Pharmacokinetics and Efficacy of Pulse Oral Versus Intravenous Calcitriol in Hemodialysis Patients\textsuperscript{1,2}

Barton S. Levine\textsuperscript{3} and Mark Song

B.S. Levine, M. Song, Departments of Medicine, West Los Angeles VA Medical Center, Los Angeles, CA, and The UCLA School of Medicine, Los Angeles, CA
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ABSTRACT

Because intravenous (iv) calcitriol has greater bioavailability than oral calcitriol, it may be more efficacious in suppressing parathyroid hormone (PTH) secretion. In this study, the pharmacokinetics and efficacy of pulse oral and iv calcitriol were compared. Patients were randomized to receive 2 \(\mu\)g of iv or oral calcitriol after each dialysis. Two pharmacokinetic studies (PK1, PK2) were performed 10 days apart, during which the patients received calcitriol after each dialysis. Calcitriol bioavailability was determined from the area under the curve (AUC\text{time interval}) in pg/mL per h. After the PK phase, PTH was lowered to < 200 pg/mL by titrating calcitriol to a maximum of 12 \(\mu\)g/wk for 4 wk. Calcitriol was then maintained for another 18 wk unless serum calcium exceeded 11.5 mg/dL or Ca \(\times\) P product exceeded 70; when these limits were reached, calcitriol was held and then restarted at a lower dose. After iv administration, peak serum calcitriol exceeded that achieved orally but by 1 h, calcitriol levels were similar. The AUC\text{0-48 h} (105 \(\pm\) 12, iv; 9 \(\pm\) 4, oral) and AUC\text{0-36 h} (68 \(\pm\) 6, iv; 30 \(\pm\) 7, oral) were higher with iv (P < 0.05), but cumulative AUC\text{0-red} did not differ. Individual \(t_{1/2}\) values ranged from 10 to 129 h for PK1 and from 10 to 50 h for PK2. The \(t_{1/2}\) for oral calcitriol was 38 \(\pm\) 14 h for PK1 and 30 \(\pm\) 4 h for PK2 (not significant (NS)). The \(t_{1/2}\) for iv calcitriol was 26 \(\pm\) 5 h for PK1 and 19 \(\pm\) 3 h for PK2 (NS, PK1 versus PK2 and oral versus iv). When the PK1 oral and iv data were combined, the mean \(t_{1/2}\) was 32 \(\pm\) 7 h whereas the \(t_{1/2}\) for PK2 (oral and iv) was 22 \(\pm\) 3 h (P < 0.05). Baseline PTH levels were 510 \(\pm\) 90 pg/mL and 499 \(\pm\) 79 pg/mL, oral and iv, respectively. Serum PTH level at 22 wk was not different between oral and iv groups, 153 \(\pm\) 38 pg/mL and 214 \(\pm\) 124 pg/mL in iv (NS). The percentage of PTH suppression was 66 \(\pm\) 7.4% in the oral group and 69 \(\pm\) 12% in the iv group (NS). A major degree of serum iPTH suppression occurred during the initial 4 wk of treatment, concomitant with a rise in serum calcium levels. Adverse effects were similar between groups, as were the average dosages of calcitriol and phosphate binders. In conclusion, the efficacy of intravenous and pulse oral calcitriol were similar in hemodialysis patients with secondary hyperparathyroidism. The early rise in serum calcium levels observed with treatment may have contributed significantly to the suppression of serum iPTH levels. The difference in bioavailability between the different routes does not have a clinically apparent effect. The \(t_{1/2}\) varied widely among individuals, whereas exposure to calcitriol may decrease the \(t_{1/2}\).

Key Words: Calcitriol, pharmacokinetics, parathyroid hormone, oral, intravenous

Treatment of secondary hyperparathyroidism remains a therapeutic problem in the dialysis population. Several factors that contribute to the pathogenesis of high parathyroid hormone (PTH) levels with renal failure include hypocalcemia, phosphorus retention, and skeletal resistance to PTH (1-3). The low levels of serum calcitriol associated with renal failure also contribute to the development of secondary hyperparathyroidism (4). Previous studies have shown that parathyroid gland cells have cytosolic receptors for calcitriol. Exposure of these cells to calcitriol, in vitro, inhibits the transcription of prePro PTH mRNA, the message for the precursor protein of PTH (5). Furthermore, both oral (6-8) and iv (9-11) administration of calcitriol are effective in suppressing the secondary hyperparathyroidism of chronic renal failure, independent of changes in serum calcium concentration. Thus, calcitriol therapy has become a mainstay for the treatment of the secondary hyperparathyroidism of chronic renal failure.

