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EDITORIAL COMMENTARY

Oral paricalcitol: expanding therapeutic options for pediatric chronic kidney disease patients

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Abstract The complex pathophysiology of progressive chronic kidney disease (CKD) and the development of mineral and bone disorder, abbreviated as CKD-MBD, is of vital importance to a pediatric patient. Paricalcitol, the 19 nor-$1,25(OH)_2D_2$ analogue was shown to be effective and safe in the treatment of secondary hyperparathyroidism (SHPT) in adults almost two decades ago. It also significantly improved survival in dialysis patients compared to the standard calcitriol. The successful treatment of CKD-MBD in children is essential if they are to grow and survive into adulthood. It can be argued that it is more important for children with CKD than adults since they have early and prolonged disease risk exposure. In this issue of *Pediatric Nephrology*, Webb et.al. report a dual trial of the safety, efficacy, and pharmacokinetics of paricalcitol in children aged 10–16 years with moderate but significant efficacy in meeting the endpoint of >30% decrease in parathyroid hormone (PTH) levels from baseline with minimal adverse events. Much more research needs to be done to expand and develop clinical pharmaceutical trials in the use of paricalcitol in children, especially in the younger age categories. This current study has done much to open the doors for future studies, with the caveat that it has been long coming and much more needs to be done to compensate for this delay in the treatment of children with CKD-MBD and cardiovascular and renal disease progression.

Keywords Vitamin D · Paricalcitol · Hyperparathyroidism · Cardiovascular disease · Chronic kidney disease

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Introduction

Webb et al., in this issue of *Pediatric Nephrology*, publish a long-awaited phase 3 trial of the safety and efficacy of oral paricalcitol in children with advanced stages 3–5 of chronic kidney disease (CKD) and secondary hyperparathyroidism (SHPT) [1]. The report actually describes two trials according to CKD staging. The first (NCT 01020487) included 36 children with CKD stages 3–4 who were randomized into a double-blind placebo-controlled trial for an initial 12-week course followed by an open-label treatment period in which all enrolled subjects received the study drug. The second trial (NCT 01382212) included children on dialysis and was an open-labeled paricalcitol treatment course of 12 weeks with no placebo control due to the health risks of untreated SHPT in this category of patients. As expected, paricalcitol was largely effective and safe in decreasing the intact parathyroid hormone (PTH) levels from baseline by 30% on two consecutive assays and within the target ranges established by the Kidney Disease Outcomes Quality Initiative (KDOQI) according to CKD stage: stage 3, 35–69 pg/ml; stage 4, 70–111 pg/ml; stage 5, 150–300 pg/ml [2].

Importantly, the pharmacokinetic studies performed on 12 children in the CKD stages 3–4 trial demonstrated adequate absorption of the drug with levels higher in children compared to adults with CKD, leading to the initial dosing of 1 mcg three times weekly (TIW) in all subjects.

Vitamin D analogues: calcitriol versus paricalcitol

Vitamin D is synthesized in the skin or ingested in the diet and is eventually converted to the active metabolite $1,25(OH)_2D_3$ (calcitriol) by the kidney. Declining kidney function leads to phosphate retention and decreased production of calcitriol, the

two principal factors in the development of SHPT, a leading complication of CKD contributing to mineralization defects, bone fractures, growth retardation, and cardiovascular risks—all encompassed in the term CKD-MBD (CKD-mineral bone disorder) [3]. The discovery of fibroblast growth factor 23 (FGF23), a hormone produced by osteocytes and osteoblasts with strong phosphaturic properties, as a major cause for the decreased calcitriol synthesis, has further clarified the mechanisms leading to calcitriol deficiency and subsequent SHPT early in the course of CKD [4]. Calcitriol regulates the expression of PTH by suppressing transcription of pre-pro-PTH messenger RNA [5]. Thus, decreased calcitriol levels result in decreased activation of vitamin D receptors (VDRs) on the parathyroid gland, leading to increased expression and secretion of PTH. The treatment of SHPT involves some form of active vitamin D along with dietary phosphorus restriction and phosphorus-binding agents. Treatment with calcitriol reduces serum PTH levels and bone turnover, but also stimulates VDRs that increase intestinal absorption of calcium and phosphorus and suppress normal bone turnover, leading to frequent elevations in serum calcium and phosphorus levels that increase the risks of vascular calcifications and cardiovascular mortality [6, 7]. In addition, intermittent calcitriol therapy may result in adynamic bone disease and adversely affect growth advancement in children with CKD [8]. Therefore, while calcitriol effectively suppresses PTH, these untoward adverse effects limit its administered dose and prompted the development of vitamin D analogues capable of inhibiting PTH secretion while minimizing the effects of VDR activation elsewhere. Paricalcitol, 19-nor-1,25$(OH)_2D_2$, the most commonly used of these vitamin D analogues, achieves its site selectivity via removal of a methylene group from the carbon at position 19, and a D_2 side chain. Like calcitriol, paricalcitol suppresses pre-pro-PTH mRNA synthesis and has a prolonged effect on PTH inhibition, but compared to calcitriol, paricalcitol displays a decreased effect on intestinal calcium absorption and bone mobilization [9, 10]. The effects of paricalcitol in CKD are shown in Fig. 1.

