NEFROLOGÍA. Volumen 26. Número 2. 2006

# *Long-term comparative study between calcitriol and alfacalcidol in patients with hyperparathyroidism secondary to hemodialysis*

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**SUMMARY**

*Calcitriol has traditionally been the most widely used treatment for secondary hyperparathyroidism (SHPT) in uremic patients. There are currently no crossover equivalence studies of alphacalcidol* versus *calcitriol establishing which of the two derivatives is more active and better tolerated. The objective of this study was to compare the long term effect on control of PTH of similar doses of alphacalcidol versus calcitriol in the treatment of SHPT in these patients.*

***Methods:*** *We conducted a retrospective study on 21 hemodialysis patients with stable SHPT of varying severity treated with intravenous calcitriol. In july 2002, the pharmacy of the reference hospital decided to substitute calcitriol for alphacalcidol based on the similarity of the two drugs. The conversion was made substituting a similar amount of drug. Mean absolute serum levels and percentage change in PTH, calcium and phosphorus were compared between the two periods and at 0, 3, 6, 9, 12 and 15 months after starting treatment with alphacalcidol. Student's t-test for paired means was used to compare the values between the two periods.*

***Results****: In the calcitriol period, mean PTH levels were 275.2 ± 111.7 pg/ml. The mean dose of drug used was 1.7 ± 0.8 mcg postdialysis, and serum calcium and phosphorus levels were 10.1 ± 0,5 mg/dl and 5,2 ± 0,9 mg/dl, respectively ($p < 0.01$). Mean dialysate calcium content was 2,9 ± 0,3 mEq/l. In the alphacalcidol period, PTH increased (441.6 ± 178.3 pg/ml) ($p < 0.001$) and the percentage of patients with PTH < 300 pg/ml decreased (24% at the end of the period), in spite of significantly increasing the mean drug dose (2,3 ± 0,9 mcg postdialysis) ($p < 0.05$). Serum calcium levels did not show significant differences (10.2 ± 0.7 mg/dl) ($p = NS$), but phosphorus control was improved (4,7 ± 0,5 mg/dl) ($p < 0.01$). The percentage of patients with PTH < 300 pg/ml decreased progressively from the start of treatment with alphacalcidol from 75% to 24% at the end of follow-up. Our results seem to suggest that the dose of alphacalcidol and calcitriol are not equivalent and we need to increase the dose of alphacalcidol to obtain a similar result to calcitriol on suppression of PTH in uremic patients with SPTH.*

Key words: ***Calcitriol. 1α-hydroxycholecalciferol. Secondary hyperparathyroidism. Parathyroid hormone.***

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## ESTUDIO COMPARATIVO A LARGO PLAZO ENTRE CALCITRIOL Y ALFACALCIDOL EN PACIENTES CON HIPERPARATIROIDISMO SECUNDARIO EN HEMODIÁLISIS


### RESUMEN

*En la actualidad existen diversos derivados de la vitamina D para tratar el hiperparatiroidismo secundario (HPTS) en la uremia. No existen estudios de equivalencia cruzados entre alfacalcidol y calcitriol que permitan establecer, cual de los dos derivados es el más activo y el mejor tolerado. El objetivo de este estudio fue comparar el efecto del alfacalcidol y el calcitriol a dosis similares en el tratamiento del HPTS a largo plazo.*

***Métodos:*** *Se estudiaron retrospectivamente 21 pacientes en HD con HPTS estable de diferente severidad en tratamiento con calcitriol intravenoso. En julio de 2002, por decisión de la farmacia del hospital de referencia y en base a la similitud entre ambos fármacos, se realizó el cambio de producto sustituyendose el calcitriol por alfacalcidol. Para el tratamiento de los pacientes la conversión se realizó sustituyendo un fármaco por otro a la misma dosis. Se comparó la media de los niveles séricos absolutos y el porcentaje de cambio de PTH, calcio y fósforo entre ambos periodos y a los 0, 3, 6, 9, 12 y 15 meses de iniciado el tratamiento con alfacalcidol. Para comparar las medias de los valores analizados entre los dos periodos se realizó un estudio de medias apareadas (test* t-*student).*

