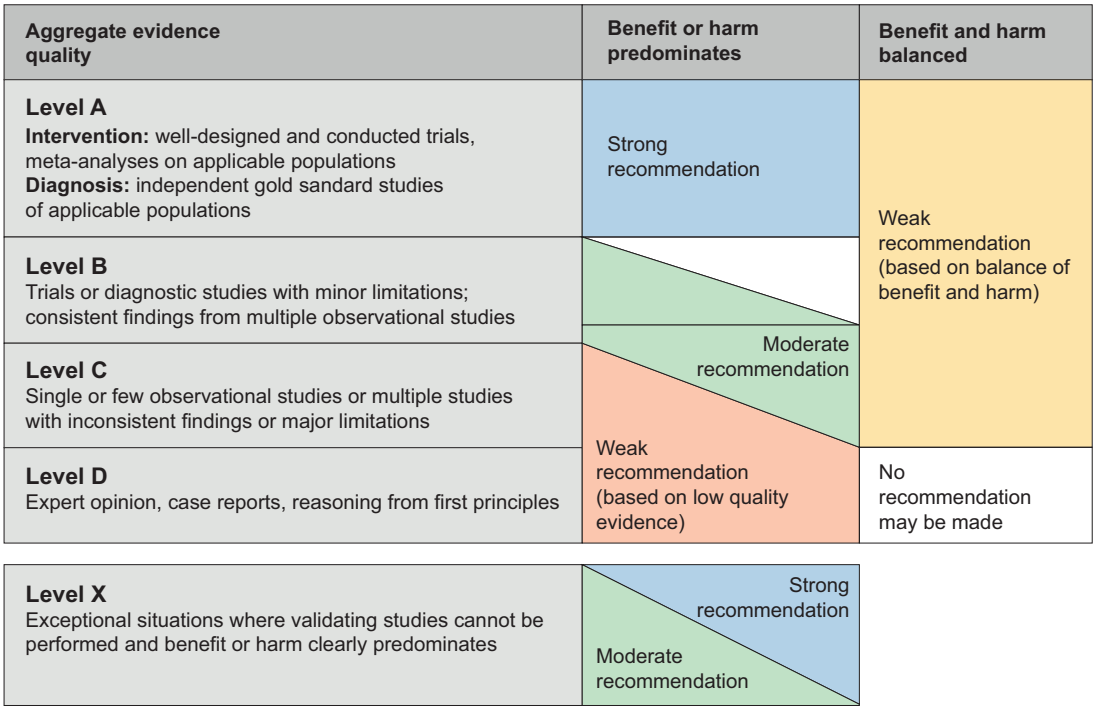

FIGURE 1: American Academy of Pediatrics grading matrix, adapted from [24].

based phosphate binders) and dialysate. In addition, active vitamin D analogues promote intestinal calcium absorption from any source. An inadequate calcium intake in pediatric CKD may impair bone mineralization [10, 33–36]. Conversely, too much calcium may be deleterious for vessels by aggravating calcification [7, 8, 37–43]. Importantly, children and adolescents have higher calcium requirements than adults in order to allow for adequate bone mineralization with growth [44]. Calcium deficiency in pediatric CKD may also further worsen SHPT, and induce mineralization abnormalities and secondary rickets; in this regard, the 2017 KDIGO guidelines suggest that serum calcium levels be maintained in the age-appropriate normal range in dialysis children [25].

Which patients may benefit from cinacalcet therapy and what are the contra-indications for its use?

4. We suggest that cinacalcet is used in children >3 years of age on dialysis who have persistent and severe hyperparathyroidism in the presence of high or high-normal calcium levels, despite optimized conventional management, including active vitamin D (grade B, moderate recommendation).

5. There is no clear threshold level of PTH above which cinacalcet therapy should be started (ungraded).

6. We recommend that cinacalcet not be started in patients with albumin-corrected calcium levels <2.40 mmol/L (grade X, strong recommendation).

