Conversion of calcitriol to 1-α-hydroxy vitamin D₃ in the treatment of peritoneal dialysis patients with renal osteodystrophy

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Abstract

Objective: Calcitriol and 1-α-hydroxy vitamin D₃ can be regarded as equivalent compounds in terms of their biochemical activity, because the latter can be rapidly converted to the former in the liver. This study aimed to examine whether calcitriol and 1-α-hydroxy vitamin D₃ could be used interchangeably on a weight-to-weight basis in treating secondary hyperparathyroidism.

Methods: We enrolled 24 (11 men and 13 women) peritoneal dialysis patients with serum intact parathyroid hormone levels greater than 10 pmol/L, who were stable on calcitriol. The mean age was 51.9 ± 12.5 years. Patients were observed for 8 weeks, and then calcitriol was changed to 1-α-hydroxy vitamin D₃ on a weight-to-weight basis. Patients were followed-up for a further 16 weeks. Twenty patients had intermittent pulse therapy; four had regular daily therapy. The average dosage of calcitriol before conversion was 0.3 ± 0.11 µg/d, or 1 µg twice weekly. The duration of dialysis was 23.5 ± 16.7 months.

Results: Serum calcium, phosphate, and alkaline phosphatase levels remained stable after conversion. Median serum intact parathyroid hormone levels before and after conversion were 54.6 and 49.4 pmol/L, respectively (p=0.414 by Friedman’s test). Two patients had mild asymptomatic hypercalcemia after conversion. Serum calcium level returned to normal within a few days after the dosage of calcium supplement and 1-α-hydroxy vitamin D₃ has been reduced.

Conclusions: We conclude that calcitriol and 1-α-hydroxy vitamin D₃ have equivalent efficacy in treating secondary hyperparathyroidism.

Key words: Hyperparathyroidism, Peritoneal dialysis, Renal dialysis/adverse effects, Renal osteodystrophy

中文摘要

目的：由於1-α-羟維生素D₃能夠透過肝臟迅速轉化為骨化三醇，因此在生物化學作用上兩者可視為等效的化合物。本研究探討在繼發性甲狀腺功能亢進症的治療中，骨化三醇是否與1-α-羟維生素D₃按劑量交替使用。

方法：本報告研究了24例（11名男性，13名女性）的完整血清甲狀腺激素水平高於10 pmol/L，情況穩定，長期骨化三醇治療及其透析的患者。患者平均年齡為51.9 ± 12.5歲。觀察8週後，改用同等劑量的1-α-羟維生素D₃，隨訪16週。二十名患者接受了周期性治療，其餘四名接受了每日的定期治療。改用前骨化三醇的平均劑量為每日0.3 ± 0.11微克，或每週兩劑1微克。透析持續23.5 ± 16.7月。

結果：患者的血清鈣、磷和磷酸鹽、及碳酸鈣酸酶水平在轉換後保持穩定。完整血清甲狀腺激素的中位水平...
INTRODUCTION
Renal osteodystrophy is a major problem in patients with end-stage renal disease (ESRD) (1). The pathogenesis of secondary hyperparathyroidism associated with ESRD is complicated. Relative or absolute deficiency of calcitriol is one of the major contributing factors of excessive parathyroid hormone (PTH) secretion (2). Calcitriol also acts directly on the parathyroid glands through specific vitamin D receptors to suppress the transcription of messenger RNA for prepro-PTH (3,4). Thus, calcitriol and 1α-hydroxy-vitamin-D$_3$ (1α[OH] D$_3$) have been used extensively to treat dialysis patients with secondary hyperparathyroidism.

Early study in patients with chronic kidney failure suggested that calcitriol was twice as potent as 1α(OH) D$_3$ (5). However, under normal physiological circumstances, 1α(OH)D$_3$ is quickly and completely hydroxylated to calcitriol in the liver. As a result, 1α (OH)D$_3$ and calcitriol could be regarded, at least theoretically, as equivalent compounds. Successful treatment of secondary hyperparathyroidism in dialysis patients by regular and pulse oral 1α(OH)D$_3$ and calcitriol has been reported (6-9). The assumption that these two compounds are clinically equivalent has not been extensively evaluated. In this study, we examined the effect of conversion from calcitriol to 1α(OH)D$_3$ on a weight-to-weight basis.