***Resultados****: En la etapa de calcitriol, la media de los niveles de PTH fue 275,2 ± 111,7 pg/ml. La dosis media de calcitriol utilizada fue 1,7 ± 0,8 microgramos postdiálisis, los niveles séricos de calcio fueron 10,1 ± 0,5 mg/dl y el fósforo 5,2 ± 0,9 p < 0,01 mg/dl. El calcio del dializado fue 2,9 ± 0,3 mEq/l. En la etapa de alfacalcidol la PTH aumentó (441,6 ± 178,3 pg/ml) (p < 0,001), y se redujo el porcentaje de pacientes con PTH < 300 pg/ml (24% al final del periodo) a pesar de haber aumentado de forma significativa la dosis media de alfacalcidol (2,3 ± 0,9 microgramos postdiálisis) (p < 0,05). Los niveles séricos de calcio no mostraron diferencias significativas (10,2 ± 0,7 mg/dl) (p = NS) y el fósforo mostró un mejor control (4,7 ± 0,5 mg/dl) (p < 0,01). El porcentaje de pacientes con PTH < 300 pg/ml fue descendiendo progresivamente en la etapa alfacalcidol, desde 75% hasta 24% al final del seguimiento. Nuestros resultados sugieren que las dosis del alfacalcidol y calcitriol no son equivalentes y que son necesarias mayores dosis de alfacalcidol para obtener niveles similares de supresión de PTH en pacientes urémicos con HPTS.*



Palabras clave: ***Calcitriol. 1α-hidroxicolecalciferol. Alfacalcidol. Hiperparatiroidismo secundario. Hormona paratiroidea.***


### INTRODUCTION

There are currently available several vitamin D analogs as therapeutic alternatives for secondary hyperparathyroidism (SHPT) in hemodialysis (HD). In Spain, the most frequently used therapy has been 1,25 $(O\ H)_2\ D_3$ (calcitriol) but there are other preparations such as 1-a $(OH)D_3$ (alfacalcidol) that have also shown to have a suppressor effect on PTH synthesis.[1]

However, therapeutic equivalence between both formulations has been little assessed. There no cross studies on equivalence of both drugs and although some studies show similar potency,[2,3] others describe half the potency with alfacalcidol suppressing PTH synthesis in uremic patients.[4,5]

The aim of this study was to analyze the long-term effect of switching calcitriol to alfacalcidol on PTH suppression in patients with SHPT.

## METHODS

### Patients

On July 2002, the Pharmacy Department of the reference hospital decided to change the vitamin D formulation used to treat SHPT by substituting intravenous (IV) calcitriol (Calcijex; Abbott) for IV alfacalcidol (Etalpha) in all patients from our Unit. The rationale was that both drugs are efficacious PTH inhibitors.[2,3] Due to the lack of literature with concluding data, the conversion was done with equal doses.

The study included all patients that had a follow-up time of at least one year, aiming at being able to analyze and retrospectively compare the same patients in two similar periods: period 1, 15 months with calcitriol therapy; and period 2, 15 months with alfacalcidol therapy. All patients received endovenous calcitriol therapy before entering into the study.

Twenty-on patients on HD with stable SHPT of varying severity requiring maintenance therapy with vitamin D derivatives have been studied. All received a regular hemodialysis dose of 4 hours 3 times a week, they used polysulphone dialyzers of 1.8-2.1 $m^2$ with different permeabilities, and hemodialysis schedule was kept constant throughput the calcitriol and alfacalcidol periods in each patient. During both periods variable doses of calcium acetate and sevelamer were prescribed to control hyperphosphatemia. There were no differences in mean doses of chelating agents used in both periods (calcitriol period: 1214.6 ± 1328.6 mg of elemental calcium and 3.5 ± 4.5 sevelamer tablets; alfacalcidol period: 1227.3 ± 12586 mg de elemental calcium and 3.2 ± 4.3 sevelamer tablets; p = NS).

### Methodology

All patients with PTH > 250 pg/mL were treated with intravenous pulses administered after hemodialysis session with aiming at maintaining a PTH level between 120 and 250 pg/mL. Dose adjustment was done based on values for calcium, phosphorus, calcium-phosphorus product, and PTH; vitamin D administration was withdrawn if serum calcium levels were > 11 mg/dL, serum phosphorus levels > 7 mg/dL, calcium-phosphorus product > 60, or PTH levels < 120 pg/mL. These criteria, and monitoring and management of vitamin D derivatives were the same during both periods.