7. We recommend that cinacalcet not be started in patients with prolonged QT interval (grade X, strong recommendation).

8. We recommend that cinacalcet be used with caution in patients with history of seizures, cardiac arrhythmia, significant liver disease or poor adherence to medications (grade X, moderate recommendation).

9. We suggest that drugs that prolong the corrected QT interval (QTc) or interact with cinacalcet are used with caution; the relative benefit of the drug or withholding cinacalcet must be considered on an individual patient basis (grade X, moderate recommendation).

Evidence and rationale. There is little evidence to define optimal PTH target levels in children with CKD, and guideline committees have suggested different targets ranging from normal in pre-dialysis stages to 1.7- to 9-fold above the upper normal limit (UNL) in dialysis children [3, 25, 31]. Likewise, there are no studies to indicate clear thresholds of PTH to initiate cinacalcet therapy in children.

In the EVOLVE trial at baseline, adult haemodialysis patients displayed median intact PTH (iPTH) levels of 693 pg/mL, although the inclusion criteria for the trial stated PTH levels >300 pg/mL [13, 45]. In the most recent large RCT comparing cinacalcet, placebo and intravenous (IV) etelcalcetide in adults undergoing chronic dialysis, the threshold of PTH levels to be included was 500 pg/mL [46]. Although children with PTH levels >300 pg/mL could be included in a pediatric RCT, mean ± SD PTH levels were 757 ± 440 pg/mL at baseline in the cinacalcet group and median (min–max) were 676 (309–2407) pg/mL [16]. Therefore, even though PTH levels and trends are usually used to guide therapeutic management, we do not have enough evidence to propose an exact threshold of PTH levels to initiate cinacalcet, but it is worth noting that actual PTH levels in the clinical trials were significantly greater than what could be expected in view of the inclusion criteria; moreover, relative PTH decline was independent of baseline values.

Uncontrolled SHPT in CKD children is a situation in which the control by diet, vitamin D analogues and phosphate binders

Table 5. References for calcium levels and calcium intake in paediatrics

Age range	Normal range for calcium (mmol/L)	Normal range for ionized calcium (mmol/L)	Daily recommended intake for calcium (mg)
Birth–5 months	2.18–2.83	1.22–1.40	210
6–12 months	2.18–2.75	1.20–1.40	270
1–5 years	2.35–2.70	1.22–1.32	500
6–12 years	2.35–2.58	1.15–1.32	800
13–20 years	2.20–2.55	1.12–1.30	1300

For calcium, the conversion factor from mmol/L to mg/dL is to multiply by 4.
The calculation formula for corrected calcium (CaC, mmol/L) using measured calcium (mmol/L) and albuminaemia (g/L) is the following: $CaC = Ca - 0.25 \times (albuminaemia - 40)$.
If albuminaemia is not available, CaC may be calculated with protidemia (g/L) with the following formula: $Cac = Ca/(0.55 + P/160)$.

Table 6. Concomitant drugs that are contra-indicated with cinacalcet

Mechanism	Example of drug that is contra-indicated in association with cinacalcet
Potential to increase QTc	Ondansetron
	Albuterol
	Salbutamol
Inhibitors of CYP3A4	Grapefruit juice
	Erythromycin
	Clarithromycin
	Ketoconazole
	Itraconazole
Inhibitors of CYP2D6	Flecanide
	Propafenone
	Metoprolol
	Desiprimine
	Nortroptyline
	Clomipramine

This list is not exhaustive: before prescribing cinacalcet or new therapies to patients already receiving cinacalcet, physicians in charge of the patients are responsible for checking the potential interferences and contra-indications.

fail. It is characterized by a sustained high PTH level in combination with a high or high-normal calcium level. SHPT gradually develops into tertiary HPT with important bone, cardiac and vascular complications, such as osteitis fibrosa and calcium efflux from bone, potentially leading to vascular calcification [42]. Parathyroidectomy is rarely performed in children [31, 47]. Cinacalcet sensitizes the CaSR to calcium and thereby decreases PTH secretion [11]. Therefore, cinacalcet use may be particularly interesting in pediatric patients whose age-specific serum calcium levels are elevated prior to treatment, since this hampers the use of active vitamin D analogues and calcium-containing phosphate binders [31].