Treatment trials: safety and efficacy

While various clinical trials conducted almost two decades ago demonstrated the effectiveness and safety of intravenous paricalcitol to attenuate SHPT in adult dialysis patients [11], data in children are limited to two studies, one prospective placebo-controlled trial [12] and one retrospective analysis comparing paricalcitol with calcitriol effectiveness [13]. Unfortunately, the use of intravenous paricalcitol has remained virtually limited to patients on maintenance hemodialysis who have regular intravenous access. Its use has not been feasible in patients with earlier stages of CKD who are not yet on dialysis but who constitute the largest segment of the CKD population with SHPT in both adults [14] and children [15]. Paricalcitol capsules were developed and approved by the US Food and Drug Administration (FDA) in 2005 for use in adults and found to have the same mechanisms of action as the intravenous preparation. Shortly thereafter, randomized trials in adults demonstrated its superior effectiveness compared with placebo to suppress PTH, high tolerability, and a low adverse effects profile [16]. A recent meta-analysis including all published studies in adults (n = 5) who received oral paricalcitol compared to placebo and that assessed changes in PTH reaching a 30% reduction from the maximum baseline at the end of treatment reported a statistically significant decreased pooled risk ratio (RR) for a decrease in PTH [RR 6.37; 95% confidence interval (CI) 4.64–8.74; $P < 0.001$]. These results underscore the significant effects of oral paricalcitol on improving SHPT in adults with CKD stages 2–4 [17]. Until now, similar data were not available in children.

Treatment targets and dosing regimens

There is a lack of consensus regarding optimal treatment targets for PTH levels in children with SHPT. The issue is particularly important for pediatric patients in that growth is a dynamic process, and serum PTH levels vary markedly with underlying bone turnover [18]. Whereas SHPT in children with advanced CKD is associated with lifelong deformities and vascular calcifications, over-suppression of PTH may cause growth arrest [8, 19]. Guidelines from the KDOQI have recommended maintaining serum PTH levels to within three- to fivefold above the upper limit of normal (200–300 pg/ml) [2]. In contrast, European guidelines advise keeping PTH levels to within two- to threefold above the upper limit of normal in children on dialysis [20], while others suggest even lower targets of 100–200 pg/ml (within 1.7- to threefold the upper limit of normal) [21].

The use of VDR activators in children with pre-dialysis CKD has been limited by regulatory issues, the lack of clearly defined recommendations [18], and the hitherto total absence of clinical trials demonstrating their effectiveness and safety in young patients [22]. In the current report by Webb et al. [1], a dose of 1 μg was given TIW as the initial dose in patients with CKD stages 3–4, all of whom had only mild elevations in PTH. This dose was extrapolated from weight-based dosing of 0.04 to 0.1 mcg/kg/dose provided in the drug brochure. In patients with stage 5 CKD, the initial dose was based on an adult-derived formula relative to the degree of hyperparathyroidism [23]. The dosing derivative formula was the PTH level in picograms per milliliter factored by 120 to provide an initial dose rounded down to the next whole number. As such, the average starting dose in the subjects with CKD stage 5 was presumably sevenfold higher (~900 pg/ml/120 = 7.5

