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Mini-Review

Administration of cinacalcet in pediatric patients with CKD; a short-review on recent concepts

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Abstract

Cinacalcet shows promise in treating secondary hyperparathyroidism (sHPT) in both pediatric and adult chronic kidney disease (CKD) populations; however, its efficacy appears more pronounced in adults. Pediatric patients face unique challenges that can hinder treatment success, necessitating careful monitoring and individualized approaches to therapy. Further research is essential to optimize dosing strategies and improve outcomes for children receiving cinacalcet.

Keywords: Cinacalcet, Dialysis, Pediatrics, Chronic kidney disease, Secondary hyperparathyroidism, Hypocalcemia, End-stage kidney disease

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Introduction

Cinacalcet is a calcimimetic agent primarily administer to manage secondary hyperparathyroidism (sHPT) in adults on dialysis (1). Its prescription in pediatric populations, particularly those with chronic kidney disease (CKD), is less established, with varying regulatory approvals across regions (2). In Europe, cinacalcet is approved for children aged three years and older who are on dialysis and have inadequately sHPT (3). However, the administration of this agent in pediatric patients with CKD has attracted attention due to its potential benefits and associated risks; However, since the FDA has not yet approved it, this reflects a cautious approach stemming from limited safety data (3-5). The recent systematic review by Zamoner et al, highlighted significant adverse events associated with cinacalcet in children. Notably, the incidence of hypocalcemia was approximately 10.7%, and severe adverse events occurred in 16% of cases (6). Common side effects included hypocalcemia (22.8% incidence), vomiting (16.5%), nausea (15.2%), systemic hypertension (11.4%), and pyrexia and also muscle spasms in around 10% for each (6). However, mortality associated with cinacalcet use was rare, occurring in cases where patients were severely hypocalcemic at the time of death (7). Since, the metabolism of cinacalcet varies between children and adults, primarily due to differences in the development of cytochrome P450 enzymes and body surface area (1,8), we aimed to study the most recent concepts on the administration of this agent in children with CKD.

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase using different keywords like cinacalcet, dialysis, pediatrics, chronic kidney disease, secondary hyperparathyroidism, end-stage kidney disease and hypocalcemia.

Efficacy of cinacalcet in pediatrics versus adults

The efficacy of cinacalcet in managing sHPT in pediatric patients with CKD differs from that in adults, reflecting variations in treatment response and clinical outcomes (3). Cinacalcet is extensively metabolized by several CYP enzymes, including CYP3A4, CYP2D6, and CYP1A2 (1,8). The activity of these enzymes develops over time, with significant maturation occurring by approximately six years of age in children (3,8). In pediatric clinical trials, the efficacy of cinacalcet has shown variable results. Approximately 7.4% to 57.1% of pediatric subjects achieved parathyroid hormone (PTH) levels within recommended target ranges (3). Additionally, between 22.2% and 70.6% of participants observed at least a 30% reduction in PTH levels after treatment with cinacalcet (3). However, the multicenter, randomized, double-blind, placebo-controlled study by Warady et al indicated that, cinacalcet is effective and safe for children older than six years on dialysis, demonstrating significant reductions in PTH levels (9). Though, many pediatric patients experienced adverse effects, leading to

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Implication for health policy/practice/research/medical education

Cinacalcet may offer therapeutic benefits for managing sHPT in pediatric CKD patients; However, its administration should be approached with caution due to the risk of serious adverse events like hypocalcemia.

discontinuation of treatment in over half of the cases due to complications like hypocalcemia and poor response (2,3). Despite some positive outcomes, the overall success rate in achieving target PTH levels has been limited, with many children not reaching the desired therapeutic goals, often due to side effects or non-adherence (2,3). In contrast to pediatric patients with CKD, this compound has been well-established as an effective treatment for sHPT in adult individuals (2,10). The previous study by Susantitaphong et al showed that a significant proportion of adult patients experience substantial reductions in PTH levels, with achieving target ranges effectively (11). Likewise, this drug has also been shown to reduce the need for parathyroidectomy in adults with end-stage kidney disease (12). Meanwhile, cinacalcet is also approved by regulatory bodies like the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in adults with sHPT on dialysis, reflecting robust evidence supporting its efficacy and safety profile (1,3). It should remember that, the variability in response among pediatric patients may be attributed to factors such as age-related pharmacokinetics, dosing challenges, and a higher incidence of adverse effects (3,13). Pediatric patients are more susceptible to serious adverse events like hypocalcemia, which can limit the effective use of cinacalcet and impact overall treatment success (2,3).

Cinacalcet dosing in pediatrics versus adults

Pediatric patients metabolize drugs differently than adults; while, their capacity to metabolize drugs matures over time (8,14,15). By age six years, they may require approximately 50% of the adult dose based on body surface area considerations. For instance, a 6-year-old child may require approximately 50% of the adult dose due to their smaller body surface area (8,13). The recommended starting dose for adults is typically 30 mg/d. Doses may be adjusted based on serum calcium and PTH levels, with increments of 30 mg as necessary (1,3). For pediatric patients, the starting dose is generally calculated based on body weight, with a common recommendation of 0.2 mg/kg/day for children receiving dialysis. Adjustments should be made based on individual response and tolerability. For children under six years old, dosing options started from 1 mg and may increase according to the condition, particularly serum PTH concentration (3). For children aged six years and over, doses can begin from 2.5 mg and may be increased to reach the optimum value of PTH. This dose adjustments reflect a broad titration range due to differences in metabolism and body surface area (3).

Adverse events associated with cinacalcet

In pediatric studies, diarrhea is reported as one of the common adverse events associated with cinacalcet (1). The systematic review by Zamoner et al indicated that serious adverse events, including diarrhea, were observed in pediatric patients with CKD (6). However, the overall incidence of diarrhea was not specified as a standalone statistic in the reviewed literature (16). In adult populations, the incidence of gastrointestinal side effects, including diarrhea, is also noted but tends to be lower than in pediatric patients (3). For instance, a meta-analysis showed that gastrointestinal issues such as nausea and vomiting are more prevalent than diarrhea specifically (17). The overall adverse event profile in adults suggests that gastrointestinal disturbances may occur, however they are often less severe compared to those seen in children (1,3).

Conclusion

The metabolism of cinacalcet differs significantly between children and adults due to variations in enzyme activity and body size. Pediatric dosing is generally lower and more individualized, reflecting the need for careful management to optimize therapeutic outcomes while minimizing risks.

Authors' contribution

Conceptualization: Paniz Pourpashang, Sayed Yousef Mojtahedi.
Data curation: Paniz Pourpashang.
Investigation: Paniz Pourpashang.
Project administration: Paniz Pourpashang.
Resources: Sayed Yousef Mojtahedi.
Supervision: Paniz Pourpashang.
Validation: Sayed Yousef Mojtahedi.
Visualization: Paniz Pourpashang.
Writing–original draft: Paniz Pourpashang.
Writing–review & editing: Sayed Yousef Mojtahedi.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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