Calcitriol may be administered orally or iv and with varying dosage frequencies. Controversy exists as to which route and dosage regimen is optimal for PTH suppression with a minimum of adverse effects. It has been hypothesized that iv administration of calcitriol should result in a greater suppression of secondary hyperparathyroidism with less hypercalcemia than daily oral therapy (9,12); this hypothesis is based on the fact that the higher blood levels of calcitriol achieved with intravenous therapy would result in a greater degree of bioavailability of calcitriol and hence a greater degree of PTH suppression.

Recent studies suggest that high-dose intermittent (pulse) oral calcitriol is associated with less hypercal-
...cemia than daily oral therapy and may be as effective as IV calcitriol in treating secondary hyperparathyroidism (7,8,13,14). However, only limited data are available (13,14) that directly compare pulse-oral to pulse-IV calcitriol therapy for the treatment of secondary hyperparathyroidism in ESRD patients. Furthermore, there is a paucity of data that compares the pharmacokinetics of calcitriol when administered to hemodialysis patients by these different routes. This study was conducted to assess the pharmacokinetics of calcitriol, administered either orally or IV, to obtain some measure of the bioavailability of calcitriol when administered via these different routes. In addition, the efficacy and safety profiles of pulse oral versus IV calcitriol were compared in this patient population.

METHODS

This was a randomized prospective open-label comparative study that consisted of a baseline period of 4 wk, during which patients were not on any calcitriol therapy, and a treatment period of 21 to 24 wk, during which patients received either pulse oral or IV calcitriol. The study was approved by the Institutional Review Board of the Veterans Administration Medical Center, West Los Angeles, CA. All patients signed an informed consent before participating in the study.

Baseline Period

During the 4-wk baseline period, serum chemistries, ionized calcium, LFT, and CBC with differentials were obtained. Baseline serum calcium, phosphorus, and PTH levels were obtained at the end of Week 4.

Treatment Period

The treatment period consisted of two phases, a pharmacokinetic phase that lasted 3 wk, and a PTH-suppression phase that lasted 21 wk.

Pharmacokinetic Phase. Sixteen male patients from the West Los Angeles Veterans Administration Chronic Hemodialysis Unit underwent pharmacokinetic studies. Selection criteria included: (1) a plasma total calcium level <9.5 mg/dL; (2) a serum PTH level >55 pg/mL; (3) hemodialysis three times/week; (4) a calcium-phosphorus product (Ca × P) <70; and (5) age between 18 to 70 yr (Table 1). Patients were randomized to receive either oral or IV calcitriol. One patient in the IV group was diabetic, whereas none in the oral group was. The pharmacokinetic studies were performed after the second and eighth dialysis (approximately 10 days apart).

After a baseline blood sample was obtained, the patient was administered either Calcijex (Abbott Laboratories, Abbott Park, IL), 2 µg IV, or calcitriol, 2 µg orally, and additional blood samples were obtained at 5 and 30 min, and 1, 2, 4, 6, 8, 24, and 48 h after the calcitriol dose. To control for background levels of calcitriol, a similar time-control study was performed at the end of the first dialysis before the initiation of calcitriol therapy.

PTH Suppression Phase. The criteria for entry into this phase of the study were: (1) a PTH level >200 pg/mL at the end of baseline; (2) a serum calcium level <9.5 mg/dL; (3) Ca × P < 70; and (4) hemodialysis 3 times/week. Of the 16 patients that completed the pharmacokinetic study, 13 qualified for the PTH-suppression phase of the study. Three patients were excluded because of their relatively low baseline serum PTH level (<200 pg/mL). To ensure an adequate number of study patients, an additional five patients were recruited who fulfilled the above criteria. These patients were randomly assigned to either the oral or IV treatment groups after completing the 4-wk baseline period. One patient, who had been assigned to oral therapy, was changed to peritoneal dialysis after 13 wk of treatment, whereas blood samples for serum calcium and phosphorus levels were lost for Months 4 and 5 in one patient each from the oral and IV group.

