REVIEW ARTICLE

**Port J Nephrol Hypert 2010; 24(4): 263-271**
Advance Access publication 27 September 2010

# Paricalcitol in the treatment of secondary hyperparathyroidism

Punit Yadav, Adriece Al-Rifai, Fouad Al Baaj

**City Hospital. Birmingham, UK.**

**Received for publication:** 01/08/2010
**Accepted in revised form:** 06/09/2010

## ABSTRACT

Secondary hyperparathyroidism is a known complication of chronic kidney disease. It occurs very early as the renal functions continue to decline and is seen in response to a series of biochemical abnormalities, namely phosphorus, calcium and $1,25(OH)_2$vitamin $D_3$. These abnormalities not only initiate but also maintain increased PTH secretion.

Dietary phosphate restriction, phosphate binders (by minimising the stimulus for development of hyperparathyroidism) and vitamin D analogues are currently used in the management of secondary hyperparathyroidism.

Paricalcitol is a new generation selective vitamin D receptor activator that lowers PTH levels by exerting a less hypercalcaemic and hyperphosphataemic effect. In addition, there is emerging evidence of the benefit of paricalcitol in preventing intravascular calcification and proteinuria.

**Key-Words:**
CKD – chronic kidney disease; HD – haemodialysis; PD – peritoneal dialysis; PTH – parathyroid hormone; VDR – vitamin D receptor; VDRA – vitamin D receptor activator; SHPT – secondary hyperparathyroidism.

## INTRODUCTION

Paricalcitol is well absorbed from the gastrointestinal tract and achieves a mean absolute bioavailability of approximately 72% following oral administration. In patients on haemodialysis the mean absolute bioavailability is 79% and is 86% in patients on peritoneal dialysis[2].

With single intravenous dosing the mean peak plasma concentrations following doses of 0.04, 0.08 and 0.24 mcg/kg in healthy subjects were found to be 256, 664 and 1242pg/mL respectively[1].

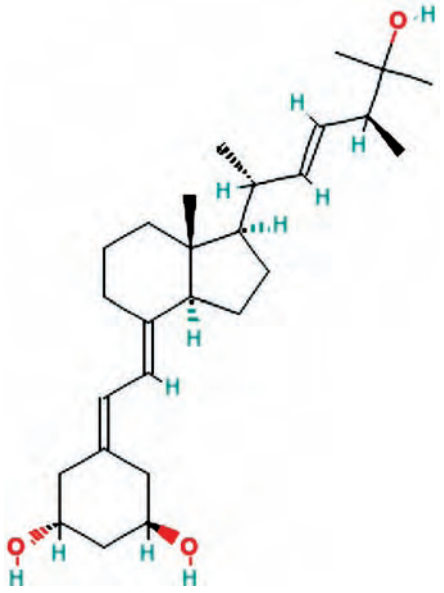

**Figure 1**

Paricalcitol (19-nor-1α-25-dihydroxyvitamin $D_2$) is a synthetic vitamin D analogue, with a molecular weight 413.636g/mol and molecular formula $C_{27}H_{44}O_3$. It differs structurally from calcitriol by the absence of an exocyclic carbon at position 19 and by the presence of a vitamin $D_2$ side chain instead of a vitamin $D_3$ side chain[1].

Following an oral administration of paricalcitol at a dose of 0.24mcg/kg, the mean maximum plasma concentration (Cmax) and time to Cmax (Tmax) are 0.630 ng/mL and 3 hours respectively. Absorption of paricalcitol is not significantly affected by consumption of food. In circulation it is extensively protein bound and achieves >99% protein binding over a wide range of concentration (1-100ng/ml)[3].

## METABOLISM

I*n vitro* data suggest that paricalcitol is extensively metabolised by multiple hepatic and nonhepatic enzymes, which include CYP24, CYP3A4 and UGT1A, with only 2% of the dose eliminated unchanged in faeces[2]. Findings from *in vivo* animal studies detected two minor metabolites in the plasma. Only one was identified, as 24(R)-hydroxy paricalcitol, which is less active than paricalcitol[2].

## EXCRETION

Paricalcitol is mainly excreted via the hepatobilary route with 63% to 75% present in faeces. Approximately 18-19% of the drug is renally excreted with no parent drug detected in the urine[3,4]. It has been proposed that the total body clearance in healthy individuals is between 2.5-45L/hr, somewhat reduced in chronic kidney disease (CKD) stage 5 to 0.7L/hr[1,2]. Clearance is independent of dose and similar after single or multiple doses in healthy subjects.

In healthy subjects, following administration of a range of doses between 0.04 and 0.16 mcg/kg, the mean elimination half-life is approximately 5-7 hours. The mean elimination half-life of paricalcitol after administration of 0.24 mcg/kg paricalcitol IV bolus dose in CKD Stage 5 HD and PD patients is 13.9 and 15.4 hours, respectively.