METHODS
We enrolled 24 stable peritoneal dialysis patients in the Prince of Wales Hospital, Hong Kong. Inclusion criteria were 1. moderate to severe hyperparathyroidism, defined as a serum intact PTH (iPTH) level greater than 10 pmol/L; 2. treatment for at least 4 months with oral calcitriol, either regular or pulse therapy, at static dosage; and 3. stable plasma biochemistry for at least 3 months.

Criteria for exclusion included 1. any underlying medical condition (eg, malabsorption syndrome or severe liver disease) that might alter the absorption or metabolism of 1α(OH)D$_3$; 2. any condition that might have precluded a patient from remaining in the study (eg, alcohol or drug abuse, malignancy, or psychiatric disorder); and 3. plans for parathyroid surgery within 4 months.

Informed consent was obtained. Patients were observed for 8 weeks and were maintained on calcitriol therapy. At week 8, calcitriol was changed to 1α(OH)D$_3$ (One-Alpha, Leo Pharmaceutical Products, Copenhagen, Denmark) on a weight-to-weight basis. To avoid rebound hyperparathyroidism, a washout period was not used. The dosage of calcium supplement and phosphate binder was not altered.

Clinical conditions of all patients were observed at the beginning of study, and at weeks 4, 8, 10, 12, 16, 20, and 24 of the study. Compliance was checked by pill count. Renal function test, plasma calcium, phosphate, albumin, and alkaline phosphatase levels were checked during every visit. Serum iPTH level was measured at weeks 0, 8, 12, 16, and 24 and was assayed by a solid-phase, two-site chemiluminescent immunometric assay (Diagnostic Products Corporation, California, US). The average iPTH levels at the beginning of study and at week 8 were taken as preconversion levels; the mean iPTH levels at weeks 12 and 16 were taken as postconversion levels. When plasma calcium level fell below 2 mmol/L, the dosage of 1α(OH)D$_3$ was increased according to clinical response. When plasma calcium levels rose above 2.8 mmol/L, the dosage of calcium supplement was reduced until the calcium level fell below 2.5 mmol/L. The dosage of 1α(OH)D$_3$ was reduced if the serum calcium level failed to normalize.

All data were described as mean values ± standard deviation unless otherwise specified. Statistical analysis was performed by using analysis of variance for repeated measures. Because the results of serum iPTH levels were significantly skewed, the data were compared by Friedman’s test for serial measures. A p value of less than 0.05 was considered significant.

RESULTS
We enrolled 24 patients; 11 (45.8%) were men and 13 (54.2%) were women. The mean age was 51.9 ± 12.5 years. Mean duration of dialysis before enrollment was 23.5 ± 16.7 months (range, 4-66 months). The underlying renal diagnoses were diabetic nephropathy (10 cases), chronic glomerulonephritis (eight), polycystic kidney (two), and unknown (four). Two (8.3%) patients were carriers of hepatitis B surface antigen, but none had any clinical or laboratory evidence of chronic liver disease.

Common clinical manifestations of secondary hyperparathyroidism were vascular calcification (10 cases),
1-α-hydroxy vitamin D₃ in peritoneal dialysis

Radiologic abnormalities (six) such as osteopenia, bone cysts, or osteosclerosis, bone pain (two), and valvular calcification (one). Fourteen (58.3%) patients had moderately raised serum iPTH levels without clinical signs and symptoms. The baseline iPTH level was 55.7 ± 39.2 pmol/L. None of the 24 patients had evidence of nodular parathyroid enlargement by ultrasonography or radioisotope scan. The patients had been taking calcitriol for 23.5 ± 16.7 months before enrollment into the study. Twenty (83.3%) patients had intermittent pulse calcitriol therapy, with median dosage of 1 µg twice weekly; four (16.6%) patients had regular daily calcitriol therapy, with a mean dosage of 0.3 ± 0.11 µg/d. All except one of the patients used calcium carbonate as a phosphate binder; the mean dosage before conversion was 4.9 ± 2.8 g/d in divided doses.

The biochemical profile and serum iPTH levels before and after conversion to 1α(OH)D₃ are summarized in Figures 1 and 2, respectively. Median serum iPTH levels before and after conversion to 1α(OH)D₃ were 54.6 and 49.4 pmol/L, respectively (p=0.414 by Friedman’s test). Serum phosphate levels began to rise 8 weeks after conversion to 1α(OH)D₃, from 1.54 ± 0.46 to 1.74 ± 0.63 mmol/L. The increase, however, was not statistically significant (p=0.265 by repeated-measure analysis of variance). Serum calcium and alkaline phosphates levels remained stable throughout the study period.