In this phase of the study, the initial dose of 2 µg calcitriol was titrated up as long as the predialysis serum calcium level was <11.5 mg/dL. The maximum dose allowed for calcitriol in both treatment groups was 12 µg/wk. The dose of calcitriol was adjusted during the first 2 to 6 wk and then maintained at this level for the remainder of the study unless the serum calcium level was >11.5 mg/dL or the Ca × P product was >70. When the limits for these parameters were exceeded, calcitriol administration was temporarily discontinued and then restarted at a lower dosage, when the serum calcium level and Ca × P product had returned to below the cutoff values. If necessary, dialysate calcium concentration was lowered from 3.5 mM to 2.5 mM to prevent the development of hypercalcemia. Phosphate binders were adjusted to maintain serum phosphorus levels at <5.5 mg/dL. One patient in the oral group and two patients in the IV group received aluminum-containing phosphate binders, whereas the remaining patients were on calcium-containing binders only.

Measurements

Serum calcium levels were measured by using atomic absorption spectroscopy and serum phosphorus level was measured by using standard autoanalyzer techniques. Intact parathyroid hormone (IPTH) was measured by the immuno-radiometric assay (Allegro; Nichols Institute, San Juan Capistrano, CA). Validation of this assay in dialysis patients has been shown previously (15). Serum calcitriol levels were measured by using a nonequilibrium assay that utilizes the cytosolic receptor for calcitriol obtained from calf thymus (16). Calcitriol levels at each time point were expressed as the difference between the calcitriol concentration after calcitriol administration and the appropriate time-control level. Bioavailability of calcitriol was determined from measurements of the area under the curve (AUC) for increases in serum calcitriol levels above baseline values (17). Determinations of
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AUC were obtained by direct measurement by using a digitizer tablet (Summagraphics Corp., Fairfield, CT) interfaced with an IBM Personal Computer (Bethesda, MD). The units for AUC are expressed as μg x mL⁻¹ x h⁻¹. Values were determined for the total AUC over 48 h (AUC₀₋₄₈), and for each of the following time intervals: first half hour (AUC₀₋₁/₂), second half hour (AUC₁₋₂), second hour (AUC₂₋₃), second to fourth hour (AUC₂₋₄), fourth to sixth hour (AUC₄₋₆), sixth to eighth hour (AUC₆₋₈), eighth to 24th hour (AUC₈₋₂₄), and 24th to 48th hour (AUC₂₄₋₄₈).

Statistical Analysis

Data are expressed as mean ± SE unless stated otherwise. For parametric data, one-way analysis of variance or analysis of variance with repeated measures were performed where indicated (18). For nonparametric data, the Kruskal-Wallis and Friedman tests were used (18). The Bonferroni t test or student t test was used to test for significance. A value of P < 0.05 was considered significant. Multiple regression analyses were performed with the statistics program Statview (Abacus Concepts, Inc., Berkeley, CA. 1992).

RESULTS

Studies were performed to compare the pharmacokinetics of calcitriol after a single dose of 2 μg was administered either orally or iv (Figure 1). As expected, there was a more pronounced rise in calcitriol levels after iv administration for both pharmacokinetic studies, but by 1 h, the serum levels were similar to those after oral administration. The individual t₁/₂ values, calculated by using values from 4 to 48 h after dose were highly variable, ranging from 9.6 to 129.3 h for the first pharmacokinetic study and 9.8 to 49.5 h for the second pharmacokinetic study (Figure 2). The t₁/₂ for calcitriol with oral administration was 38.4 ± 13.6 h for the first kinetic period and 24.9 ± 4.1 h for the second kinetic period (P = 0.12). The t₁/₂ for calcitriol after iv administration was 26.0 ± 5.0 h for the first kinetic period and 19.4 ± 3.1 h for the second kinetic period (P = 0.07). There was no difference in t₁/₂ when the oral route was compared with the iv route. To determine if prior exposure to calcitriol, regardless of the route of administration, alters the t₁/₂ for calcitriol, the data for t₁/₂ for the oral and iv groups were combined. The mean t₁/₂ for the first pharmacokinetic study was 32.2 ± 7.2 h and 22.1 ± 2.6 h for the second pharmacokinetic study (P < 0.05). One patient in the oral group had a t₁/₂ for calcitriol more than twice that of any other patient during the first pharmacokinetic study. However, when this patient is excluded from the analysis, the t₁/₂ for calcitriol remains longer during the first pharmacokinetic period; the t₁/₂ with the oral and iv groups combined were 25.7 ± 2.9 h and 26.3 ± 2.0 h for the first and second pharmacokinetic periods, respectively (P < 0.05), and 25.4 ± 4.5 h and 21.4 ± 2.5 h, respectively, with oral therapy (NS). Multiple regression analysis failed to uncover any relationship between the t₁/₂ for calcitriol and baseline serum levels for iPTH, calcitriol, calcium, or phosphorus (r² = 0.087, P > 0.05).