## INTERACTIONS

Ketoconazole, a potent cytochrome P450 isoenzyme CYP3A4 inhibitor, can potentially increase the bioavailability of paricalcitol by 50%, which in turn prolongs the half-life of paricalcitol from 9.8 to 17 hours. Thus the theoretical interaction with other potent inhibitors of the cytochrome p450 isoenzyme CYP3A4 (protease inhibitors, azole antifungal and macrolides) cannot be ruled out and PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor such as ketoconazole.

A small study reviewing the concurrent administration of paricalcitol and omeprazole concluded the pharmacokinetics of paricalcitol were unaltered[4].

Drugs that impair intestinal absorption of fat-soluble vitamins, such as cholestyramine, may interfere with the absorption of paricalcitol capsules.

## PARICALCITOL AND VDR SELECTIVITY

Paricalcitol is a biologically active synthetic vitamin D analogue indicated for prevention of secondary hyperparathyroidism in patients with chronic kidney disease. It lowers parathyroid hormone level by inhibiting PTH synthesis and release. It acts by binding to the vitamin D receptor (VDR) and subsequent activation of the vitamin responsive pathways. The vitamin D receptor is ubiquitous and has been detected in tissues such as parathyroid glands, cardiac myocytes, arterial smooth muscle cells, osteoblasts, intestines, kidney (renal tubules, podocytes) and bone marrow[5].

*In vivo*, biologically active vitamin D [1, 25-$(OH)_2D_3$] promotes intestinal absorption of calcium, phosphorus and aids bone mineralisation. This activity is mediated via vitamin D receptors. 1,25-$(OH)_2D_3$ bind to VDR leading to a conformational change, which allows it to bind to retinoid X receptor (RXR). This complex binds to a specific sequence in the vitamin responsive element leading to either an increase or decrease in gene transcription[6].

Structural and conformational differences exist between the selective and nonselective VDRA which is responsible for the therapeutic selectivity[7]. The difference in selectivity results from variable interaction with vitamin D receptor, coactivator recruitment and tissue selectivity. This in turn is responsible for selective suppression of parathyroid hormone and differential effect on the small intestine and bone[8]. Paricalcitol

with modification in the side chain (D2) and A ring (19-nor) is noted to exert less hypercalcaemic and hyperphosphataemic effect than 1,25-$(OH)_2D_3$[8,9].

Paricalcitol has been shown to induce differential binding between coactivators and VDR compared with calcitriol. Certainly, these differences were not explained by the difference in the dose of the VDRAs. In animal studies, treatment with calcitriol was associated with an increase in intestinal VDR contents, whereas treatment with paricalcitol was not[35]. Furthermore, a 10-fold greater dose of paricalcitol compared with calcitriol was needed to produce similar increase in calcium levels. Moreover, paricalcitol did not increase serum phosphate levels at any dose but calcitriol was associated with significant rise. On the contrary, paricalcitol produced a similar decrease in PTH at doses similar to these of calcitriol[9,35].

## PARICALCITOL AND PTH

Paricalcitol is the first selective vitamin D receptor analogue approved for use in secondary hyperparathyroidism in patients with chronic kidney disease.

### Paricalcitol vs. placebo

Safety and efficacy of paricalcitol in reducing intact parathyroid hormone level in patients on haemodialysis was assessed over a 12-week study in three double-blind, placebo-controlled, dose-escalating, randomised multicentre trials. Subjects were started on paricalcitol at a dose 0.04 mcg/kg three times a week and titrated up to the maximal acceptable dose of 0.24 mcg/kg or until at least a 30% decrease in serum PTH was achieved. Patients on paricalcitol achieved a significant 60% reduction in PTH and the target reduction of more than 30% was attained in 87% of patients at some point during the study period. Minor increment in serum calcium was noted; however levels remained within the reference range. Serum phosphate levels were not significantly different for the total duration of the study[10].

Long term safety and efficacy of paricalcitol was evaluated in a 13-month multicenter open-label study conducted by Lindberg *et al.* on 164 patients with end-stage renal failure on haemodialysis. Patients were commenced on paricalcitol at a dose of 0.04-0.393 mcg/kg given two to three times per week. The mean PTH levels (baseline mean 628.3 ± 27.65 pg/ml) decreased rapidly during the first 4 months of therapy, and reached the designated target range (100-300 pg/ml) by month 5 (mean 295.3 ± 25.69 pg/ml). A maximum mean decrease in PTH level of 409 ± 35.01 pg/ml was seen at month 13. Mean serum calcium, serum phosphorus and calcium×phosphate product remained within the reference range for the total duration of the study[11].

Similarly, Ross *et al.* investigated the effect of oral paricalcitol on PTH levels in patients receiving chronic haemodialysis and peritoneal dialysis. 88 patients were randomised in a double-blind placebo-controlled study over a period of 12 weeks. Patients on paricalcitol had a significant decrease in PTH after the first week with a mean 30% reduction by the third week. Importantly, a greater proportion of patients on haemodialysis (83%) and peritoneal dialysis (100%) achieved two consecutive more than 30% reductions in PTH. They also noted improvement in markers of bone activity in paricalcitol treated subjects[12].

