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Successful Conversion From Parenteral Paricalcitol to Pulse Oral Calcitriol for the Management of Secondary Hyperparathyroidism in Hemodialysis Patients

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Objective: The management of hyperparathyroidism in hemodialysis patients involves the administration of phosphate binders, vitamin D receptor activators, and calcimimetics. Intravenous paricalcitol has been preferred over oral calcitriol as it may cause less hypercalcemia and hyperphosphatemia. However, there is little data looking at the efficacy and tolerability of oral calcitriol in the calcimimetic era particularly in a real practice-based experience. The University of California, Irvine free-standing dialysis center converted from routine intravenous paricalcitol to oral calcitriol due to pharmacy purchasing preferences. We report the efficacy, safety, and cost of such a change.

Subjects: Ninety-three preconversion intravenous paricalcitol and 91 postconversion oral calcitriol.

Intervention: Conversion to in-center, pulse, oral calcitriol (0.25 mcg = 1 mcg paricalcitol) 3 times a week from intravenous paricalcitol. Additional dose adjustments were made by the nephrologists based on clinical indications.

Main Outcome Measure: Five-month average serum calcium, phosphorous, and intact parathyroid hormone levels and cardiovascular events pretransition and posttransition.

Results: There were 93 patients on intravenous paricalcitol between April 2013 and August 2013, of which 74 converted to oral calcitriol and were included in the postconversion group evaluated between October 2013 and February 2014. An additional 17 new patients had initiated calcitriol such that 91 patients were on oral therapy in the postconversion period. Sevelamer use increased from 41 (44.1%) patients preconversion to 48 (52.7%) postconversion, whereas calcium acetate use significantly dropped from 62 (66.7%) to 46 (50.5%) (P = .026). Cinacalcet use dropped slightly from 37 (39.7%) patients preconversion to 35 (38.4%) postconversion. Average serum calcium, phosphorus, and intact parathyroid hormone levels remained unchanged after conversion. Percent of values within Kidney Disease Outcome Quality Initiative guidelines were similarly maintained. Estimated vitamin D cost savings were $564 per person/year. No increase in the incidence of cardiovascular events was observed.

Conclusions: We conclude that in-center distributed pulse oral calcitriol may be an effective, safe, and economical treatment option for the management of hyperparathyroidism in hemodialysis patients.

Introduction

IN THE UNITED States, there are over 400,000 end-stage renal disease (ESRD) patients maintained on hemodialysis with an average cost per year of over $88,000.[1] With the recent changes in Medicare payment practices, reimbursement for dialysis centers continues to evolve, with more aspects coming under the domain of bundling, including the cost of intravenous vitamin D receptor activators (VDRAs) that are used for the management of secondary hyperparathyroidism (SHPT). Approximately 75% of US ESRD patients receive intravenous VDRA preparations to manage mineral bone disease[1] at increasing costs per patient per year. Intravenous paricalcitol is among the most widely used VDRA preparations in US hemodialysis centers, but several other oral and intravenous compounds are available for use in the United States, Europe, and Asia, including intravenous doxercalciferol,[2] one-alpha hydroxycholecalciferol, and maxacalcitol.[3] Calcitriol, especially in oral format, is the least costly of these preparations,[4] but previous concerns regarding the incidence of hypercalcemia and hyperphosphatemia led to reduced utilization.[5] Cinacalcet, a calcium sensor agonist that effectively suppresses parathyroid hormone (PTH) secretion, may result in more frequent or more severe hypocalcemia and reduced serum phosphorous levels and is regularly prescribed with VDRA preparations. There is

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minimal published data looking at the efficacy and tolerability of oral calcitriol in the calcimimetic era to manage SHPT in hemodialysis patients, particularly in a real practice-based experience. In mid-2013, the University of California, Irvine free-standing dialysis center converted from routine intravenous paricalcitol therapy to oral, in-center calcitriol treatment motivated by pharmacy purchasing preference. We report our experience with this therapeutic conversion on overall costs, efficacy, and safety in a population of ESRD hemodialysis patients.

Materials and Methods

Patients

We performed a retrospective observational assessment on patients undergoing hemodialysis between April 2013 and August 2013 and between September 2013 and February 2014 to describe a dialysis center's experience in response to a change in VDRA therapy type. All hemodialysis patients at the dialysis unit previously treated with intravenous paricalcitol were converted to oral pulse calcitriol on September 1, 2013. Patient data were compared 5 months prior (April 2013-August 2013) and 5 months after (September 2013-February 2014) the conversion. We collected demographic characteristics, medical history and monthly laboratory data, average doses of paricalcitol and calcitriol, phosphate binders, and cinacalcet from April 2013 through February 2014 on all hemodialysis patients treated in the University of California, Irvine hemodialysis center. Patients who were transient or were frequently hospitalized and therefore did not have available laboratory measurements were excluded. Data were collected from patient chart review. Patient-reported medication-related complications were compiled, and data on hospitalizations for cardiovascular events (including myocardial infarction, acute decompensated heart failure, cerebrovascular accident, and peripheral arterial disease) and death were reviewed.