Vitamin D doses used according to PTH levels were: 0.5-3 mg 3 times a week if PTH levels were 250-450 pg/mL; 1-2 mg if PTH levels were 450-750 pg/mL; and 2-3 mg if PTH levels were > 750 pg/mL, whenever calcium and phosphorus levels would allow it. Dose adjustment was done according to the response obtained until reaching the target PTH level, and the dose that allowed maintaining that level was kept. Switch to alfacalcidol was done with no wash out period using the same dose that each patient was receiving of calcitriol at the time of change.

Calcium content in the dialyzate was individualized according to serum calcium levels and dose of vitamin D administered. As a rule, 3 mEq/L of calcium were used whenever serum calcium levels would allow it, and 2.5 mEq/L in those patients with serum calcium levels increase or high doses of calcium chelating agents.

Average PTH, calcium and phosphorus blood levels and vitamin D doses were compared between the calcitriol period and the alfacalcidol period, as well as the percentage of change of these values during both periods. We also analyzed the course of these values, every three months, from the beginning to the end of both periods.

### Objectives, standards, and monitoring

The objectives and quality standards were those established before the publication of the DOQI guidelines in October of 2003: maintaining PTH levels between 120-250 pg/mL, pre-dialysis serum calcium level between 10-10.5 mg/dL, phosphorus levels between 3.5-5.5 mg/dL, and calcium-phosphorus product < 60 $mg^2/dL^2$. PTH was determined every 3 months, and calcium and phosphorus levels monthly. In those patients having dose modification, PTH, calcium, and phosphorus determinations were done more frequently (PTH monthly, and calcium and phosphorus fortnightly or weekly).

### Laboratory tests

For the study, we have used calcium (photometry Vis- UV, normal laboratory values: 8.6-10.4 mg/dL) and phosphorus (photometry Vis- UV, normal laboratory values: 2.7-4.5 mg/dL) determinations done at the same time than intact PTH determinations done every 3 months electrochemiluminescent technique, normal laboratory values: 10-65 pg/mL) immediately before the dialysis session in the middle of the week. There were no modifications in laboratory techniques or commercial kits used during both periods.

### Statistical analysis

To compare the means of analyzed values during both periods we performed a study of paired means (Student's t test). Comparison of means in relation to a factor has been done with the ANOVA test. For comparison of percentages, we have used McNemar' s test. We considered a p value < 0.05 as being statistically significant.

## RESULTS

Mean age of the studied population was 57 ± 15.2 years (range 28-81) and mean duration on hemodialysis was 151.8 ± 104.8 months (range 13-359). There were 10 women and 14 men. There were no statistically significant differences between mean kTv values between calcitriol treatment period (1.54 ± 0.3) and alfacalcidol treatment period (1.56 ± 0.2) (P = NS). There was no significant difference either in mean hemoglobin between both periods (mean hemoglobin during calcitriol treatment period 12 ± 0.3 g/dL; and mean hemoglobin during alfacalcidol treatment period 11.9 ± 0.2 g/dL). Eight patients had anti-HCV antibodies, and 13 were seronegative.

As shown in table I, during the alfacalcidol treatment period PTH levels significantly increased as compared with the previous stage, in spite of having considerably increased the average drug dose used. Calcium serum levels did not show significant differences and phosphorus levels showed a significantly better management. Calcium content in the dialyzate was significantly reduced during this period.

The individual patient data at the time of switching to alfacalcidol and within 12 months of follow-up are shown in table II.

During the alfacalcidol period, PTH levels were increased by 88% (p < 0.01), and in spite of an increase by 78% of vitamin D dose (p < 0.01) there were no significant changes in calcium and phosphorus serum levels. During the calcitriol period, changes in the different variables were not significant.

Detailed analysis of progression of PTH, drug dose and percentage of patients with PTH < 300 pg/mL is shown in figures 1 and 2. It may be observed that PTH levels and vitamin D dose were kept relatively constant during the calcitriol period (p = NS), whereas during the alfacalcidol period PTH significantly and progressively increased (p < 0.01). During the calcitriol treatment period, 75% of the patients kept PTH levels < 300 pg/dL, this percentage being reduced to only 25% during the alfacalcidol treatment period.