Efficacy of paricalcitol capsules in treatment of secondary hyperparathyroidism in patients with CKD stages 3 and 4 was assessed by Coyne *et al.* in three randomised, placebo-controlled phase-3 trials. Out of the three trials two studies used a thrice-weekly dosing regimen and one study used a once-daily dosing regimen based on baseline PTH levels over 24 weeks. Out of the 227 patients 91% in the paricalcitol group met the primary endpoint of two consecutive decreases in intact parathyroid levels of 30% or more than the placebo group. Incidences of hypercalcaemia, hyperphosphataemia and elevated calcium-phosphorus product levels were not significantly different between the paricalcitol and placebo groups. Likewise, no significant differences in urinary calcium and phosphorus excretion or deterioration in kidney function were detected in the two groups. Paricalcitol was well tolerated and there was no significant difference in the incidence of adverse events when compared to placebo[13].

### Paricalcitol vs. nonselective VDRA

Several studies have confirmed the ability of paricalcitol in achieving quicker and sustained reduction of PTH levels when compared to a nonselective VDRA.

Sprague *et al*. compared paricalcitol with calcitriol in treatment of secondary hyperparathyroidism. A double-blind, randomised, multicentre study was conducted comparing the safety and effectiveness of intravenous paricalcitol and calcitriol in suppressing PTH levels in patients on haemodialysis. Paricalcitol was dosed at a 4:1 ratio to calcitriol, initiated at 0.04µ/kg and 0.01µ/kg respectively, and titrated to a maximum of 0.24µ/kg and 0.06µ/kg respectively. Results obtained from the study over the period of 32 weeks revealed paricalcitol treated patients achieved primary endpoint, i.e. a more than 50% reduction in baseline PTH significantly faster than the calcitriol group. Mean reduction of PTH into a desired therapeutic range (100-300pg/ml) was achieved at approximately week 18 whereas the calcitriol group was unable to achieve the same. Moreover, fewer sustained episodes of hypercalcaemia and or increased calcium×phosphorus product was noted with paricalcitol[14].

Llach and colleagues assessed the efficacy of paricalcitol for the treatment of secondary hyperparathyroidism in a long-term, prospective, open-label study of 37 patients with end-stage renal failure resistant to intravenous calcitriol. Fourteen patients were commenced on paricalcitol at a 4:1 ratio and the remaining twenty-three were initiated at a 3:1 dose conversion ratio to calcitriol. They noted no significant change in mean levels of serum calcium or serum phosphorus over the 16 months of therapy with paricalcitol. There was a significant decline in the mean PTH levels (from 901±58 pg/ml) during the first two months which was sustained for the total duration of the study with mean PTH levels of 165±24 pg/ml at the end of 16 months. Mean paricalcitol dose was significantly reduced almost six to seven times over the total duration of the study whilst maintaining sustained suppression of PTH. A 3:1 paricalcitol dosage was seen to provide the smoothest control of PTH throughout the course of the study[15].

A single centre cross-over study evaluated the efficacy of paricalcitol in patients who were switched to the selective VDRA after 6 months' treatment on calcitriol. Results obtained showed significantly lower serum calcium, calcium×phosphorus product, PTH and serum alkaline phosphatase levels in patients after 6 months' treatment with paricalcitol than calcitriol. Patients were found to have missed fewer doses of paricalcitol compared with calcitriol in this study, emphasising the better tolerability and efficacy of paricalcitol[16].

Another cross-over study demonstrated significant improvement in PTH levels in 6 patients on haemodialysis with uncontrolled secondary hyperparathyroidism who were converted to intravenous paricalcitol from intravenous alfacalcidol whilst maintaining stable serum calcium and phosphorus levels[17].

## PARICALCITOL AND CALCIUM

Calcitriol usage in secondary hyperparathyroidism is associated with an increase in serum calcium levels whereas paricalcitol promotes less calcium resorption.

Lund and colleagues recently conducted a study which compared intestinal calcium absorption in patients with end-stage renal failure on haemodialysis treated with calcitriol versus paricalcitol (dose ratio 1:3). Twenty-two patients on haemodialysis were involved in a single centre, double-blind, active-controlled, randomised cross-over trial. Results obtained revealed approximately 14% less calcium absorption in paricalcitol-treated patients and hence less availability of calcium for deposition in bone and other soft tissues[9].

Sprague and colleagues also found the incidence of hypercalcaemia and or increased calcium×phosphorus product significantly lower in the paricalcitol group compared to calcitriol (18% *vs*. 35%, p=0.008)[14].

## PARICALCITOL AND VASCULAR CALCIFICATION

The mechanisms by which vascular calcification is produced are complex. Vascular calcification in patients with chronic kidney disease may occur as a result of disequilibrium between promoters and inhibitors of vascular calcification. There is a growing list of inhibitors and promoters of vascular calcification; some have traditionally been considered "modifiable factors", such as PTH, calcium, and phosphorus.