The AUC values after either oral or iv administration of calcitriol, 2 μg, are shown in Figure 3. The AUC results from the two pharmacokinetic studies were combined because the data for the two periods were similar. Baseline serum calcitriol levels were similar in the two treatment groups. During the first hour after calcitriol administration, the AUC₀₋₀.₅ and AUC₀₋₁₀ were greater after iv administration. However, no differences in AUC values between groups were observed at any period beyond 1 h. Despite the higher values of AUC₀₋₀.₅ and AUC₀₋₁₀ after iv administration, AUC₀₋₂₄ and AUC₀₋₄₈ were not different between treatment groups.

Demographic data for the patients receiving either oral or iv calcitriol during the PTH suppression phase of the study are shown in Table 2. There were no

Figure 1. Serum calcitriol levels after the oral or iv administration of a single dose of calcitriol, 2 μg. After dialysis, a baseline blood sample was obtained, the patient was administered either Calcijex, 2 μg Iv, or calcitriol, 2 μg orally, and additional blood samples were obtained after dose at the times shown. As a control, blood samples were also obtained at similar time points as above, but without administration of drug (background curves). Pharmacokinetic studies were performed (A) before calcitriol therapy, and (B) after treatment with calcitriol, 2 μg/dialysis, for 2 wk. Data are given as mean ± SE, N = 6 in each group. * = P < 0.05, iv versus oral.
differences in age, duration of hemodialysis (HD), the number of episodes of hypercalcemia, or elevations in their the Ca × P product (>70) between treatment groups. The number of occasions that calcitriol treatment was withheld because of hypercalcemia or a high Ca × P product also did not differ between groups. The total amount of phosphate binder (calcium and aluminum binders combined) in both groups was also similar, as was the average dose of calcitriol/hemodialysis. Four patients in the IV treatment group and three from the oral calcitriol group were on a 2.5 mEq/L calcium bath before they began the PTH-suppression phase. During the titration phase, an additional two patients from each group required a lowering of the dialysate calcium to prevent hypercalcemia.

Levels for serum calcium, phosphorus, and Ca × P product throughout the study for each treatment are shown in Figures 4A and 4B. The data include only those subjects who completed the study and had values for each time period (N = 7 for the oral group and N = 8 for the IV group). Serum calcium levels ranged between 7.8–10.2 mg/dL at baseline, with 11 patients having a serum calcium below the normal range. Serum calcium levels increased from baseline with treatment, but the increment was only significant with IV therapy. The rise in serum calcium levels appeared to occur earlier with IV therapy and exceeded the rise in serum calcium levels observed with oral calcitriol at 3 months. By Weeks 18 and 24 of treatment, serum calcium levels were similar between treatment groups. Serum phosphorus levels also tended to rise with calcitriol therapy, but the increment was not significant at any time for either group (Figure 4A). The serum Ca × P product increased significantly from baseline in the IV group and was
higher than the levels achieved with oral therapy (Figure 4B); the Ca × P product did not increase significantly in the oral group. By Week 24 of treatment, however, there was no difference in the Ca × P product between treatment groups.

The changes in serum iPTH levels with either oral or iv therapy are shown in Figure 5. Baseline serum iPTH was 510 ± 252 and 476 ± 275 pg/mL in the oral and iv group, respectively (P = NS). At the end of treatment, serum iPTH levels decreased to 153 ± 88 pg/mL and 195 ± 333 in the oral and iv group, respectively (P < 0.05 compared with their respective baseline values). The magnitude of the decrease in serum iPTH levels from baseline was similar between treatment groups; the percentage suppression of PTH (100\% x [baseline iPTH - end of study iPTH]/baseline iPTH) at the end of study compared with baseline was 66 ± 7% with oral therapy and 69 ± 12 with iv therapy.

To determine if the initial iPTH level influenced the response to calcitriol therapy, patients whose baseline serum iPTH levels were >500 pg/mL were analyzed separately from those whose serum iPTH levels were <500 (Figure 6); no difference in the response to calcitriol administration was observed between treatment groups, whether their initial serum iPTH level was greater or less than 500 pg/mL. As shown in Figure 7, all patients except one had a lower iPTH at the end of study than at baseline. The one patient who failed to respond to calcitriol administration maintained a high serum phosphorus level despite the use of phosphate binders and dietary counseling. Multiple-regression analysis was performed to determine the relationship between serum calcium and phosphorus levels and serum PTH levels. Neither serum calcium nor serum phosphorus levels showed any relationship to serum iPTH levels (r² = 0.005, P > 0.05).