Five industry-sponsored RCTs or open label trials (two of which are only disclosed in the cinacalcet product information [48], and published as abstracts at international conferences) [16, 21] and six uncontrolled studies or series of off-label use of cinacalcet in children on dialysis have been reported and are summarized in Tables 2–4 [5, 17–23]. In the two RCTs patients presenting with intact PTH levels >300 pg/mL (6-fold UNL) and calcium levels >2.2 mmol/L were included. The primary endpoint of at least a 30% reduction from baseline of mean PTH levels was met in only one trial (Table 2) [16]; in the second RCT (not published to date) that included 27 children aged 6–18 years who received cinacalcet compared with 28 children receiving standard of care therapy, the proportion of subjects who achieved a >30% reduction in PTH was not statistically different between groups. In the single-arm study, PTH levels were reduced by at least 30% in 71% (12 out of 17) of patients. In five other prospective studies reporting on efficacy data of cinacalcet, iPTH levels were >300 pg/mL or 500 pg/mL (9-fold UNL) before initiation of cinacalcet, respectively (Table 3). In all these studies, PTH levels were reduced compared with baseline values within 4 weeks to 2 years. Taken together, the current available data suggest that cinacalcet is efficacious at reducing PTH levels in pediatric dialysis patients presenting with PTH levels >300 pg/mL.

In the summary of product characteristics published by the EMA for the use of cinacalcet in pediatric dialysis, it is recommended to initiate cinacalcet in children aged >3 years in whom SHPT is not adequately controlled with standard of care therapy, when serum calcium is in the upper range of, or above, the age-specified interval [48]. Calcium levels before initiating cinacalcet therapy are of importance, because of the risk of subsequent hypocalcaemia. In the EVOLVE trial, 12% of adults on cinacalcet experienced hypocalcaemia, which was significantly greater than in the placebo group (2%) [13]; in that study, median serum calcium levels before starting cinacalcet were 2.45 mmol/L whilst inclusion criteria were calcium levels were >2.1 mmol/L, with a nadir at 4 months and a stabilization thereafter, with median calcium levels of 2.20 and 2.35 mmol/L, respectively [13, 45]. During the titration phase, calcium levels were assessed every 2 weeks. A recent report from the EVOLVE trial demonstrated that calcimimentic-induced hypocalcaemia was virtually harmless in adults [53], but these conclusions were nuanced by experts [54]. However, the pathophysiological mechanisms inducing hypocalcaemia in patients receiving cinacalcet are not fully elucidated, and one may hypothesize that hypocalcaemia may also occur depending on the degree of bone demineralization, PTH levels and cinacalcet dose rather than only on the calcium pool and the induced calcium flux. Notably, even though a recent RCT in 43 children aged between 6 and 18 years allowed serum calcium levels >2.20 mmol/L at inclusion, the mean ± SD calcium levels at baseline were 2.48 ± 0.14 mmol/L, and median (min–max) were 2.51 (2.23–2.70) mmol/L in the cinacalcet group [16]. Despite this, five patients (23%) in the cinacalcet group (versus 5% in the placebo group) developed hypocalcaemia (serum calcium <2 mmol/L) at any time during the double-blind phase. Three patients

Table 7. Proposed overview of therapeutic schedule in a pediatric dialysis patient eligible to receive cinacalcet therapy