Cardus and colleagues aimed to assess the effects of calcitriol and its analogue paricalcitol on vascular smooth muscle cell (VSMC) calcification *in vitro* and *in vivo*. Calcitriol was noted to be associated with increased calcification of VSMCs cultured in the calcification media. Moreover they also noted increased expression of (receptor activator for nuclear factor κ B ligand) RANKL or osteoprotegerin in cells incubated with calcitriol. Despite having similar levels of serum calcium and serum phosphorus as animals treated with calcitriol, this increase in calcification was not noted in the arteries of animals treated with paricalcitol[18].

Mizobuchi *et al*. compared the effects of treatment with calcitriol, paricalcitol and doxercalciferol on vascular calcification in uraemic rats over a period of 1 month. Both calcitriol and doxercalciferol were associated with a significant increase in the serum Ca×P product and aortic calcium content confirmed by von Kossa staining. In addition, to ascertain if increased aortic calcium content was due to increased Ca×P product or due to a differential effect of the two VDRA, the investigators lowered the dose of doxercalciferol and increased the dose of paricalcitol. A lowered dose of doxercalciferol did not increase the Ca×P product but was still associated with increased aortic calcium content which was not seen with higher doses of paricalcitol. Doxercalciferol but not paricalcitol was also associated with increased protein expression of the bone-related markers Runx2 and osteocalcin in the aorta. Hence this data suggested a mechanism other than high Ca×P product in induction of vascular calcification as noted with doxercalciferol and lack of calcification with paricalcitol in uraemic rats[19].

Similar finding were observed by Noonan and colleagues who demonstrated differential effects of paricalcitol and doxercalciferol on aortic calcification and pulse wave velocity which was independent of serum calcium, phosphorus and calcium×phosphorus, suggesting different mode of action amongst vitamin D receptor activators[20].

## PARICALCITOL AND BONE HISTOLOGY

The effect of vitamin D analogues paricalcitol and calcitriol on bone mineral was studied by Balint and colleagues using a neonatal mouse calvariae. They determined calcium flux, osteocalcin, acid and alkaline phosphatase activity and interleukin-6 (IL-6) release after incubating the mouse calvariae with either paricalcitol or calcitriol for 48 hours. Their data revealed that at low concentrations both compounds were associated with similar calcium efflux from the cultured bone but paricalcitol had no effect on osteocalcin, acid and alkaline phosphatase activity. At higher doses both calcitriol and paricalcitol had a similar effect on acid phosphatase and osteocalcin activity but calcitriol and not paricalcitol was noted to inhibit alkaline phosphatase release. They concluded that paricalcitol at therapeutic doses did not seem to inhibit osteoblast activity, which may explain the lower hypercalcaemic property associated with paricalcitol[21].

Jokihaara *et al*. aimed to explore the effects of paricalcitol on bone structure and strength in a model of advanced renal disease. Forty-five 8-week-old rats were randomly assigned to either surgical 5/6 nephrectomy or Sham operation. After 15 weeks of postoperative period these rats were further randomly allocated to uraemic control or treatment groups receiving paricalcitol for a subsequent 12 weeks. At the femoral neck the uraemic control group was associated with 8.1% decrease in bone mineral density and similarly 6.6% decrease at the femoral midshaft region, whereas paricalcitol treatment completely prevented these changes[22].

## PARICALCITOL AND RENIN ANGIOTENSIN SYSTEM (RAS)

The role of ACE inhibitors in controlling blood pressure, decreasing proteinuria and preventing left ventricular remodelling is well known.

Mizobuchi *et al*. tried to establish any additional benefits of combination therapy with angiotensin converting enzyme inhibitor and vitamin D analogue in suppressing the progression of renal insufficiency in uraemic rats. The rats were made uraemic by 5/6 nephrectomy and treated in the following groups namely, uraemic + vehicle (UC), uraemic + enalapril (E), uraemic + paricalcitol (19 nor) and uraemic + enalapril + paricalcitol (E+ 19 nor). The results obtained revealed decreased urinary protein

excretion in the enalapril and enalapril + paricalcitol group. Both the glomerulosclerotic index and tubulointerstitial volume were significantly decreased in both the enalapril and enalapril + paricalcitol groups. TGF-beta1 mRNA and protein expression were virtually normalised in the enalapril + paricalcitol group, which is considered to be a major stimulating factor for fibrogenesis. Hence paricalcitol in combination with angiotensin converting enzyme inhibitors can suppress the progression of renal impairment via the mediation of TGF-beta signalling pathway[23].