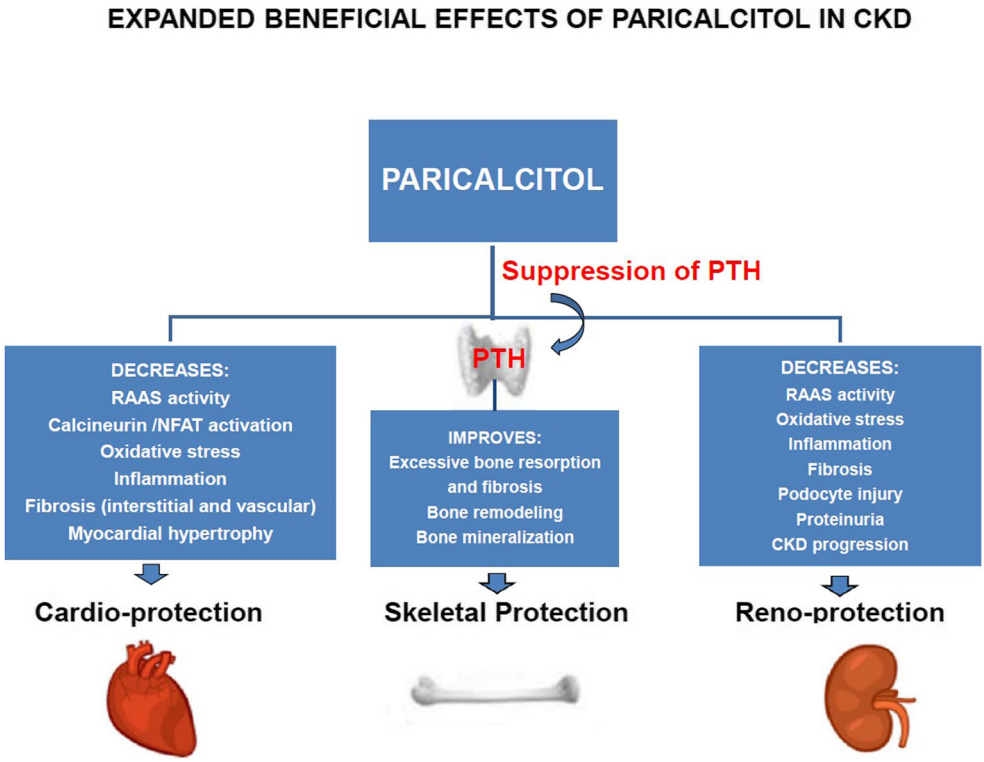

Fig. 1 Schematic depicting the expanded beneficial effects of paricalcitol, a vitamin D receptor (*VDR*) activator. In addition to its salutary role in suppression of parathyroid hormone (*PTH*) for the treatment of secondary hyperparathyroidism and chronic kidney disease (*CKD*)-mineral bone disorder, paricalcitol provides cardiac and renal protection, both of which are mediated through suppression of the renin–aldosterone–angiotensin system (*RAAS*) which decreases oxidative stress, inflammation, and fibrosis. Cardioprotection also occurs through inhibition of the calcineurin signaling regulator of nuclear factor of activated T lymphocytes (*NFAT*) which helps to decrease myocardial hypertrophy. Renoprotection is afforded through decreasing proteinuria via RAAS inhibition as well as by preservation of podocyte integrity

mcg/dose) than that in the CKD stage 3–4 group. A comparison of both dosing regimens demonstrated that the proportion of patients who achieved the primary outcome was twofold higher in the subjects with stage 5 CKD than in those with CKD stages 3–4 (62 vs. 28%, respectively) [1]. This result suggests that future trials in children should focus on dosing efficacy relative to the severity of hyperparathyroidism rather than on body weight, particularly in the smaller and younger patients who would be more likely to be under-dosed [13, 23].

Extended cardiovascular and renal protection

The low rate of adverse effects in the CKD 3–4 group is reassuring, particularly the absence of changes in estimated glomerular filtration rate (eGFR). The decline in the eGFR observed in some patients while receiving VDR activator therapy has been a lingering concern about their potential detrimental effects on kidney function and progression of CKD [24, 25]. To clarify this question, Agarwal et al. conducted a 1-week course study of oral paricalcitol, 2 mcg daily given to adults with CKD stages 3–4, and observed an increase in serum creatinine and urine creatinine, but no changes in clearance of creatinine, urea, or iothalamate [26]. These findings are consistent with the interpretation that VDR activator therapy alters creatinine metabolism but does not harm kidney function. In the most recent systematic review and meta-analysis of randomized clinical trials evaluating the effects of VDR activators on GFR and adverse events, the subgroup analysis of those studies where serum creatinine-based eGFR measurements were not used did not indicate lower eGFR in the VDR activator-treated groups compared to controls (weighted mean difference in eGFR of −0.97 ml/min/1.73 m^2, 95% CI −4.85 to 2.92) [27]. These findings have practical implications when designing clinical studies and remind us of the importance of selecting the most appropriate method to measure renal function in patients taking VDR activators, such as iothalamate, iohexol, or cystatin C, in pediatric studies [28], as was done appropriately in the recent study by Webb et al. [1].

This new study also opens new opportunities to evaluate potential benefits of VDR activator therapy on various aspects linked to reduced activation of the VDR in CKD, such as proteinuria, progression rate of CKD, and cardiovascular complications [24, 25]. Apart from modulating mineral metabolism, recent research with different experimental models of kidney disease has provided new insights into the cardio–renal protective properties of vitamin D and its analogues [29–32]. These protective effects are largely mediated via activation of the VDRs found ubiquitously throughout the body, including the kidney, myocardium, and blood vessels, and thus the VDRs participate in the regulation of blood pressure, volume homeostasis, protection of renal cellular integrity, and myocardial function [32–34].