In a child >3 years of age	Requirements before initiating cinacalcet therapy	Titration phase	Maintenance phase
Clinical parameters	Optimization of conventional management of CKD-MBD	Evaluation of potential side effects at every visit	Evaluation of potential side effects at every visit
		Cinacalcet withdrawal in case of symptomatic hypocalcaemia, long QTc interval or severe side effects	Cinacalcet withdrawal in case of symptomatic hypocalcaemia, long QTc interval or severe side effects
	Evaluation of calcium intake from diet, medications and dialysate	Evaluation of calcium intake from diet, medications and dialysate	Evaluation of calcium intake from diet, medications and dialysate
	Calculation of QTc interval	Realization of an ECG in case of hypocalcaemia	Realization of an ECG in case of hypocalcaemia; if ECG performed for another reason and increased QTc interval, cinacalcet withdrawal
	Evaluation of comorbidities of interest (seizures, cardiac arrhythmia, liver disease)		
	Explanation to parents		
Biological parameters	Calcium level ≥2.40 mmol/L	Weekly evaluation of calcium and phosphate levels	At least monthly evaluation of calcium and phosphate levels, target range for calcium within the normal range for age and in any case >2.2 mmol/L
		Cinacalcet withdrawal if calcium levels <2 mmol/L	Cinacalcet withdrawal if calcium levels <2 mmol/L and decrease/withdrawal if calcium levels between 2 and 2.2 mmol/L
	Persistent and secondary SHPT, no PTH threshold level clearly identified	Weekly evaluation of PTH levels, 12–24 h after cinacalcet administration	At least monthly evaluation of PTH levels, 12–24 h after cinacalcet administration, target range 100–200 pg/mL
		Cinacalcet withdrawal if PTH levels <100 pg/mL	Cinacalcet withdrawal if PTH levels <100 pg/mL
Therapeutic parameters	Verification of concomitant therapies that can interfere with cinacalcet	Starting dose of ≤0.2 mg/kg/day, increments by 0.2 mg/kg/day to a maximum of 2.5 mg/kg/day. Dose titration intervals should be at least 4 weeks	

(14%) in the cinacalcet group (versus none in the placebo group) displayed calcium concentration <1.87 mmol/L at any time during the double-blind phase. Visits to measure calcium levels were scheduled 5–7 days after any change in investigational product dose.

Potential symptoms of hypocalcaemia in children included muscle spasms (14% in the cinacalcet group versus 5% in the placebo group), myalgia (14 and 5%, respectively) and tremor (14 and 0%, respectively) [16]. A fatal adverse event in an adolescent girl with prolonged QT interval before starting cinacalcet therapy may have been caused by cinacalcet-induced hypocalcaemia. Although this could not be proven, this potential serious side effect should be kept in mind [16]. Overall, as illustrated in Tables 2–4, four prospective pediatric trials and one retrospective study demonstrated various incidences of hypocalcaemic episodes after cinacalcet exposure [16, 17, 19, 21, 22]. Based on the studies in children and the EVOLVE data showing a median decrease of 0.25 mmol/L of serum calcium levels in adults after cinacalcet initiation, we suggest a serum calcium level of 2.40 mmol/L (corresponding to a ionized calcium of ∼1.2 mmol/L) before initiating cinacalcet therapy in pediatric patients.

Before initiating cinacalcet, because of an increased risk of cardiac rhythmic abnormalities in case of hypocalcaemia, specific attention should also be given to baseline electrocardiogram (ECG, with a calculation of corrected QT, QTc), concomitant drugs and other comorbidies, especially if the patient is already at risk of cardiac complications. A calcium-independent effect on QTc has been suggested by one retrospective analysis [55]. The existence of a history of congenital long QT syndrome, second- or third-degree heart block, ventricular tachy-arythmias or other conditions associated with prolonged QT interval were exclusion criteria in the industry-sponsored trials evaluating cinacalcet in children: a QTc >500 ms using Bazett's formula was a formal contra-indication to cinacalcet, whilst a QTc between 450 and 500 ms required a consultation with a pediatric cardiologist.

The use of concomitant medications with the potential to increase the QTc or to interfere with cinacalcet metabolism needs to be carefully considered by the treating physician (Table 6). Subjects on anticonvulsive medication who received a stable dose of anti-epileptic drugs with a therapeutic blood level of the anti-convulsivant before cinacalcet therapy could be included.

