Case Report

Role of Cinacalcet in Treating Cardiac Dysfunction Secondary to Hyperparathyroidism: A Case Series

Abstract

Cardiovascular disease is a leading cause of death in children with chronic kidney disease (CKD). A strong correlation exists between disturbed calcium–phosphate metabolism and cardiac dysfunction. Studies with use of cinacalcet in CKD are few and limited to older children and adults and in improving growth and bone deformities. We present three children with CKD on CAPD with cardiac dysfunction with refractory hyperparathyroidism. Patients were initiated on lowest adult weight-adjusted dose of 0.2 mg/kg/day. Dose was titrated every 30 days to achieve decline in iPTH to a goal of 200– 300 pg/ml. Serum calcium, phosphorus and iPTH levels were checked monthly. Complications of therapy related to cinacalcet monitored. Monthly echocardiography done to monitor cardiac dysfunction. None of them experienced significant adverse effects of cinacalcet therapy.

Keywords: *Cardiac dysfunction, chronic kidney disease, cinacalcet, pediatric, peritoneal dialysis*

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Introduction

Cardiovascular disease is leading cause of death in children with chronic kidney disease (CKD). Increased parathyroid hormone (iPTH) secretion, hyperphosphatemia and hypercalcaemia contribute to cardiovascular morbidity and mortality by causing vascular calcification. Children with CKD often develop high iPTH levels that remain uncontrolled even after activated vitamin D analogues and phosphate binders.[1,2] Studies with use of cinacalcet in CKD are few, limited to older children, and have only studied effects on growth. This is the first report to our knowledge evaluating role of cinacalcet in treating cardiac dysfunction associated with refractory hyperparathyroidism in children.

Cases

We present three patients with ages 51, 57, 60 months (mean 56 ± 4.6 months); 2 male and one female. Their dialysis vintage was 39, 21, 12 months. Underlying aetiology was CAKUT in all the 3 patients. All of them were CKD stage 5 on CAPD with cardiac dysfunction with refractory sHPT on optimum CAPD prescription, well-controlled anaemia, hypertension and were treated with cinacalcet. Cardiac dysfunction was defined as episodes of respiratory distress with edema resolving with vigorous ultrafiltration (use of rapid cycles/2.5% dextrose) with corroborative echocardiography. Left ventricular hypertrophy was defined as LVMI >+2 Z scores.[3] Refractory sHPT was defined as sustained elevation of iPTH above 500 pg/ml for ≥30 days despite conventional therapy with phosphate binders, maintenance vitamin D and calcitriol.[4]

Initial dose of cinacalcet used was 0.2 mg/kg/day. Titration of dose was done every 30 days to achieve decline in iPTH to a goal of 200– 300 pg/ml as per Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. Serum calcium, phosphorus and iPTH levels were checked monthly. Complications of therapy related to cinacalcet monitored. Monthly echocardiography done to monitor cardiac dysfunction. All these patients also received ACE inhibitors/ARBs, anti-hypertensive medication, carvedilol and levocarnitine. Calcium supplementation with calcium carbonate was prescribed to maintain an albumin-corrected serum calcium between 8.5 and 10.5 mg/dl. Phosphate binders included the non-calcium binders sevelamer at doses of 800 to 2400 mg divided three to four times per day. Targets for serum phosphorus were set according to the KDOQI guidelines.

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Table 1: Summary of cinacalcet therapy

Patient no.	Initial dose (mg/kg/day)	Maximum dose used (mg/kg/day)	Peak iPTH (pg/ml)	Nadir iPTH (pg/ml)	Highest calcium (mg/dl)	Lowest calcium (mg/dL)
1	0.2	1.1	2337	302	12	9.8
2	0.2	0.4	2538	900	9.3	8.1
3	0.2	0.8	2683	627	9.6	9.1

Table 2: Comparison of biochemical, cardiac and growth parameters pre and post cinacalcet therapy

	Mean parameters 6 months pre-cinacalcet	Mean parameters on cinacalcet therapy	*P*
Mean Hb	10.57±0.25	10.27±1.1	0.67
Mean Ca X PO4	44.57±11.64	57.4±10.67	0.23
Mean EF	34.6±9.06	48.73±14.39	0.22
LVMI (*Z* scores)	2.45±0.3	1.67±0.5	0.08
Mean height gain	0.34±0.09	0.32±0.48	0.94

Mean duration of cinacalcet therapy 6.67 ± 1.52 months (5, 7, 8 months respectively). Initial dose used 0.2 mg/kg/day. Mean dose used 0.77 ± 0.35 mg/kg/day. Average iPTH pre-therapy was 2365.8 ± 362.3 pg/ml. Mean iPTH at last follow up was 609.67 ± 299.38 pg/ml. Average percentage decline in iPTH was 74.25%. [Table 1] There was significant clinical improvement in cardiac symptoms i.e., decrease in episodes of respiratory distress with edema, decreased requirement of vigorous ultrafiltration (use of rapid cycles/2.5% dextrose). Echocardiographic improvement in the form of improvement in mean EF from 34.6 ± 9.06% to 48.73 ± 14.39% and improvement in Z scores of LVMI was observed. Also, there was no significant difference in the haemoglobin levels, calcium and phosphorus products before and after therapy with cinacalcet which could have contributed to cardiac dysfunction and acted as a confounding factor [Table 2]. None of them experienced significant adverse effects of cinacalcet therapy.

Discussion

It is well recognized that consequences of poorly controlled sHPT are most severe in the young children, but paradoxically guidelines for management in this age group are not available. In adults, with uncontrolled sHPT, a calcimimetic is added to the therapeutic regimen and has been included in the KDIGO recommendations since 2009.[5]

In 2019, the results of 2 trials of cinacalcet in pediatric CKD patients were published in tandem.[6,7] The first was an open-label, single-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of cinacalcet in children aged 28 days to <6 years with CKD. Twelve subjects received a single dose of cinacalcet (0.25 mg/kg) orally or by nasogastric or gastric tube. Reductions in serum PTH levels from baseline were observed at 2 to 8 h post-dose which returned to baseline by 12–72 h. Single-dose cinacalcet was well-tolerated with safety profile similar to adults, concluding that, a single 0.25 mg/kg dose of cinacalcet was a safe starting dose in children aged <6 years. The second was a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet in pediatric patients with CKD and sHPT. However, due the death of a 14-year-old from what was believed to be a hypocalcemic seizure in February 2013, the study was terminated, but the results were still significant. After that the enthusiasm for use of cinacalcet decreased. No further published clinical trials have been undertaken by pharma or the pediatric nephrology community.

However, there are several case series published documenting the efficacy and safety of cinacalcet in pediatric population. In February 2018, Morales A *et al*. published their experience with cinacalcet in 10 paediatric CKD patients and studied their growth during treatment and had favourable results.[4] Several previous reports have demonstrated the safety and efficacy of cinacalcet treatment in suppressing iPTH secretion in children with normal renal function.[8–12] But none of these studies have used cinacalcet in patients with cardiac dysfunction. 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. However, evidence-based guidelines are lacking. Also use of cinacalcet in pediatric population has not been approved by FDA.[13]

This report entails our experience with a small cadre of young patients with advanced CKD who developed refractory sHPT leading to cardiac dysfunction and were safely and effectively treated with cinacalcet. In addition to safety and efficacy, we report improvement in cardiac dysfunction following reduction in iPTH levels after treatment with cinacalcet.

Conclusion

Cinacalcet may be used effectively in children <5 years with refractory sHPT with cardiac dysfunction on CAPD.

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Conflicts of interest

There are no conflicts of interest.

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