Laboratory Values

Blood samples were drawn using standardized techniques and were transported to ASCEND centralized laboratory in Redwood City, CA, typically within 24 hours, where they were measured using automated and standardized methods. Serum laboratory values including phosphorus, calcium, intact parathyroid hormone, and alkaline phosphatase were recorded monthly. Delivered dialysis dose was estimated by single-pooled Kt/V using the urea kinetic model. Patients each contributed 5 measurements to the averaged group value unless they were censored for death, transfer to another dialysis facility, transplantation, or change of dialysis modality to peritoneal dialysis (16% in preconversion group and 12% in postconversion group did not contribute exactly 5 measurements to the group average).

Statistical Methods

We compared 5-month averaged laboratory and clinical data in patients treated with paricalcitol before conversion compared to those treated with calcitriol after conversion. Averaged laboratory values before and after conversion are reported as mean (±standard deviation) and as percent within Kidney Disease Outcome Quality Initiative (KDOQI) guidelines.[6] KDOQI guidelines advise that normal serum calcium levels are between 8.4 and 10.2 mg/dL, serum phosphorous levels between 3.5 and 5.5 mg/dL, and serum PTH levels between 150 and 300 mg/dL. Chi-squared statistics were used to compare preintervention and postintervention values within KDOQI guidelines. P values $< .05$ were considered statistically significant.

Results

There were 93 ESRD HD patients treated in our center between April 2013 and August 2013 and receiving IV paricalcitol. In September 2013, all hemodialysis patients were converted to in-center, oral calcitriol (0.25 mcg calcitriol = 1 mcg paricalcitol) given orally 3 times a week at the end of the hemodialysis treatment. Additional dose adjustments were made by the nephrologists based on clinical indications. There were 74 of the 93 patients that converted from intravenous paricalcitol to oral agent, and an additional 17 new patients had initiated calcitriol such that 91 patients were on oral therapy in the postconversion period. Patients from the preconversion period that were not on oral agent postconversion may have been transplanted, transferred off hemodialysis, transferred to another dialysis facility, or no longer needed the vitamin D therapy. Overall, oral calcitriol was well tolerated, and only one patient developed gastrointestinal discomfort and was transitioned back to intravenous paricalcitol. Patient characteristics were similar between the preconversion and postconversion groups (55 and 51% female and age 55 ± 16 and 53 ± 16 years, respectively). Mean dialysis dose and ranges preconversion and postconversion were 1.52 ± 0.31 (min: 0.69-max 2.34) and 1.53 ± 0.30 (min: 0.63-max 2.41), respectively.

Average serum calcium, phosphorus, intact parathyroid hormone, and alkaline phosphatase levels remained unchanged after conversion. Percent of values within KDOQI guidelines and monthly average number of hyper and hypocalcemia events were similarly maintained. Sevelamer use increased from 41 (44.1%) patients preconversion to 48 (52.7%) postconversion, whereas median sevelamer dose did not increase for any patients and decreased in only 2 patients. Calcium acetate use significantly dropped from 62 (66.7%) to 46 (50.5%) ($P = .026$), whereas the median dose increased in 38 patients and decreased for 48 patients. Lanthanum carbonate was used only by a small minority of patients and remained largely unchanged after conversion (3 patients preconversion and 4 patients

postconversion). Cinacalcet use dropped slightly from 37 (39.7%) patients preconversion to 35 (38.4%) postconversion. After conversion to calcitriol, the median dose of cinacalcet did not change. These data are shown in Table 1 and Figure 1.

There was no overall increase in cardiovascular events, defined as acute coronary syndrome, acute decompensated heart failure, cerebrovascular accident, and peripheral arterial disease in the 5 months preconversion when compared to the 5 months postconversion (Table 2). There were 0 deaths from all causes in the 5 months preconversion (during paricalcitol use) and 3 deaths in the 5 months postconversion to oral calcitriol group.

There was a significant decrease in the cost per month for VDRA medication after conversion to oral calcitriol. The monthly average cost for paricalcitol over 5 months was $7,854 compared with $1,603 for calcitriol (Supplement Figure 1). Calcitriol use resulted in monthly savings that ranged from $5,644 to $7,161. Estimated VDRA cost savings were $564 per person/year.