The 2017 KDIGO guidelines suggest that adult dialysis patients can receive cinacalcet as a first- or second-line monotherapy or in combination with vitamin D analogues [25], but there is currently no evidence whether cinacalcet can be given as first-line therapy in pediatric patients on chronic dialysis.

Finally, even though some studies included infants and young children, as recommended by the EMA, we do not have evidence to support the use of cinacalcet in children <3 years of age. As summarized in Table 2, in the two RCTs, children were >6 years old [16].

What is the treatment schedule?

10. We recommend a starting dose of cinacalcet of ≤0.2 mg/kg/day based on dry weight rounded to the nearest whole dose unit (grade B, moderate recommendation).

11. The cinacalcet dose may be increased in increments of 0.2 mg/kg/day to a maximum daily dose of 2.5 mg/kg (not exceeding 180 mg) based on PTH levels provided that albumin-corrected calcium serum levels remain >2.2 mmol/L. Dose titration intervals should be at least 4 weeks (grade B, moderate recommendation).

12. Cinacalcet can be given orally or by nasogastric/gastric tube, once daily (ungraded).

13. We suggest that the minimal effective cinacalcet dose is used to maintain PTH levels in the desired PTH target range, taking into account its effects on calcium and phosphate concentrations (grade B, moderate recommendation).

14. We suggest to decrease cinacalcet dose when PTH levels are in the lower target range between 100 and 150 pg/mL, low for the individual patient or declining too rapidly, and to discontinue cinacalcet when PTH concentrations are below the target range (grade B, moderate recommendation).

15. We recommend that serum calcium levels are maintained within the normal range for age, by titrating conventional therapy including nutritional calcium intake, calcium-based phosphate binders, vitamin D analogues and dialysate calcium, and by titrating cinacalcet dose (grade B, moderate recommendation).

16. We suggest decreasing or withdrawing cinacalcet when albumin-corrected serum calcium levels fall <2.2 mmol/L (grade X, moderate recommendation).

Evidence and rationale. In the initial studies, the most common cinacalcet dose at initiation was 0.25 mg/kg/day, but higher doses of 0.4–1.1 mg/kg/day have been reported (Tables 2–4). In the two RCTs, the initiation dose was lower, namely 0.2 mg/kg/day based on dry weight [16]. Therefore, the EMA recommends a starting dose of ≤0.2 mg/kg/day in children undergoing dialysis. Cinacalcet is available as 1, 2.5 and 5 mg granules in capsules and 30, 60 and 90 mg tablets. For use in small children, capsules can be opened and the content mixed with purified water or United States Pharmacopeia/National Formulary (NF) (USP-NF) sucrose syrup as performed in the clinical trials; it is noteworthy that in the EMA, no particular food or liquid is specified. The mixture can then be administered orally through a syringe or by nasogastric (NG) or gastric tube [21]. Although administration of crushed cinacalcet tablets by NG is carried out in clinical practice [50], there is no data demonstrating bioequivalence between intact tablet and crushed tablet. Thus, tablet should not be crushed for NG administration given that the alternative of 'granules in capsule' exists, which is authorized for NG administration. It is important that capsules are not swallowed intact, as all the studies have been carried out based on opening capsules: as such, swallowing capsules may impact on bioavailability. Cinalcalcet is best being taken with food or shortly after a meal to improve bioavailability.

Based on the RCTs, cinacalcet dose may be titrated in steps of 0.2 mg/kg to a maximum daily dose of 2.5 mg/kg, and not exceeding 60 mg/day as per the pediatric RCTs, although doses as high as 180 mg/day are permitted as per the EMA report. In the recent pediatric RCT, the average prescribed weight-adjusted daily dose during the maintenance phase was 0.66 mg/kg, and the highest daily cinacalcet dose was 60 mg, the mean (range) maximum daily prescribed weight-adjusted daily dose being 0.70 (0.2–1.9) mg/kg [16]. The titration of cinacalcet dose should be based on serum calcium levels for safety issues and on PTH levels for efficacy issues. Intervals for dose adjustments should be at least 4 weeks. Obviously, in case of side effects like hypocalcaemia, there is no additional risk of acutely stopping cinacalcet therapy whatever the dose was.