None of the patients needed an increase in the dosage of phosphate binder after conversion to 1α(OH)D₃. Two patients had mild hypercalcemia after conversion, with peak calcium levels of 2.9 and 3 mmol/L. Both patients

Figure 1. Biochemical profiles during the study period. (A) Serum calcium level; (B) serum phosphate level; (C) serum alkaline phosphates level. Error bars denote standard errors of mean.

ALP = alkaline phosphates
were asymptomatic and required reduction in the dosage of oral calcium supplement. In one patient, serum calcium level normalized only after reduction in the dosage of 1α(OH)D$_3$. There was no other significant adverse effect reported for either vitamin D supplement.

**DISCUSSION**

The production of 1,25(OH)$_2$D$_3$ by the kidney has a pivotal physiological role in maintaining serum calcium levels by modulating active intestinal calcium absorption, facilitating the release of calcium from bone, and enhancing renal tubular calcium reabsorption. Serum 1,25(OH)$_2$D$_3$ levels decline progressively as renal function deteriorates. This change accounts at least partially for the impaired intestinal calcium absorption and moderate decreases in serum calcium concentrations in patients with moderate to advanced kidney failure. In patients with ESRD, active vitamin D analog is an effective treatment of renal osteodystrophy.

Although 1α(OH)D$_3$ is rapidly and completely converted to calcitriol in the liver, and the two compounds could be considered chemically equivalent, one study in patients with chronic renal failure suggested that calcitriol was twice as potent as 1α(OH)D$_3$ (5). Nevertheless, some investigators still believe that the action of 1α(OH)D$_3$ and calcitriol are similar. In this study, we examined whether calcitriol and 1α(OH)D$_3$ could be used interchangeably on a weight-to-weight basis, for the treatment of secondary hyperparathyroidism complicating ESRD.

We found that 1α(OH)D$_3$ could be used in place of calcitriol in most patients without alteration of dosage. We therefore conclude that calcitriol and 1α(OH)D$_3$ had equivalent efficacy in the treatment of secondary hyperparathyroidism in patients with ESRD.

There was no washout period between the conversion of calcitriol to 1α(OH)D$_3$ in this study, because it would not be ethical to withhold vitamin D therapy in patients with significant secondary hyperparathyroidism. Furthermore, it is often difficult to achieve satisfactory control of serum calcium and PTH levels after vitamin D therapy has been stopped for a period of time (10).

This study focused on the short-term biochemical effects. A longer period of observation is important in studying the long-term effects of conversion to 1α(OH)D$_3$, because the increase in PTH level and secondary hyperparathyroidism may take some time to manifest.

The population in this study was heterogeneous by design. We enrolled patients with variable severity of secondary hyperparathyroidism (iPTH level, 10.1-128.5 pmol/L) who were taking either intermittent pulse oral or regular daily calcitriol therapy. Further study on different cohorts according to the different levels of PTH

![Figure 2. Serum parathyroid hormone levels in patients before and after conversion to 1α(OH)D$_3$.](image)
level would help us understand the effects of conversion to 1α(OH)D3 among different populations. In this study, a trend was observed that patients with higher PTH levels responded differently to those with lower levels of PTH (Fig. 2). However, the number of observations was too small for further meaningful subgroup analysis.

Calcitriol and 1α(OH)D3 were largely equivalent in most cases of this study. Because the pharmacological half-life of calcitriol is less than 2 days (11), it was unlikely that the control of hyperparathyroidism after conversion to 1α(OH)D3 was a delayed effect of calcitriol. We did not examine the effects of conversion from 1α(OH)D3 back to calcitriol, because 1α(OH)D3 has a longer half-life (11) and a washout period is not desirable for patients in this study. The nature of this study also limited the comparison of the long-term efficacy of the two agents.

We observed a gradual increase in serum phosphate levels after conversion to 1α(OH)D3 (Fig. 1), which may be caused by an increase in dietary phosphate intake, or an increase in phosphate absorption because of better compliance to the medication. An increase in hyperparathyroid bone activities is less likely, possibility because serum PTH levels remained stable (Fig. 2).

Both agents were well tolerated, and 1α(OH)D3 was also effective in chronic hepatitis B carriers (data not shown). There were case reports of using 1α(OH)D3 in cirrhotic patients (12). Although prolonged hypercalcemia was a theoretical risk of 1α(OH)D3 (8,13), this problem was not observed in this study. Both patients in whom hypercalcemia developed after conversion to 1α(OH)D3 responded in a few days to the reduction of calcium supplementation and 1α(OH)D3.

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**REFERENCES**