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Paricalcitol Therapy for Secondary Hyperparathyroidism

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ABSTRACT

Chronic kidney disease (CKD) is characterized by reduced synthesis of 1,25-dihydroxyvitamin D_3 (calcitriol), inadequate renal phosphate (P) clearance, and hypocalcemia, which together contribute to the development of secondary hyperparathyroidism (SHPT). Although the skeletal effects of SHPT have been appreciated for decades, emerging evidence now suggests that abnormalities in mineral, parathyroid and vitamin D physiology in CKD patients might also be linked to their excess rates of cardiovascular disease, particularly those patients on dialysis. The cornerstone of therapy for SHPT in dialysis patients has been intravenous vitamin D and until recently, the most widely used preparation was calcitriol. However, calcitriol treatment is associated with significant risk of hypercalcemia and/or hyperphosphatemia, due to increased gastrointestinal tract absorption of calcium (Ca) and P. Increased Ca and P may be important risk factors contributing to the progression of cardiovascular disease in CKD and thus, these shortcomings of calcitriol spurred the development of novel vitamin D analogs with greater specificity for PTH suppression relative to their gut effects. One such analog is 19-nor-1,25-dihydroxyvitamin D_2 (paricalcitol), which is widely used in the United States. Differences in the biology of calcitriol and paricalcitol led to a large study that detected a significant survival advantage of paricalcitol over calcitriol. In this review, we provide an overview of normal vitamin D physiology, its disordered regulation in CKD and present the literature regarding paricalcitol therapy for the management of SHPT, emphasizing the survival data.

NORMAL VITAMIN D PHYSIOLOGY

The precursor to calcitriol (pro-vitamin D_3) can be ingested orally (in fortified milk or fish,

for example) or formed endogenously in the skin where the sun catalyzes the temperature-dependent conversion of 7-dehydrocholesterol, pro-vitamin D_3, to pre-vitamin D_3 in the presence of ultra violet (UVB) radiation from the sun.[1-3] In most human beings, 90-100% of vitamin D originates from exposure to sunlight.[4] Orally ingested or endogenously formed vitamin D_3 circulates in the blood bound to vitamin D binding protein (DBP) and is transported to the liver where it is converted to 25-hydroxyvitamin D_3 by 25-hydroxylase in an unregulated step. The 25-hydroxyvitamin D_3 is the storage form of vitamin D. When stimulated by hypophosphatemia, PTH or hypocalcemia (which acts via increased PTH), renal 1-α-hydroxylase converts 25-hydroxyvitamin D_3 to biologically active 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), or calcitriol.[5]

Calcitriol is essential for normal bone development, promotes GI absorption of dietary Ca and P renal tubular reabsorption of these minerals. Calcitriol also exerts feedback inhibition at the level of the parathyroid, which serves to suppress PTH secretion and limits glandular hyperplasia. These actions are mediated by calcitriol-induced alterations in gene transcription in target tissues that express the vitamin D receptor (VDR).[6] Importantly, VDR is expressed in far more tissues that those limited to mineral and PTH metabolism, leading to so-called non-traditional actions of vitamin D.[7-10] Indeed, among these non-traditional actions include inhibitory effects on the renin-angiotensin system and the development of left ventricular hypertrophy, potentially important factors in the development of cardiovascular disease among the CKD population.[11-18]

VITAMIN D IN CHRONIC KIDNEY DISEASE

Calcitriol levels decrease early and progressively across the spectrum of CKD.[19,20] The cause is multifactorial and includes nutritional vitamin D deficiency, insufficient vitamin D uptake, urinary loss of vitamin D in patients with high grade proteinuria, hyperphosphatemia, uremia and, of course, reduced activity of the renal 1-α-hydroxylase.[21-23] Either way, the reduction in calcitriol leads to loss of feedback inhibition on the parathyroids, which along with the development of hypocalcemia and hyperphosphatemia, results in increased PTH secretion and progressive glandular hyperplasia.[24-27] As CKD progresses, the severity of this SHPT worsens necessitating treatment.