**DISCUSSION**

The study presented here demonstrates that intermittent high-dose calcitriol administered either orally or iv is efficacious in suppressing serum iPTH levels in hemodialysis patients, data similar to previous studies with these therapeutic modalities (6–11, 13, 19–22). However, only two studies have directly compared...
pulse oral versus iv administration of calcitriol. The response rate to calcitriol treatment was of greater magnitude in the present study than that achieved in the study of Quarles et al. (22), perhaps reflecting the higher initial PTH and serum phosphorus levels in the latter study; a higher serum phosphorus level is thought to blunt the response to calcitriol therapy (22). Furthermore, in the study of Quarles et al. (22), the calcitriol dosage was reduced when serum calcium level exceeded 10.5 mg/dL rather than the level of 11.5 mg/dL that was used in the present study. Of the 18 patients who participated in the PTH-suppression phase of the study, only one patient failed to respond to calcitriol therapy. The serum phosphorus level in this patient was initially 3.7 mg/dL and rose to 7.2 mg/dL by 3 months.

A major decline in serum iPTH levels occurred in the first month of treatment, concomitant with a rise in serum calcium levels (Figures 4A and 5). Thus, a normalization or frank increase in serum calcium level induced by oral and iv calcitriol appeared to play a significant role in iPTH suppression. Because many dialysis patients have either low or low-normal calcium levels, a normalization of serum calcium could play an important role in lowering serum iPTH levels in this patient population.

It has been hypothesized that iv administration of calcitriol may be more efficacious than daily oral therapy in suppressing iPTH secretion and may have a lower incidence of hypercalcemia. However, recent studies have shown that pulse oral calcitriol therapy is effective in suppressing iPTH secretion in dialysis patients and may be as efficacious as iv administration (13,22). Other studies suggest that there may be, in fact, little difference in pulse oral versus daily oral
therapy (23,24). In the study presented here, the degree of iPTH suppression was similar with oral and iv calcitriol therapy. The severity of the secondary hyperparathyroidism did not appear to influence the outcome, as iPTH suppression was similar whether the initial iPTH was greater or less than 500 pg/ml. Serum calcium levels rose with calcitriol therapy, as did the Ca × P product. The incidences of hypercalcemia and hyperphosphatemia were similar with either therapeutic regimen, and there was no difference in the quantity of phosphate binders used or the number of times calcitriol therapy was interrupted. Thus, there appears to be little difference in pulse oral versus pulse iv calcitriol therapy in the patient population studied with regard to safety or efficacy, confirming and extending the results of other studies (13,14,22).

The observation that higher blood levels of calcitriol are achieved with iv compared with oral administration of calcitriol (25) provided the rationale for postulating that iv calcitriol may have a greater suppressive effect on secondary hyperparathyroidism, with less hypercalcemia than daily oral therapy (9,12); degradation of 1,25 (OH)2 D3 may occur in the intestine, which is bypassed with iv administration (26). Thus the oral administration of calcitriol may increase intestinal calcium absorption, with a greater likelihood of producing hypercalcemia, but delivery of hormone to other target organs may be more limited (26). Indeed, studies by Slatopolsky et al. (9) demonstrated that oral administration of calcitriol in sufficient doses to maintain serum calcium levels at the upper limits of normal did not alter iPTH levels, whereas marked suppression of iPTH levels was seen in patients given iv calcitriol. Further evidence for the importance of high serum calcitriol levels in iPTH suppression is provided by a study in “uremic” rats, comparing the effects of a continuous calcitriol infusion versus pulse iv therapy (27). Both groups of rats received the same dose of calcitriol either as a continuous infusion or by intermittent administration at 72-h intervals. The rats that received pulse therapy had higher peak serum calcitriol levels but a lower AUC, compared with rats that received the continuous infusion. PTH suppression was greater in the rats treated with pulse therapy, suggesting that peak plasma levels rather than the AUC is a major determinant in iPTH suppression. In contrast to these data, Quarles et al. (22) found that oral calcitriol and CaCO3 in doses sufficient to normalize serum calcitriol and calcium concentrations resulted in marked suppression of iPTH in the absence of hypercalcemia in dialysis patients; prolonged oral therapy resulted in suppression of iPTH comparable in magnitude to that reported after iv calcitriol therapy, whereas the degree of hypercalcemia was similar to that that occurred with iv therapy.