**Table I.** Comparison o mean calcium content in the dialyzate, mean dose of administered vitamin D, and mean PTH, calcium and phosphorus serum levels between the periods of treatment with calcitrio and with alfacacidol

| | Calcitriol (N = 21) | Alfacalcidol (N = 21) | P |
|---|---|---|---|
| PTH (pg/mL) | 275.2 ± 111.7 | 441.6 ± 178.3 | P<0.001 |
| Serum calcium (mg/dL) | 10.1 ± 0.5 | 10.2 ± 0.7 | P=NS |
| Serum phosphorus (mg/dL) | 5.2 ± 0.9 | 4.7 ± 0.5 | P<0.01 |
| Calcium content in the dialyzate (mEq/L) | 2.9 ± 0.3 | 2.7 ± 0.2 | P< 0.01 |
| Drug dose | 1.7± 0.8 | 2.3 ± 0.9 | P<0.05 |

### Comparison by hepatopathy

Mean PTH during the calcitriol period in the group of 8 patients with anti-HCV antibodies was 268.0 ± 101.7 pg/mL and in the group of 13 seronegative patients was 279.5 ± 101.7 pg/mL (P = 0.82). Mean PTH during the alfacalcidol period in the group of anti-HCV positive antibodies was 367.2 ± 190.5 pg/mL and in the seronegative group was 484.4 ± 156.9 pg/mL (P = 0.14). There were no differences in administered vitamin D doses between both groups of patients, nor during the calcitriol treatment period (1.6 ± 0.8 in the anti-HCV-positive group and 1.7 ± 0.7 in the seronegative group), nor during the alfacalcidol treatment period (2.3 ± 0.6 in the anti-HCV-positive group and 2.3 ± 1.0 in the seronegative group). In both groups, PTH levels were similarly increased in spite of increasing vitamin D dose.

### Comparison by calcium levels in the dialyzate

Calcium content in the dialyzate was significantly reduced during the alfacalcidol treatment period (2.7 ± 0.2 mEq/L), as compared to the calcitriol treatment period (2.9 ± 0.3 mEq/L; p < 0.01).This decrease was essentially due to the results obtained in 9 patients (group A). However, when comparing these 9 patients in whom calcium content had been reduced with those that did not have any change in calcium content in the dialyzate (12 patients, group B), we did not find significant differences between both groups in PTH levels (group A: 367.2 ± 176.3; group B: 457.1 ± 148.2, p = NS), serum phosphorus levels (group A: 4.6 ± 0.5; group B: 4.8 ± 0.5, p = NS), or vitamin D dose received either before or after switching to alfacalcidol (group A: 2.2 ± 1.0; group B: 2.4 ± 1.8, p = NS) (fig. 3).