The 2006 recommendations of the European Paediatric Dialysis WG suggest keeping PTH levels up to 2–3 times the UNL in dialysed children. Findings from the prospective observational studies performed since then are in line with these recommendations; respective RCTs have not been accomplished. As such, we do not have any evidence to change these recommendations with cinacalcet use [31, 56]. Therefore, based on limited evidence, we suggest that cinacalcet dose may be decreased in case of PTH levels between 100 and 150 pg/mL, and withdrawn if PTH levels fall <100 pg/mL.

How should a child on cinacalcet therapy be monitored?

17. We suggest that serum calcium levels are monitored within 1 week of starting cinacalcet therapy, weekly during the titration phase and at least monthly when maintenance dose has been established in a stable patient (grade C, moderate recommendation).

18. We suggest that PTH serum levels are checked on a monthly basis (grade B, moderate recommendation).

19. We recommend that children and their caregivers are informed of symptoms of hypocalcaemia, the importance of adherence to taking all medications regularly as well as instructions regarding serum calcium monitoring and caution about other medications which may prolong QTc interval or interact with cinacalcet (grade X, moderate recommendation).

20. We recommend that cinacalcet is withhold when albumin-corrected serum calcium levels are <2 mmol/L and/or ionized calcium levels are <1.0 mmol/L. Cinacalcet may be restarted in a lower dose when serum calcium levels return to the higher end of the normal range (grade X, moderate recommendation).

21. Withdraw cinacalcet in case of symptomatic hypocalcaemia, including paraesthesia, myalgia, cramps, tetany and

convulsions, long QT interval or severe side effects (grade X, strong recommendation).

Evidence and rationale. After a single-dose of cinacalcet, the nadir of serum calcium occurs at about 8 h [21]; depending on age, it may occur between 4 and 24 h, but in all age subgroups, calcium normalizes within 48 h [19], and may remain low for 48 h [57]. In this study including 12 pediatric patients on dialysis, 50% of subjects displayed asymptomatic moderate hypocalcaemia [19].

Cinacalcet also induces a dose-dependent decline in PTH levels [57]. After a single-dose of cinacalcet, the nadir of PTH occurs at 2 h, with a return to baseline levels between 8 and 12 h, and a secondary decrease at 48 h [19]. When cinacalcet is given daily, the nadir of calcium levels occur at 4 months, corresponding to a 0.25 mmol/L decrease from baseline in median calcium levels, with a stabilization of both calcium and PTH levels thereafter [13]. In adults, cinacalcet is suggested to be given in the evening, but it may also be given in the morning.

In line with the EMA, we recommend that during the titration period calcium, phosphate and PTH levels are monitored weekly in order to prevent symptomatic hypocalcaemia, and reducing cinacalcet dose or even withhold the drug if necessary. In addition to modifying cinacalcet dosing schemes, other measures to restore serum calcium levels into the normal range such as adapting conventional therapy (including calcium containing phosphate binders and active vitamin D) and nutritional calcium intake should be considered [31]. We recommend to maintain albumin-corrected serum calcium levels >2.2 mmol/L as a safety margin before symptomatic hypocalcaemia may occur (Table 7). In case of symptomatic hypocalcaemia, increased QTc or severe side effects, cinacalcet should be stopped immediately.

Once the maintenance dose has been established, weekly measurements of serum calcium are proposed by the EMA. However, this may be impractical especially in children on peritoneal dialysis. Since we propose a higher threshold of calcium levels before initiating cinacalcet, so as to stay in the 'safe zone', we suggest that follow-up may be reduced stepwise in stable and compliant patients, with at least a monthly assessment during long-term follow-up. In addition, we suggest that an ECG is performed in case of clinical symptoms pointing to hypocalcaemia or arrhythmia (e.g. tachycardia, bradycardia, shortness of breath, dizziness, syncope or near fainting). If an ECG demonstrates the presence of a prolonged QTc interval, cinacalcet should be withdrawn.