The skeletal effects of SHPT are well known and include osteitis fibrosa cystica with its associated increased risk of fracture.[28-30] Only in the last few years, however, has evidence emerged to suggest that abnormalities in mineral, PTH and vitamin D in patients with CKD might also be linked to their excess rates of cardiovascular disease, particularly those patients on dialysis. Interestingly, most of the studies that have identified an association between altered mineral metabolism and increased risk of mortality on dialysis have not consistently taken into account the impact of vitamin D therapy.

VITAMIN D THERAPY FOR SECONDARY HYPERPARATHYROIDISM

Intravenous calcitriol was introduced in the 1980s and was found to effectively reduce serum PTH levels in hemodialysis (HD) patients.[31] In the parathyroids, calcitriol decreases PTH gene transcription, increases VDR expression, suppresses parathyroid hyperplasia and increases expression of the calcium-sensing receptor on the cell surface.[5,32-35] However, intravenous calcitriol was found to be associated with hypercalcemia and/or hyperphosphatemia, owing to its effects in the gastrointestinal tract

to increase the intestinal absorption of Ca, P, and the calcium-phosphorus product (CaxP).[36,37] Furthermore, increased serum Ca, P, and Cax P, which are the main side effects associated with calcitriol therapy, may contribute to increased cardiovascular morbidity and mortality in patients with end-stage renal disease (ESRD).[38-42] Clinical guidelines have suggested that treatment with vitamin D should be interrupted if these side effects develop, and the result is often a rebound increase in PTH levels. These limitations of calcitriol therapy stimulated the development of novel vitamin D analogs. The goal was to design compounds that could retain the desirable PTH suppressive effects while minimizing the undesirable hypercalcemic and hyperphosphatemic side effects.

PARICALCITOL: A NOVEL VITAMIN D STEROL

Currently, there are several commercially available vitamin D analogs worldwide. This review focuses on paricalcitol or 19-nor-1,25-dihydroxyvitamin D_2. In pre-clinical studies of uremic rats, paricalcitol was as effective as calcitriol in suppressing PTH levels but did not cause significant increases in Ca or P.[43] Other rat studies showed that paricalcitol is approximately 10-fold less effective in mobilizing Ca and P from the skeleton compared with calcitriol.[44,45] In a more recent study of intestinal Ca and P absorption in normal and uremic rats, 2 weeks of treatment with paricalcitol caused significantly less Ca and P absorption relative to calcitriol.[46] Consistent with these animal studies, Coyne, *et al* showed that in human HD patients paricalcitol provides profound PTH suppression while stimulating bone resorption and/or intestinal absorption of Ca and P to a lesser degree than calcitriol, resulting in less elevation of serum Ca and P.[47]

These preliminary data were extended in additional human studies of paricalcitol. Llach, *et al* demonstrated that paricalcitol safely and effectively suppressed PTH with no clinically relevant increases in serum Ca or P levels.[48] These results were verified in additional studies.[49-51] Finally, Llach and Yudd showed that paricalcitol could provide long-term control of moderate to severe SHPT in HD patients considered to be resistant to calcitriol therapy, and mean Ca and P levels did not change significantly during the treatment period.[52] In the first head-to-head comparisons of calcitriol and paricalcitol by Sprague, *et al*, paricalcitol was associated with more rapid achievement of PTH control than calcitriol and with significantly fewer sustained episodes of hypercalcemia or increased Ca X P product than calcitriol therapy.[53,54]