**Table II.** PTH levels (pg/mL) and mean vitamin D doses (mcg/week) administered per patient in both periods

| Patient | HCV | Months of treat. with calcitriol prior to switching to alfacalcidol | Months on HD | Mean PTH calcitriol (pg/mL) | Mean PTH alfacalcidol (pg/mL) | Mean Dose calcitriol (µg/wk) | Mean Dose alfacalcidol (µg/wk) |
|---|---|---|---|---|---|---|---|
| 1 | No | 19 | 250 | 163.4 | 293.1 | 1 | 2.5 |
| 2 | No | 28 | 34 | 188.8 | 337.0 | 1.8 | 1.3 |
| 3 | Yes | 16 | 16 | 186.2 | 197.4 | 1.1 | 1.8 |
| 4 | Yes | 43 | 125 | 217.5 | 822.5 | 1.3 | 1.5 |
| 5 | Yes | 18 | 249 | 343.9 | 212.8 | 1 | 1.6 |
| 6 | No | 34 | 104 | 222.3 | 616.2 | 1.2 | 2.5 |
| 7 | Yes | 27 | 241 | 240.3 | 327.3 | 1.8 | 2.7 |
| 8 | No | 24 | 41 | 363.9 | 406.1 | 1.4 | 3.3 |
| 9 | No | 17 | 220 | 230.7 | 334.1 | 1.8 | 1.8 |
| 10 | Yes | 15 | 13 | 441.3 | 231.0 | 1.5 | 2 |
| 11 | No | 18 | 101 | 134.6 | 531.7 | 0.7 | 1.7 |
| 12 | No | 16 | 78 | 222.9 | 468.1 | 1.7 | 2.5 |
| 13 | No | 15 | 51 | 155.8 | 521.9 | 1 | 1.4 |
| 14 | Yes | 50 | 309 | 222.0 | 277.6 | 1.7 | 2.9 |
| 15 | No | 16 | 134 | 149.9 | 489.1 | 1.5 | 1.1 |
| 16 | No | 15 | 146 | 415.9 | 805.0 | 2.3 | 4.5 |
| 17 | No | 17 | 182 | 492.8 | 601.3 | 3 | 3 |
| 18 | No | 15 | 43 | 247.6 | 366.5 | 1.3 | 1.1 |
| 19 | No | 52 | 195 | 367.4 | 610.8 | 3.3 | 3.9 |
| 20 | Yes | 15 | 296 | 296.6 | 472.7 | 1.6 | 2.7 |
| 21 | Yes | 18 | 359 | 474.8 | 352.5 | 3.6 | 3 |
| Mean | | 18.9 | 152.0 | 275.2 | 441.6 | 1.7 | 2.3 |
| SD | | 14.9 | 104.6 | 111.7 | 178.3 | 0.8 | 0.9 |

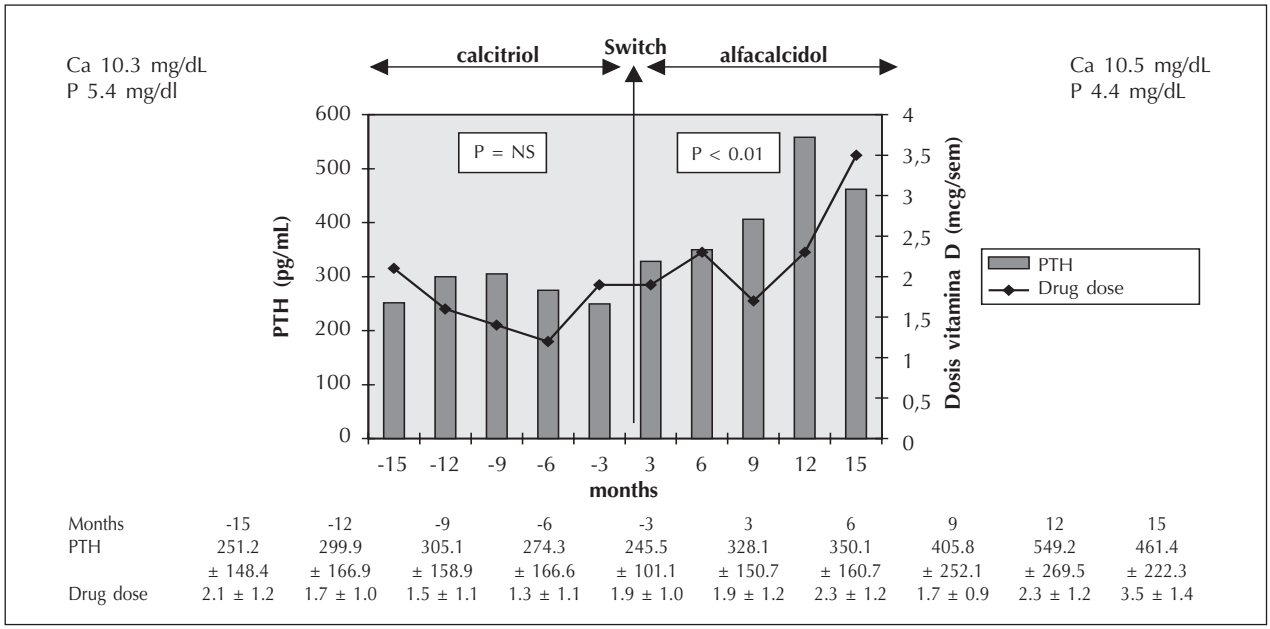
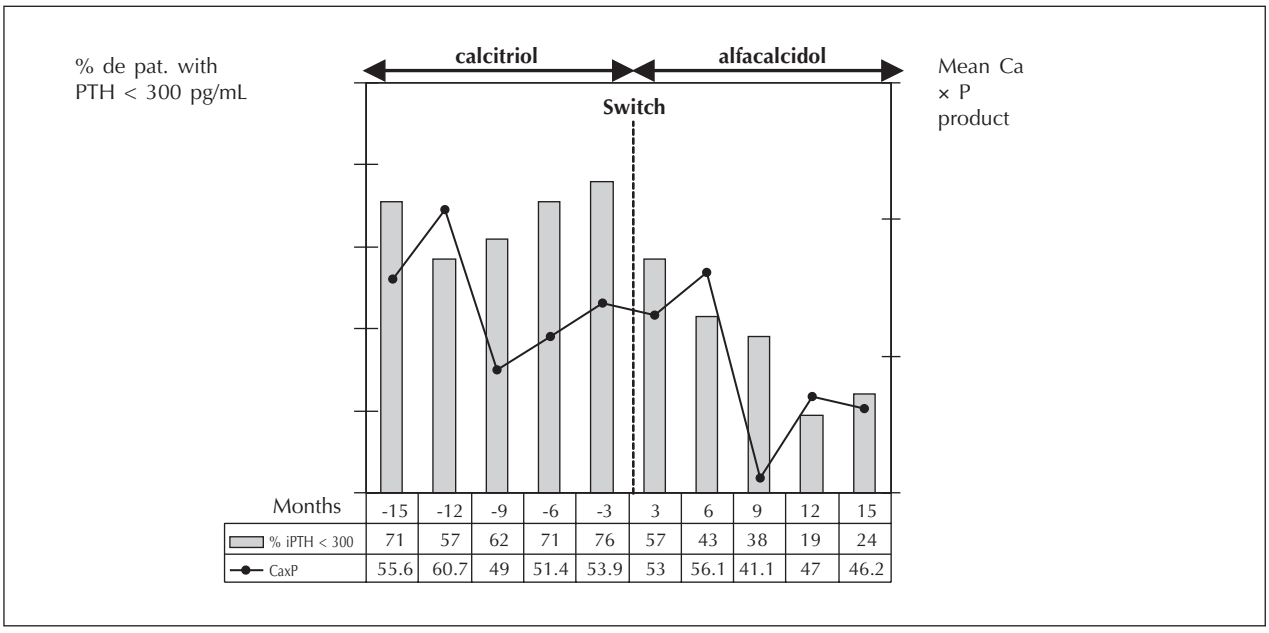