In another study Husain and colleagues investigated the benefit of combination therapy with enalapril and paricalcitol on cardiac oxidative stress in uraemic rats. After 4 months of treatment they observed significant reduction in cardiac NAPH oxidase activity. Cardiac malondialdehyde, a biochemical marker of coronary artery disease, was significantly increased in the uraemic rats. Only combination therapy was associated with inhibition of malondialdehyde activity. Combination therapy was also noted to protect against the reduction of cardiac glutathione and alterations in cardiac superoxidase dismutase activity[24].

Freundlich and colleagues demonstrated the benefit of paricalcitol in decreasing levels of angiotensinogen, renin, renin receptors, and vascular endothelial growth factor mRNA levels by 30-50% in animal studies. Animals on paricalcitol also exhibited improvement in glomerular and tubulointerstial damage, hypertension and proteinuria. This study did suggest the benefit of the vitamin D receptor activator, at least in part due to the down-regulation of renin-angiotensin (RAS) pathway[25].

The role of combination therapy (losartan and paricalcitol) in more effective renin-angiotensin system (RAS) inhibition by blockage of compensatory renin release was demonstrated by Zhang and colleagues in a streptozotocin (STZ)-induced type 1 diabetes model. The investigators encountered complete prevention of albuminuria, restoration of glomerular filtration barrier structure, and marked reduction in glomerulosclerosis with combined losartan and paricalcitol treatment. Combination treatment was not only associated with suppression of fibronectin, TGF-beta and monocyte chemotactic protein-1, but also was noted to reverse the decline of slit diaphragm proteins nephrin, Neph-1 and alfa actinin-4. Hence combined treatment is clearly effective in inhibition of RAS and progression of diabetic nephropathy[26].

Similar benefits were seen in a model of type 2 diabetes by Deb and colleagues when combination treatment was used[27].

## PARICALCITOL AND PROTEINURIA

Proteinuria is a known marker of cardiovascular disease and progression of renal impairment in patients with chronic kidney disease and reduction in proteinuria is associated with improvement in cardiovascular and renal outcome.

In three double-blind, randomised, placebo-controlled trials, Agarwal and colleagues aimed to assess the safety and efficacy of paricalcitol in patients with stages 3 and 4 chronic kidney disease over a period of 24 months. In addition to other parameters, proteinuria was measured at the start and end of the trial period. Out of the total 107 patients on oral paricalcitol 57 patients presented with baseline proteinuria. 29 (51%) of the 57 patients had significant reduction in proteinuria at the end of the trial period. The investigators concluded that paricalcitol was associated with significant reduction in proteinuria and this action was independent of demographics, comorbidities and use of medications that block the rennin-angiotensin system[28].

Alborzi *et al.* conducted a double-blind randomised trial in 24 patients with chronic kidney disease to understand the effects of vitamin D on endothelial function (by measuring flow-mediated dilatation and highly sensitive CRP), blood pressure, albuminuria and inflammation in patients with renal impairment. In the study patients were randomly allocated equally to 3 groups to receive 0, 1, or 2 mcg of paricalcitol orally for a period of 1 month. Results obtained revealed no difference in GFR measurement, 24-hour ambulatory blood pressure or parathyroid hormone with treatment or on washout. Albuminuria increased by 35% in the placebo group and decreased by 48% in the 1mcg paricalcitol group and 46% in the 2mcg paricalcitol group. Likewise highly sensitive CRP was noted to increase by 50% in the placebo group and decrease by 20% in the 1mcg paricalcitol group and 30% in the 2mcg paricalcitol group[29].

Similar findings were echoed by Fishbane and colleagues in a recent study with significant reduction in protein excretion in patients with proteinuric renal disease[30].

The VITAL (Selective VITamin D Receptor Activator (Paricalcitol) in Albuminuria Lowering) study is a phase 2, prospective, randomised, double-blind, placebo-controlled, multicentre study to evaluate the safety and efficacy of Paricalcitol capsules on reducing albuminuria in Type 2 diabetic nephropathy subjects who are currently being treated with renin-angiotensin inhibitors. In this trial patients were equally allocated to receive paricalcitol 1mcg/day, 2 mcg/day or placebo. Initial results revealed a significant 17% decrease in albuminuria in patients on 1mcg/day paricalcitol and similarly 19% reduction in patients on 2mcg/day paricalcitol. Moreover, there was a 5mmHg drop in systolic blood pressure in patients who were on 2mcg/day paricalcitol. Detailed report from the VITAL study is due to be published later this year[37].

## PARICALCITOL AND MORTALITY/ SURVIVAL

Several studies have pointed towards significant survival benefit for patients with end-stage renal disease on haemodialysis.

A landmark historical cohort study compared 36-month survival rate of paricalcitol or calcitriol in 67,399 patients receiving long term haemodialysis. A subgroup of patients who switched treatment was analysed separately. Results obtained showed a significant difference and improvement in survival as early as 12 months of treatment, which increased with time in patients on paricalcitol. The 2-year survival rate amongst the patients who switched to paricalcitol from calcitriol exhibited a similar result (73% amongst patients on paricalcitol *vs.* 64% on calcitriol)[31]. However, this study left many unanswered questions; importantly it did not examine VDRA *vs.* no VDRA therapy. It was also unclear if observed mortality benefits of paricalcitol existed when compared to agents other than calcitriol. Moreover, it was not apparent if these findings can be extended to nondialysis populations. In addition, no dose response effect was examined. Finally, it was as-treated analysis rather than intention-to treat (ITT).