As summarized in Tables 2–4, the most important adverse events reported in pediatric trials of cinacalcet are the following: vomiting (32%), hypocalcaemia (23%), nausea (18%), abdominal pain (14%), headache (14%), hypertension (14%), muscle spasms (14%), myalgia (14%), tremor (14%), anxiety (9%), diarrhoea (9%), dizziness (9%), hypotension (9%), musculoskeletal stiffness (9%), constipation (5%), chills (5%) and cough (5%) [16]. In adults, increased QTc interval, worsening of cardiac function in patients with pre-existing impaired (systolic) cardiac function and hypophosphataemia have also been reported. We suggest that patients are made aware of the clinical symptoms of hypocalcaemia and remind any physician involved in the care of the child of cinacalcet use, so as to avoid drug interactions. An information sheet may be prepared in different languages and given to the child/parents at the time of cinacalcet initiation.

How should a pediatric patient with persistent severe SHPT despite conventional therapy and cinacalcet be treated?

22. We suggest that parathyroidectomy is considered in case of severe and persistent SHPT despite optimized cinacalcet and conventional therapy, including active vitamin D (grade C, weak recommendation).

Evidence and rationale. There are no data in the literature concerning pediatric patients with persistent severe SHPT despite conventional therapy and cinacalcet. A recent meta-analysis in adults showed that parathyroidectomy (as compared with cinacalcet therapy) significantly improved quality of life in dialysis patients treated for SHPT, but it did not compare directly these two strategies [58]. Nevertheless, we suggest that parathyroidectomy may be considered in case of persistent and severe SHPT after 6 months of appropriate dose cinacalcet treatment or earlier at the physician's discretion, if compliance problems have been ruled out, e.g. by giving cinacalcet during the haemodialysis sessions under supervision.

RESEARCH TOPICS TO BE DEVELOPED AND AUDITS TO BE PERFORMED

Clinical and experimental questions remain open in the field; audits may be performed on the safety and efficacy on long-term use of cinacalcet in children undergoing maintenance dialysis. The following research topics are suggested:

(i) To evaluate the efficacy and safety of long-term treatment with cinacalcet in dialysed children with special emphasis on bone health, cardiovascular comorbidity, longitudinal growth and side effects, including symptomatic hypocalcaemia in a 'real-world' setting. Outcomes may be better when using cinacalcet with low to moderate active D doses and an earlier start of cinacalcet, but this hypothesis will need to be evaluated.

(ii) Cinacalcet causes major diurnal fluctuations of PTH plasma concentrations [57], which may have anabolic actions on bone. Besides the parathyroid gland, the CaSR is also expressed in osteoblasts and osteoclasts [59]. Therefore, the direct effects of cinacalcet on bone should be evaluated *in vitro* and *in vivo*.

(iii) To design specific studies aiming at evaluating the use of cinacalcet in the youngest children (i.e. <3 years) that tend to have severe forms of SHPT.

(iv) The impact of cinacalcet therapy pre-transplant on nephrocalcinosis, bone health and vascular status after renal transplantation should be assessed.

(v) The outcomes of cinacalcet therapy after renal transplantation in case of persistent hyperparathyroidism with increased renal phosphate loss should be evaluated.

(vi) In adults, the 2017 KDIGO updated guidelines suggest to use calcimimetics, vitamin D analogues or a combination of both for SHPT [25]. Therefore, concepts of cinacalcet use as a first-line versus a second-line therapy should be evaluated in children on dialysis especially with respect to their differential impact on bone and vascular parameters.

(vii) An IV calcimimetic (etelcalcetide) is currently under investigation in pediatric populations and novel oral calcimimetics (evocalcet) are being developed; their potential use in pediatric populations will require a separate consensus.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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