More recent studies suggest that high-dose pulse oral calcitriol is associated with less hypercalcemia than daily oral therapy and may be as effective as iv calcitriol in treating secondary hyperparathyroidism (7,8); these data suggest that the high initial peak serum levels attained with iv calcitriol administration are not critical. In the study presented here, iv calcitriol administration resulted in higher peak serum calcitriol levels, but by 1 h, serum calcitriol levels did not differ substantially between treatment groups. Furthermore, the bioavailability of calcitriol, as judged by AUC measurements, was greater with iv administration for only the first hour after dose; bioavailability did not differ between the iv and oral groups for the 24 or 48 h calcitriol administration. These results differ somewhat from those of Salusky et al. (25), in which iv calcitriol administration to pediatric peritoneal dialysis patients resulted in higher blood levels of calcitriol for up to 3 h and a higher AUC24 compared with oral calcitriol. However, Salusky et al. (25) administered larger doses of calcitriol as compared with the present study and measured serum calcitriol levels for only 24 h after dosing. Furthermore, the study of Salusky et al. (25) was performed in a much younger patient population than that in the study presented here. Thus, from the study presented here, it appears that the early difference in the bioavailability of calcitriol between the different routes of administration and the higher peak levels of serum calcitriol achieved with iv administration are not critical in determining the safety or efficacy profile of calcitriol therapy.

In this study, the t1/2 of calcitriol was similar whether the drug was administered orally or iv. Interestingly, there was a marked tendency for the t1/2 for calcitriol to decrease after exposure to oral or iv calcitriol. Although these results did not reach statistical significance, when the results from the two treatment modalities were combined, there was a significant decrease of the t1/2 for calcitriol with therapy. This result differs from that of Kimura et al. (28), who did not find a change in t1/2 of calcitriol with exposure to the drug. However, in the latter study, only a few patients were studied, which, because of the marked interindividual variation in t1/2, may have precluded the possibility of detecting a change in t1/2. The reason for this decrease in t1/2 is speculative. Studies have shown that calcitriol and the calcitriol-receptor complex can activate genes coding for degradation enzymes; activation of these enzymes could result in a more rapid clearance of the hormone from the circulation (29). Some studies also suggest that calcitriol may upregulate its own receptors, which could also lead to a more rapid degradation of the hormone (30). This is in contrast to the study of Koyama et al. (31) in uremic animals, in which upregulation of VDR in duodenum of uremic rats was blunted, compared with nonuremic animals. However, in the latter study, only a single dose of calcitriol was administered, whereas in the study of Patel et al. (30), multiple doses of calcitriol were administered.

The t1/2 for calcitriol in the patients in the study presented here was somewhat longer than that previously estimated for normal individuals (32). Similarly, data in rats suggest that the clearance of calcitriol
may be reduced after a substantial reduction in renal mass (30). Furthermore, in the study presented here, there was considerable variation among individuals in the $t_{1/2}$. Which factors may account for this variability are unknown. In the study presented here, no relationship was found between the $t_{1/2}$ and baseline serum calcium, phosphorus, calcitriol, or iPTH levels. Previous studies have shown that uremia results in a downregulation of calcitriol receptors, which could explain, at least in part, the prolonged $t_{1/2}$ for calcitriol in this patient population (30,31,33,34). Data in rats suggest that a uremic toxin present in the ultrafiltrate of rats with renal failure may be responsible for downregulation of VDR. Low circulating levels of calcitriol present in uremia may also contribute to this downregulation of VDR, as might the presence of elevated PTH levels (30). Finally, whether the individual variation in $t_{1/2}$ and the change in $t_{1/2}$ after exposure to calcitriol will affect the dosage requirements for calcitriol in a given individual remains to be determined. Other factors, such as the development of hypercalcemia because of suppressed bone turnover, will probably play a more important role in determining the dosage level of calcitriol.

In conclusion, the study presented here demonstrates that pulse oral and iv calcitriol administration are equally efficacious in suppressing iPTH levels in hemodialysis patients despite the higher peak serum calcitriol levels achieved via the iv route. Furthermore, the $t_{1/2}$ for calcitriol varies widely in the hemodialysis population, a factor that could effect dosing in a given patient. Finally, exposure to calcitriol may alter the $t_{1/2}$ for calcitriol, another factor that may alter dosing requirements in an individual patient.

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