Similar findings were discovered in another study which compared all-cause and cardiovascular deaths in patients on haemodialysis receiving vitamin D analogue versus no vitamin D treatment. Mortality rates were found to be similar in patients on doxercalciferol (15.4%) and paricalcitol groups (15.3%) and on the other hand calcitriol (19.6%) was associated with a higher mortality rate[32].

Shinaberger and colleagues studied 3-year mortality predictability of administered paricalcitol to serum parathyroid level in patients on maintenance haemodialysis. Subjects were divided into 4 groups and various variables such as unadjusted, case mix-adjusted and malnutrition-inflammation complex syndrome was evaluated. Study revealed higher weekly paricalcitol dose was associated with greater survival in patients on haemodialysis[33].

## PARICALCITOL AND HOSPITALISATION

Dobrez and colleagues investigated the influence of vitamin D therapy on the total number of hospital admissions, total number of hospital days and time to first hospitalisation in a retrospective study which included 11443 adult haemodialysis patients. When compared to patients on calcitriol, the paricalcitol group of patients had lower first all-cause hospitalisations (14% less, $p<0.0001$), less admission to a hospital per year (0.642 less, $p<0.001$) and fewer hospital days spent (6.84 fewer, $p<0.001$). Based on their findings a total cost saving from $7600 to $1100 per patient per year was estimated from reduced hospitalisation days of initiating treatment with paricalcitol. They also found that paricalcitol was generally well tolerated; almost 94.4% of patients who were commenced on paricalcitol remained on it compared to only 58.7% in the calcitriol group[36].

## LOCAL EXPERIENCE

We have been using paricalcitol in our satellite haemodialysis unit for some time with good results. Out of total 70 haemodialysis patients, 25 were commenced on paricalcitol. Paricalcitol was not used as a first-line and only in very difficult patients

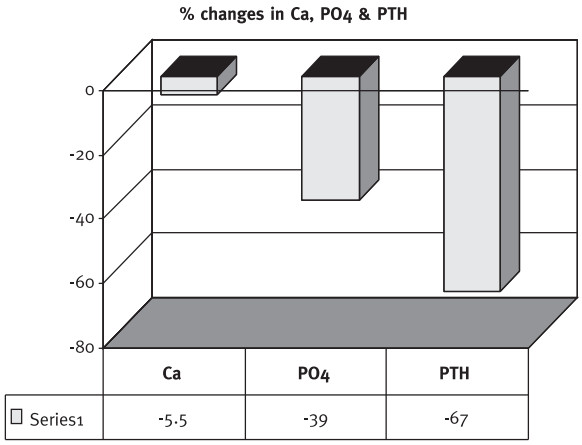


**Figure 2**

Local experience with Paricalcitol.

who failed to respond to alfacalcidol and experienced hypercalcaemia secondary to the disease or to treatment. We present our results/data in patients who have adequate haemodialysis and have been on paricalcitol for one year or more. Paricalcitol dose ranged 2-8 mcg three times weekly. We found significant reduction in PTH (67%, mean 1175 pg/ml to 365 pg/ml), phosphate (39%) and calcium (5.5%) levels from baseline. Furthermore, paricalcitol was well tolerated in all our patients (Figure 1). In addition, we found that use of paricalcitol resulted in lowering PTH and subsequently smaller doses will be needed in future treatment. This was also experienced by LLach and colleagues[15].

## FUTURE DEVELOPMENT

Currently, there are several ongoing studies aiming to highlight the efficacy of paricalcitol. The IMPACT SHPT study aspires to evaluate the improved management of PTH with paricalcitol-centred therapy *vs.* cinacalcet with low dose vitamin D in haemodialysis patients with secondary hyperparathyroidism. A randomised, double-blind, placebo-controlled trial is in progress to assess the vascular benefits of paricalcitol in kidney transplant recipients. This study will primarily assess graft function and secondly left ventricular and large blood vessels pulse velocity response with paricalcitol.

## CONCLUSION

Paricalcitol is selective VDRA with minimal impact on serum calcium and phosphorus levels. It has been largely used in haemodialysis patients for its efficacy in the treatment and prevention of secondary hyperparathyroidism. Treatment with paricalcitol demonstrated improved survival, fewer hospitalisations and shorter hospital days. It is generally well tolerated. There is increasing body of evidence about its properties in modulating proteinuria, reducing blood pressure, cardiovascular remodelling and attenuating renal fibrosis. We think its usage is likely to expand further in future by involving patients with chronic kidney disease and renal transplant recipients.