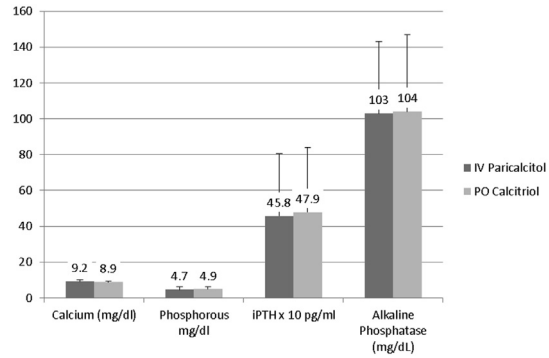

Figure 1. Average serum calcium, phosphorous, intact parathyroid hormone (iPTH), and alkaline phosphatase levels in patients treated with vitamin D receptor activators and percent use of phosphate binders and cinacalcet 5 months prior and 5 months after conversion from intravenous (IV) paricalcitol to oral (PO), and pulse calcitriol therapy.

Table 1. Average Serum Calcium, Phosphorous, Intact Parathyroid Hormone (iPTH), and Alkaline Phosphatase Levels in Patients Treated With Vitamin D Receptor Activators and Percent Use of Phosphate Binders and Cinacalcet 5 Months Prior and 5 Months After Conversion From Intravenous (IV) Paricalcitol to Oral (PO), and Pulse Calcitriol Therapy

Variable	IV Paricalcitol n = 93	PO Calcitriol n = 91	*P* Value
Calcium mg/dL	9.2 ± 0.77	8.9 ± 0.58	
*Calcium values within KDOQI guidelines (%)	N = 72 (77.4)	n = 73 (80.2)	.505
Monthly hypocalcemia episodes	12	11	
Monthly hypercalcemia episodes	3	2	
Phosphorous mg/dL	4.7 ± 1.7	4.9 ± 1.23	
*Phosphorous values within KDOQI guidelines (%)	N = 46 (49.5)	n = 54 (59.3)	.06
iPTH pg/mL	458.1 ± 348.4	478.8 ± 361.58	
*PTH values within KDOQI guidelines (%)	N = 55 (59.1)	N = 62 (68.1)	.082
Alkaline phosphatase mg/dL	103 ± 40	104 ± 43	
Calcium acetate use (n) (%)	(62) 66.7	(46) 50.5	.001
Sevelamer use (n) (%)	(41) 44.1	(48) 52.7	.09
Cinacalcet use (n) (%)	(37) 39.7	(35) 38.4	.74

PTH, parathyroid hormone.

Data are presented as mean ± standard deviation. Percent of the values that fall within the Kidney Disease Outcome Quality Initiative (KDOQI) guidelines are listed for each laboratory parameter.

*KDOQI guidelines advise that normal serum calcium levels are between 8.4 and 10.2 mg/dL, serum phosphorous levels between 3.5 and 5.5 mg/dL, and serum PTH levels between 150 and 300 mg/dL.

Discussion

We report the successful conversion of VDRA therapy from intravenous paricalcitol to pulse, oral calcitriol in a group of hemodialysis patients treated in a free-standing, academic, hemodialysis center. The conversion resulted in a substantial overall cost reduction in VDRA expenditures without impacting the control of SHPT parameters or patient safety.

The management of mineral bone metabolism and SHPT in dialysis patients usually involves the administration of some combination of phosphate binders, VDRA preparations, and most recently calcimimetics. VDRA are known to suppress PTH secretion very effectively and are the mainstream of therapy.[7] However, their use can result in increases of calcium and phosphorus levels, which can aggravate vascular calcifications, promote cardiovascular complications, and add to the morbidity and mortality of dialysis patients.[8–11] Calcitriol was the first available VDRA analog that effectively lowered serum PTH in hemodialysis patients but was found to be associated with

Table 2. Number of Cardiovascular Events and Deaths in Patients Treated With Vitamin D Receptor Activators 5 Months Prior and 5 Months After Conversion From Intravenous (IV) Paricalcitol to Oral (PO), and Pulse Calcitriol Therapy

	IV Paricalcitol	PO Calcitriol
Cardiovascular events	12	9
Acute coronary syndrome	3	6
Acute decompensated heart failure	4	1
Cerebrovascular accident	1	0
Peripheral artery disease	4	2
Deaths	0	3