Cardioprotection

Although the cardiovascular system is not traditionally regarded as a target of vitamin D, changes in VDR activation

are important in the development of left ventricular hypertrophy (LVH) in CKD, in part by modulating the renin–angiotensin–aldosterone system (RAAS) [29]. Experimental studies in the VDR-ablated and in the 1-α-hydroxylase knockout mouse show the development of hyperreninemia and LVH [29, 30]. Treatment with VDR activators, including paricalcitol, improves cardiac hypertrophy in hypertensive rats with normal renal function [30, 35]. Also, paricalcitol prevents cardiac hypertrophy and downregulates renin and other RAAS components in the myocardium of uremic rats [36]. In clinical studies, paricalcitol reduces cardiovascular mortality in dialysis patients [37], and calcitriol administration to treat SHPT in maintenance dialysis patients results in attenuated cardiac hypertrophy and improved longevity [38]. Further, emerging clinical trials provide supporting evidence that intravenous paricalcitol may contribute to cardiovascular and renal disease health in patients with advanced CKD [39, 40]. However, studies with oral paricalcitol in adults with moderate CKD found no significant effects on left ventricular mass index (LVMI) or LVH [25, 41], but lower left atrial volume index and brain natriuretic peptide levels were observed [42]. Similar studies are lacking in pediatric patients with CKD and suboptimal vitamin D status, a patient population with high rates of LVH [43–45] and cardiac-related deaths [46]. In contrast to adults whose blood pressure reductions are tightly related to reductions in LVM and LVH, in children with CKD, improved LVMI and LVH may be independent of blood pressure, suggesting that the observed echocardiographic changes may be related to other undetermined non-hemodynamic factors [47]. Among the potential non-traditional factors, the phosphaturic hormone FGF23 has emerged as a strong pro-hypertrophic molecule capable of causing myocardial hypertrophy [48]. Recent observations in children with advanced CKD indicate that treatment with paricalcitol can attenuate LVH despite persistently elevated FGF23 levels, suggesting that VDR activators may possess anti-hypertrophic properties independent of hemodynamic changes [34]. Children are particularly suited to evaluate the response of cardiovascular changes to therapeutic agents without the confounding factors frequently prevalent in adults, such as diabetes, chronic smoking, coronary artery disease, and aging. The study by Webb et al. [1] provides sound and safe dosing guidelines for oral paricalcitol and should open new opportunities for collaborative trials in pediatric patients to evaluate the effects of this VDR activator on various clinical endpoints described in this commentary.

Renoprotection

Vitamin D receptor activation regulates the expression of a large number of genes in the kidney, including the RAAS via suppression of the renin gene expression [29]. These landmark findings [31] provided the rationale for a series of experimental studies showing that the renoprotective efficacy of paricalcitol is largely mediated by suppression of the intrarenal RAAS [31]. The renoprotective effects of paricalcitol were enhanced when it was used in combination with a RAAS inhibitor [49]. This enhanced renoprotective effect by the combination therapy is the result of VDR-mediated blockade of the compensatory renin induction and angiotensin II (Ang II) accumulation frequently encountered with the use of RAAS inhibitors. In addition, $1,25(OH)_2D_3$ ablation causes proteinuria by directly affecting podocyte integrity and glomerulo-tubular damage, which is reversed following $1,25(OH)_2D_3$ administration [50]. These preclinical observations help explain the anti-proteinuric effects of paricalcitol in patients with mild to moderate non-diabetic CKD [51–53] and the results of the VITAL study of diabetic nephropathy patients [24]. This anti-proteinuric effectiveness was confirmed in a recent systematic review of randomized controlled trials which revealed that VDR activators reduced proteinuria by 16% on average, whereas, proteinuria increased by 6% in patients receiving control treatment ($P < 0.001$) [54]. Most of these patients were already taking chronic RAAS blocking agents, underscoring the capacity of vitamin D analogues to reduce residual proteinuria. To date, similar studies in children have not been attempted. Since an increase in albuminuria/proteinuria, with or without RAAS blockade, is a strong predictor of long-term renal disease progression in adults [55, 56], similar studies in children with proteinuric early to moderate stage CKD are needed. The aim of adjunctive therapies, such as paricalcitol, with or without RAAS blockade, would be to improve renal (and cardiovascular) protection in the long term.

Conclusion

Although we applaud the publication of the multi-center trial on the safety and efficacy of paricalcitol in the treatment of children with CKD and SHPT by Webb et al. [1], it is important to emphasize the ongoing need to study therapeutic options in children related to CKD-MBD and the cardiorenal syndrome in early life. This study should also serve as a wake-up call since studies in children have lagged almost two decades behind landmark studies in adults. Why is this the case? Younger children (<10 years of age) and dosing regimens have not been addressed. More research is needed to define appropriate PTH targets in children. Most importantly, the urgency for including children of all ages in pharmaceutical trials must be squarely addressed if we are to advance treatment regimens to support growth and longevity.

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