PARICALCITOL AND HEMODIALYSIS PATIENT SURVIVAL

Recent studies have implicated disorders of mineral and PTH metabolism in the excessive risk of cardiovascular mortality in ESRD patients.[38-42,55] Given these observations and the differential effects of paricalcitol and calcitriol on PTH suppression and their relative incidence of hypercalcemia and hyperphosphatemia, Teng *et al* performed an observational study that compared the survival of patients treated with either of the two injectable, active vitamin D preparations.[56] The study population consisted of HD patients from over 1,000 dialysis centers in the United States operated by Fresenius Medical Care, the largest dialysis provider in the US. Patients were included in the study if they initiated treatment with intravenous paricalcitol or calcitriol treatment between January 1, 1999 and December 31, 2002. The primary analysis fo-

cused on patients who were treated exclusively with the same vitamin D formulation throughout the follow up period but a secondary analysis of patients who switched from one vitamin D formulation to the other was also performed. Demographic and clinical data along with laboratory values were collected prospectively by Fresenius staff, in real time, at the individual dialysis units during the study period. The primary outcome was patient survival. Importantly, Fresenius offered its physicians management guidelines to target iPTH levels to <300 pg/mL and calcium phosphate products (Ca x P) to <70 but they did not delineate specific management strategies to achieve these goals.

Absolute mortality rates were calculated by dividing the number of patients who died during the follow up period by the number of person years of observation within each treatment group. Kaplan Meier time-to-event (all cause mortality) analysis was used to evaluate crude survival. Patients were censored if they reached the end of the study period, underwent kidney transplantation, or transferred to a non-Fresenius facility. Cox proportional hazards regression analysis was used to adjust for potential confounders, including age, sex, race, etiology of ESRD, diabetes status, duration of dialysis, study entry period, standardized mortality rates of individual dialysis units, dialysis access, and baseline laboratory values.

The overall study population included 67,399 patients, 29,021 of who were treated with paricalcitol and 38,378 treated with calcitriol. Among the baseline measurements, Ca, P, and iPTH were significantly higher in paricalcitol treated patients compared to calcitriol treated patients (Table 1). Paricalcitol treated patients were more likely to be black (P<0.01) and have arteriovenous fistulas for vascular access (P<0.01) and less likely to have diabetes (P<0.01). Other baseline measurements were similar between the 2 groups.

During the 36 month study period, the mortality rate in the paricalcitol group was 3,417 per 19,031 person years of observation (0.18 per person year), compared to 6,805 deaths per 30,471 person years (0.223 per person year) in the calcitriol group (relative risk ratio 0.80; 95% confidence interval, 0.77 to 0.84; P < 0.001). This survival difference became evident at 12 months and continued to increase with time (P<0.001) (Figure 1A). After adjusting for potential confounders using Cox proportional hazards models, paricalcitol treated patients demonstrated a 16% survival advantage compared to calcitriol treated patients (95% confidence interval, 10% to 21%; P < 0.001). Paricalcitol was associated with a reduction in mortality due to cardiovascular disease, infection, and other causes. Furthermore, the 14,862 patients who switched from calcitriol to paricalcitol demonstrated a significant survival advantage compared to the 1,621 patients who switched from paricalcitol to calcitriol (Figure 1B: subsequent 2-year survival 73% versus 64%; P = 0.04).

Stratified analyses were performed to assess for effect modification (Figure 2). Factors that were stratified were age, gender, race, diabetes, etiology of ESRD, access type, duration of dialysis prior to starting vitamin D therapy, and Ca, P and PTH levels at the start of therapy. Paricalcitol treated patients demonstrated a significant survival advantage in 28 of the 42 strata examined and in no stratum was calcitriol superior. While increases in the baseline Ca, P, and iPTH levels were independently associated with increased mortality as has been shown in previous studies[38-42], the risk of death for the paricalcitol group was lower than calcitriol in each of the quintiles of Ca, P, and iPTH.