*Fig. 1.—Course of PTH levels before and after alfacacidol administration (month 0). (At month 15 two parathyroidectomies were performed).*




| Months | -15 | -12 | -9 | -6 | -3 | 3 | 6 | 9 | 12 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|
| % iPTH < 300 | 71 | 57 | 62 | 71 | 76 | 57 | 43 | 38 | 19 | 24 |
| CaxP | 55.6 | 60.7 | 49 | 51.4 | 53.9 | 53 | 56.1 | 41.1 | 47 | 46.2 |

*Fig. 2.—Percentage of patients with PTH < 300 pg/mL and calcium-phosphorus product before and after starting on alfacalcidol therapy (at month 15 two parathyroidectomies are performed).*

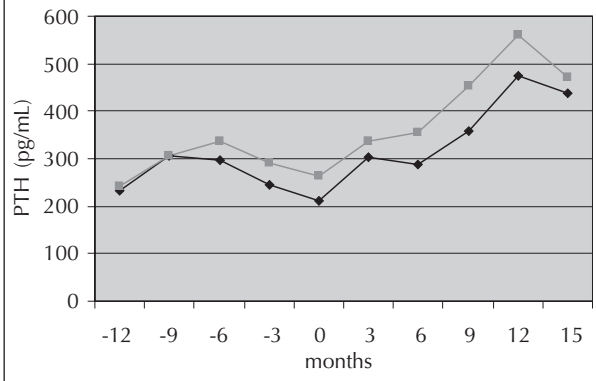
## DISCUSSION

We have found significant differences in mean PTH levels between both treatment periods, PTH being higher during the alfacalcidol treatment period. Besides, PTH levels increased almost by 90% from initial values, in spite of having significantly increased the vitamin D dose (2.5 mg postdialysis with alfacalcidol and 1.8 mg postdialysis with calcitriol).