***Conflict of interest statement.*** F.A.B. received consulting and speaking fees from Shire, Amgen and Abbott.

**Table I**

Studies examining outcomes associated with treatment with Paricalcitol.

| Study | Year | No of patients | Populations | Examined treatment |
|---|---|---|---|---|
| Lutwak (38) | 1998 | 197 | HD | Paricalcitol *vs.* Calcitriol |
| Llach F | 1998 | 35 | HD | Paricalcitol *vs.* Placebo |
| Martin KJ | 1998 | 88 | HD | Paricalcitol *vs.* Placebo |
| Teng M | 2003 | 67399 | HD | Paricalcitol *vs.* Calcitriol |
| Sprague SM | 2003 | 263 | HD | Paricalcitol *vs.* Calcitriol |
| Hansen D (39) | | 117 | HD | Paricalcitol *vs.* Alfacalcidol |
| Teng M | 2005 | 51037 | HD | Paricalcitol, Calcitriol *vs.* no treatment |
| Kalantar-Zadeh | 2006 | 1007 | HD | Paricalcito *vs.* no treatment |
| Tentori | 2006 | 7731 | HD | Any VDRA *vs.* no treatment |
| Coyne D | 2006 | 220 | CKD 3+4 | Paricalcitol *vs.* Placebo |
| Ross EA | 2008 | 88 | HD and PD | Paricalcitol *vs.* Placebo |