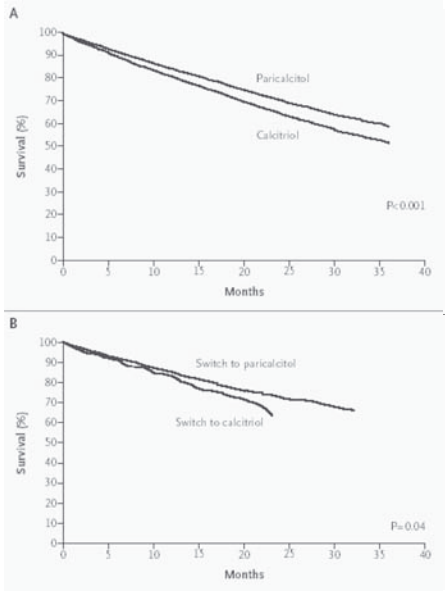
The results of this large historical cohort study suggest that among HD patients treated with vitamin D, patients treated with paricalcitol had a significant survival advantage compared to

Table 1. Baseline characteristics according to vitamin D therapy

Characteristic	Paricalcitol	Calcitriol	P Value
Ca (mg/dL)	8.7±0.8	8.5±0.9	<0.01
P	5.6±1.6	5.3±1.5	<0.01
iPTH	496±364	413±336	<0.01

Derived from 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(5):446 456. Copyright © 2003, Massachusetts Medical Society. All rights reserved.

Figure 1.



Kaplan Meier Analysis of Survival According to the Type of Vitamin D Therapy. Panel A shows the survival of patients treated with either paricalcitol or calcitriol who received the same therapy for the duration of the follow up. Panel B shows the survival of patients who switched from calcitriol to paricalcitol or from paricalcitol to calcitriol during the follow-up period. The time of switching was approximately 900 days after the initiation of dialysis for both groups. *P* values were calculated with the use of the log-rank test.

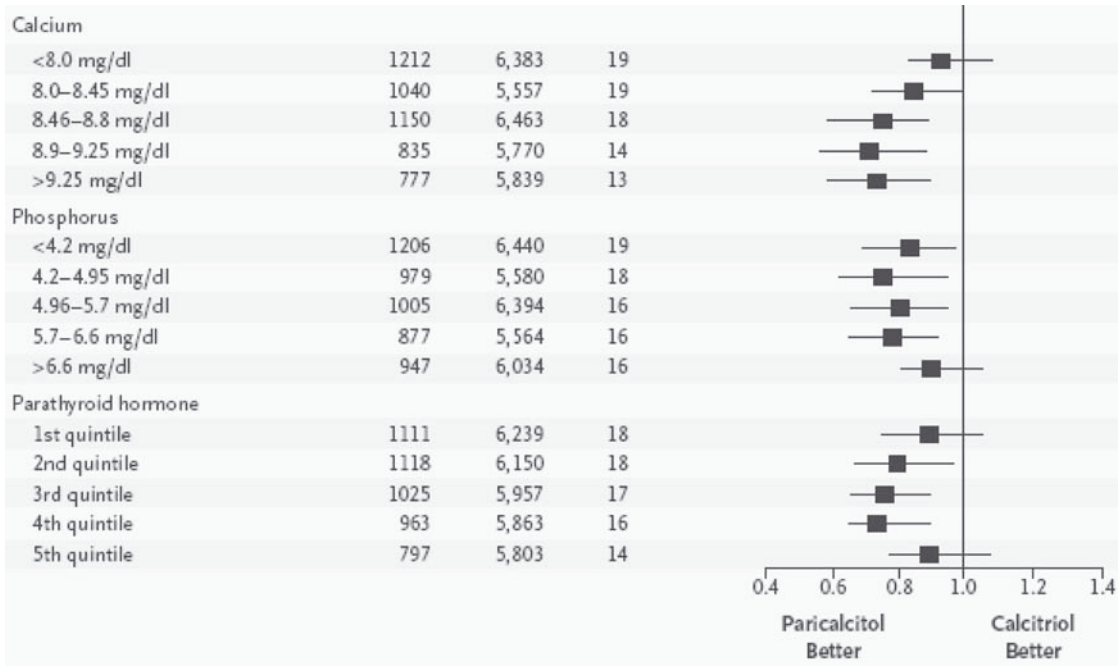
From Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med*. 2003;349(5):446 456. Copyright © 2003, Massachusetts Medical Society. All rights reserved.