hypercalcemia.[10–12] Paricalcitol was approved for the treatment of hyperparathyroidism in CKD in 1998 and gained wide acceptance as it was shown to have comparable effects of PTH suppression while resulting in less hypercalcemia and hyperphosphatemia.[5,13] Initial reports suggested that there was reduced mortality in paricalcitol-treated patients. However, in a large study conducted at a not-for-profit dialysis provider, Tentori et al., reported that the observed survival advantage among hemodialysis patients treated with paricalcitol when compared with calcitriol diminished substantially and became statistically insignificant when the data were adjusted for important potential confounders such as age, gender, race, cause of ESRD, dialysis vintage, and time on dialysis before first VDRA therapy.[14] However, in large observational studies, a survival advantage with paracalcitol over calcitriol was seen[15] and thus based on this information most dialysis centers in the United States, including the XXX Dialysis Center, chose to use paracalcitol for the treatment of hyperparathyroidism in hemodialysis patients. Most recently, cinacalcet, a calcium sensor agonist that effectively suppresses PTH secretion, has been introduced to the mineral bone disease therapeutic regimen. It can result in hypocalcemia and thus is routinely prescribed with VDRA. There is little published data looking at the efficacy and tolerability of oral calcitriol in the calcimimetic era to manage SHPT in hemodialysis patients and no information regarding real practice-based experience of such a treatment regimen in a US dialysis center setting. A study in Italy, focusing on management of SHPT in incident hemodialysis patients, found little to no differences (including no cost differences) between 105 patients using oral calcitriol compared to 33 patients using intravenous paricalcitol, but found that intravenous paracalcitol had slightly increased the percentage of patients at KDOQI targets at 6-month follow-up.[16] In our study, there were no significant differences in percentage of patients achieving KDOQI targets preconversion and postconversion. Although costs between the two therapies were similar in the Italian study, pharmaceutical costs to dialysis centers and patients may differ in Europe compared to the United States, where payments are often provided by Medicare under the domain of bundling. Our report outlines a clinic experience on the effectiveness, safety, and cost savings of oral calcitriol, in the management of SHPT in hemodialysis patients up to 5 months postconversion in a United States dialysis center.

A recent randomized, open-label study in ESRD patients (IMPACT SHPT study) found that intravenous paricalcitol was more cost effective[17] and better in controlling PTH when compared to oral cinacalcet plus fixed dose intravenous doxercalciferol.[18] The investigators estimated incremental cost-effectiveness ratios by comparing the cost of the dosages of study drugs (paricalcitol vs. cinacalcet) and phosphate binders in the two study groups with their ability to achieve the primary outcome of intact PTH levels between 150 and 300 pg/mL. The reported unit price of both intravenous paricalcitol and doxercalciferol was noted to be comparable ($3.03/mcg vs. 3.13/mcg, respectively); thus, the additional expense was driven by the cost of cinacalcet. The improved cost effectiveness of paricalcitol was further enhanced by its improved effectiveness in reaching the target PTH values. We compared the costs of intravenous paricalcitol to oral calcitriol, a less costly VDRA (unit price for our dialysis center was approximately $1.60/mcg), and found substantial reductions in cost while maintaining comparable treatment goals. In our center, the use of cinacalcet did not increase after conversion to oral calcitriol. At the start of our evaluation, 39.7% of paricalcitol-treated patients were maintained on this agent, and after 5 months of calcitriol therapy, there was no appreciable change in number of patients treated. Thus, the use of cinacalcet reflects the current prescribing standards in our center and does not appear to be significantly affected by the type of VDRA used. The use of the more expensive binder, sevelamer did increase in the calcitriol group while the use of calcium acetate decreased. Furthermore, in addition to being more expensive, we acknowledge that sevelamer may also increase patient pill burden and thereby increase patient's water intake. Although we did not account for the cost of increase use of sevelamer or cinacalcet or the pill burden impact on the patient, it is reasonable to assume that increase use of these more expensive (possibly more burdensome) agents can offset the total health care savings obtained with use of oral calcitriol. However, the cost of this therapy was not part of our analysis because it is currently not included in the bundle payment for hemodialysis, thus not included in our centers' cost analysis. Further studies would be needed to evaluate the impact of the conversion on patient's cost and quality of life.

We have provided a report on the experience of a hemodialysis clinic undergoing conversion of VDRA therapy from intravenous paracalcitol to oral calcitriol. Conclusions based on our findings are limited as they do not represent the results of an epidemiological cohort analysis or randomized control trial and only cover a short 5-month follow-up postconversion. There is a lack of comparability directly between the two patient groups. However, the focus of this report is not on specific patient outcomes, but instead on observations for the center as whole in its real-world experience. Our observations may also be limited by small sample size and may not be generalizable to all hemodialysis clinics, particularly those outside the United States where medication costs differ. Further studies on this topic conducted in larger dialysis centers would be useful.

Conclusion

In summary, we report that in-center, pulse, oral calcitriol may be an effective, safe, and economical treatment

option for the management of hyperparathyroidism in hemodialysis patients.

Practical Application

We sought to examine whether switching from more expensive IV to less expensive PO types of active vitamin D analogue would achieve same quality outcomes.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1053/j.jrn.2016.02.006.

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