## References


1. Goldenberg MM, Paricalcitol, a new agent for the management of secondary hyperparathyroidism in patients undergoing chronic renal dialysis, Clin Ther 1999;2:432-41
2. http://emc.medicines.org.uk/medicine/20464/SPC/Zemplar
3. Summary basis of decision (SBD), paricalcitol
4. Palaparthy R, Pradhan RS, Chan J, *et al.* Effect of omeprazole on the pharmacokinetics of paricalcitol in healthy subjects, Biopharm Drug Dispos 2007;28:65-71
5. Cozzolino M, Brancaccio D. Emerging role for the vitamin D receptor activator (VDRA), paricalcitol, in the treatment of secondary hyperparathyroidism, Expert Opin Pharmacother 2008;9:947-54
6. Slatopolsky E, Dusso A, Brown A, New analogs of vitamin D3, Kidney Int (Suppl.) 1999;73:S46-51
7. Carlberg C, Quack M, Herdick M, Bury Y, Polly P, Toell A. Central role of VDR conformations for understanding selective actions of vitamin D3 analogues. Steroids 2001;66:213-21
8. Brown AJ, Coyne DW. Vitamin D analogs: new therapeutic, agents for secondary hyperparathyroidism. Treat Endocrinol 2002;1:313-27
9. Lund RJ, Andress DL, Amdahl M, Williams LA, Heaney RP. Differential effects of paricalcitol and calcitriol on intestinal calcium absorption in hemodialysis patients, Am J Nephrol 2010;31:165-70
10. Martin KJ, González EA, Gellens M, Hamm LL, Abboud H, Lindberg J. 19-Nor-1-alph a-25-dihydroxyvitamin D2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis, J Am Soc Nephrol 1998;9:1427-32
11. Lindberg J, Martin KJ, González EA, Acchiardo SR, Valdin JR, Soltanek C. A long-term, multicenter study of the efficacy and safety of paricalcitol in end-stage renal disease, Clin Nephrol 2001;56:315-23
12. Ross EA, Tian J, Abboud H, *et al.* Oral paricalcitol for the treatment of secondary hyperparathyroidism in patients on hemodialysis or peritoneal dialysis, Am J Nephrol 2008;28:97-106
13. Coyne D, Acharya M, Qiu P, *et al.* Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD, Am J Kidney Dis 2006;47:263-76
14. Sprague SM, Llach F, Amdahl M, Taccetta C, Batlle D. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism, Kidney Int 2003;63:1483-90
15. Llach F, Yudd M. Paricalcitol in dialysis patients with calcitriol-resistant secondary hyperparathyroidism, Am J Kidney Dis 2001;38(Suppl 5):S45-50
16. Mittman N, Khanna R, Rani S, Chattopadhyay J, Avram MM. Paricalcitol therapy for secondary hyperparathyroidism in patients on maintenance hemodialysis previously treated with calcitriol: A single-center crossover study Paricalcitol after calcitriol therapy in HD, Kidney Int 2006;70:S64-S67
17. Vervoloet MG, Grooteman MP, Ter Wee PM. Improved parathyroid hormone levels after conversion from intravenous alfacalcidol to intravenous paricalcitol(abstract number PUB343), American Society of Nephrology (ASN) 39th Renal Week Meeting;2006 Nov 14-19; San Diego (CA).
18. Cardus A, Panizo S, Parisi E, Fernandez E, Valdivielso JM. Differential effects of vitamin D analogs on vascular calcification. J Bone Miner Res 2007;22:860-6
19. Mizobuchi M, Finch JL, Martin DR, Slatopolsky E. Differential effects of vitamin D receptor activators on vascular calcification in uremic rats. Kidney Int 2007; 72:709-15
20. Noonan W, Koch K, Nakane M, Ma J, Dixon D, Bolin A, Reinhart G. Differential effects of vitamin D receptor activators on aortic calcification and pulse wave velocity in uraemic rats, Nephrol Dial Transplant 2008;23:3824-30
21. Balint E, Marshall CF, Sprague SM. Effect of the vitamin D analogues paricalcitol and calcitriol on bone mineral in vitro, Am J Kidney Dis 2000;36:789-96
22. Jokihaara J, Porsti I, Pajamaki I, *et al.* Paricalcitol [19-nor-1,25-(OH)2D2] in the treatment of experimental renal bone disease, J Bone Miner Res 2006;21:745-51
23. Mizobuchi M, Morrissey J, Finch JL, Martin DR, Liapis H, Akizawa T, Slatopolsky E. Combination therapy with an angiotensin-converting enzyme inhibitor and a vitamin D analog suppresses the progression of renal insufficiency in uremic rats, J Am Soc Nephrol 2007;18:1796-806
24. Husain K, Ferder L, Mizobuchi M, Finch J, Slatopolsky E. Combination therapy with paricalcitol and enalapril ameliorates cardiac oxidative injury in uremic rats, Am J Nephrol 2009;29:465-72
25. Freundlich M, Quiroz Y, Zhang Z, *et al.* Suppression of renin-angiotensin gene expression in the kidney by paricalcitol, Kidney Int 2008;74:1394-402
26. Zhang Z, Zhang Y, Ning G, Deb DK, Kong J, Li YC, Combination therapy with AT1 blocker and vitamin D analog markedly ameliorates diabetic nephropathy: blockade of compensatory renin increase, Proc Natl Acad Sci U S A. 2008 Oct 14;105(41):15896-901.
27. Deb DK, Sun T, Wong KE, *et al.* Combined vitamin D analog and AT1 receptor antagonist synergistically block the development of kidney disease in a model of type 2 diabetes, Kidney Int 2010;77:1000-9
28. Agarwal R, Acharya M, Tian J, *et al.* Antiproteinuric effect of oral paricalcitol in chronic kidney disease, Kidney Int 2005;68:2823-8
29. Alborzi P, Patel NA, Peterson C, Bills JE, Bekele DM, Bunaye Z, Light RP, Agarwal R. Paricalcitol reduces albuminuria and inflammation in chronic kidney disease: a randomized double-blind pilot trial. Hypertension 2008;52:249-55
30. Fishbane S, Chittineni H, Packman M, Dutka P, Ali N, Durie N. Oral paricalcitol in the treatment of patients with CKD and proteinuria: a randomized trial, Am J Kidney Dis 2009;54:647-52
31. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med 2003;349:446-56
32. Tentori F, Hunt WC, Stidley CA, *et al.*Mortality risk among hemodialysis patients receiving different vitamin D analogs, Kidney Int 2006;70:1858-65
33. Shinaberger CS, Kopple JD, Kovesdy CP, McAllister CJ, van Wyck D, Greenland S, Kalantar-Zadeh K. Ratio of paricalcitol dosage to serum parathyroid hormone level and survival in maintenance hemodialysis patients, Clin J Am Soc Nephrol 2008;3:1769-76
34. Lee GH, Benner D, Regidor DL, Kalantar-Zadeh K. Impact of kidney bone disease and its management on survival of patients on dialysis, J Ren Nutr 2007;17:38-44
35. Slatopolsky E, Finch J, Ritter C, Takahashi F. Effects of 19-nor-1,25(OH)2D2, a new analogue of calcitriol, on secondary hyperparathyroidism in uremic rats. Am J Kidney Dis 1998;32(Suppl 2):S40-7
36. Dobrez DG, Mathes A, Amdahl M, Marx SE, Melnick JZ, Sprague SM. Paricalcitol--treated patients experience improved hospitalization outcomes compared with calcitriol-treated patients in real-world clinical settings, Nephrol Dial Transplant 2004;19:1174-81
37. Dick de Zeeuw. The effect of Paricalcitol on Proteinuria in stage ¾ CKD patients (the VITAL study). Selective VDR Activation and the Cardio-Renal Syndrome Congress. 12-13 March 2010; Paris
38. Lutwak L. Medical officer's review. Paricalcitol injection (on-line). Available from: URL:http://fda.gov/cder/foi/nda/98/20819_Zemplar.htm.
39. Hansen D, Brandi L, Rasmussen K. Treatment of secondary hyperparathyroidism in haemodialysis patients: a randomised clinical trial comparing Paricalcitol and alfacalcidol. BMC Nephrol 2009;10:28



**Correspondence to:**
Dr Fouad Al Baaj
170 Ravenhurst Road
Harborne
Birmingham B17 9HS
U.K.
fouad.albaaj@swbh.nhs.uk