those treated with calcitriol, independent of baseline Ca, P, and iPTH levels and other potential confounders. The benefit of paricalcitol was also observed in most subgroups, including black patients and those with diabetes. Furthermore, patients who switched from calcitriol to paricalcitol also gained a significant survival advantage over those who switched from paricalcitol to calcitriol, which corroborated the primary analysis. Whether the primary mechanism of the survival benefit reflects a direct effect of paricalcitol, independent of its mineral and PTH effects, or is due to a reduced mineral load owing to decreased intestinal absorption and bone resorption of Ca and P on paricalcitol treatment compared with calcitriol remains unclear. Alternatively, the survival benefit could reflect an overall benefit of vitamin D therapy itself with patients in the paricalcitol group being "exposed" to more vitamin D because of less frequent episodes of hypercalcemia and/or hyperphosphatemia effects of paricalcitol compared to calcitriol. Further studies are clearly needed. Finally, the authors caution that these are the results of an observational study and residual confounding cannot be completely excluded. Only a prospective, randomized controlled study would eliminate all potential confounding and allow definitive conclusions to be drawn.

CONCLUSION

What are the potential mechanisms of the observed survival advantage? Activated vitamin D is a freely circulating hormone that binds its receptor, the VDR, setting off a molecular cascade culminating in alteration of gene transcription.[6] The vast cellular distribution of the VDR suggests that the effects of vitamin D (and consequences of vitamin D deficiency) extend beyond those limited to mineral and PTH metabo-

Figure 2.



Hazard Ratios for Death Associated with Paricalcitol Treatment, as Compared to Calcitriol Treatment, with Stratification According to the Characteristics of the Patients*

*The percentages represent the fractions of patients within each stratum who died, the boxes represent point estimates, and the horizontal lines represent 95% confidence intervals. The reference category for each analysis is the corresponding group receiving calcitriol. Data on the duration of dialysis were missing for 1 patient. To convert values for calcium to millimoles per liter, multiply by 0.250, and to convert values for phosphorus to millimoles per liter, multiply by 0.3229.

From 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(5):446 456. Copyright © 2003, Massachusetts Medical Society. All rights reserved.

lism. Indeed, vitamin D has been shown to modulate inflammation and play a role in immune system regulation,[57-67] to mitigate glomerular and tubulointerstitial fibrosis in animal models of CKD,[68-71] and perhaps, to slow the rate of progression of chronic allograft nephropathy.[70,72,73] Moreover, vitamin D's potential role as a therapy for cancer (e.g., prostate) and psoriasis has been well-documented.[74-83] From a cardiovascular standpoint, vitamin D has been shown to downregulate plasma renin activity[11-15] and to inhibit cardiomyocyte proliferation and left ventricular hypertrophy.[16,17] In addition, vitamin D deficiency has been associated with heart failure and increased coronary calcification in human subjects.[18] Also, two recent studies looked at a potential cardiovascular benefit of vitamin D specifically in HD patients.[84,85]

Vitamin D deficiency is a common complication of CKD that contributes to the development of SHPT. Emerging evidence suggest several non-traditional actions of vitamin D, beyond the well known mineral and PTH effects, including an impact on factors associated with car-

diovascular disease, the leading cause of mortality among HD patients. Among HD patients who are treated with intravenous vitamin D at dialysis, paricalcitol appears to be superior to calcitriol in terms of patient survival. Despite this progress, clearly, more work needs to be done. For example, we need to further investigate the mechanisms of the survival advantage, examine potential dose effects that have not been examined previously and also study peritoneal dialysis patients. More fundamentally, while we have identified an advantage of paricalcitol among HD patients in whom intravenous vitamin D is initiated; further studies are needed to determine whether or not *any* vitamin D therapy is superior to *none*. These studies are ongoing.

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