In our analysis, PTH levels were kept constant throughout calcitriol treatment period, which rules out that PTH increase would have started during this period and we would be witnessing the progression of SHPT. Time on dialysis of our patients does not seem to have an influence either on PTH levels in both periods since there were no significant differences in PTH levels by time on HD during the calcitriol period, and these levels did significantly increased during the alfacalcidol period in all groups (data not shown).

SHPT severity does not seem to have an influence on response to alfacalcidol either. A lower PTH suppression with alfacalcidol was observed both in the group of patients maintaining PTH levels > 300 pg/dL and in the group of patients having achieved PTH control with this drug.

On the other hand, the increase in PTH levels after alfacalcidol therapy does not seem to be related with a poorer management of phosphorus levels either,




| | $Ca^{++}$ decrease in bath (N = 12) | No change of $Ca^{++}$ in bath (N = 9) | P |
|---|---|---|---|
| PTH (pg/mL) | 457 ± 1<10 | 365 ± 120 | P = NS |
| Serum calcium (mg/dL) | 10.2 ± 0.5 | 10.3 ± 0.5 | P = NS |
| Serum phosphorus (mg/dL) | 4.8 ± 0.6 | 4.7 ± 0.5 | P = NS |
| Drug dose | 2.4 ± 0.7 | 2.2 ± 1 | P = NS |

*Fig. 3.—Comparison between the group of patients with decrease in calcium content in the dialyzate and those not having changes during the alfacalcidol period.*

on the contrary, alfacalcidol-treated patients had significantly lower phosphorus levels. Serum calcium levels, which could have justify and increase in PTH, were not modified either after therapy modification.

Finally, as shown in Figure 1, mean value of calcium content in the dialyzate was significantly lower during the alfacalcidol period (2.9 mEq/L to 2.7 mEq/L, $p < 0.01$). In order to rule out that this factor could have an influence on PTH increase,[9] patients were divided into tow groups: one in which calcium content in the dialyzate was reduced during the alfacalcidol period (n = 9 patients), and another group in which this value was not modified (n = 14). As shown in figure 3, there were no significant differences in calcium, phosphorus, PTH, or drug dose values between both periods.

Eight patients had anti-hepatitis C virus (HCV) antibodies, but the behavior after drug switching was similar to that of the group of seronegative patients.

Therefore, once all previously mentioned factors have been rule out, the lower response in PTH management during alfacalcidol treatment might be likely explained by an insufficient dose of the drug. The short-term results obtained in Brandi's study[10] would support this idea since the percentage of PTH suppression that followed acute administration of calcitriol was 60%, whereas it was only 20% after alfacalcidol administration.

This suggests that in the acute phase, alfacalcidol potency is 3 times lower that of calcitriol, a fact that was not taken into account in our study when switching drugs, since the dose was not initially increased. However, although there are not similar studies to ours in the long term, the peculiar pharmacokinetic characteristics of both molecules seem to support our hypothesis.[4] Alfacalcidol needs 25-hydroxylation in the liver to become active, and this would explain the lower and more stable blood alfacalcidol levels as compared to calcitriol, which would have higher but shorter levels after the administration of similar doses of both drugs.[4,5-8] Therefore, it seems easier to achieve the transient supraphysiologic 1,25 $(OH)_2$ $D_3$ levels required for an effective suppression of PTH receptors in parathyroid glands with lower calcitriol doses.[8] In our case, during alfacalcidol therapy, PTH dose was increased in a progressive but possibly delayed way.

In summary, there are no randomized crossover studies comparing both drugs in the intermediate term. Moreover, this study was not designed as such, but as the consequence of a non-programmed change of one molecule for the other, so that conclusions on equivalence doses have not been adequately established.[10-12,17-21] Our study does not allow for establishing equivalence dosing between both drugs and we do not know the required dose of alfacalcidol to achieve a similar effect to that of calcitriol on PTH suppression in the short-, intermediate-, and long-term. However, our results suggest that intravenous doses of calcitriol and alfacalcidol are not equivalent and when switching calcitriol to alfacalcidol higher doses of the latter are needed to obtain a similar degree of PTH suppression in dialysis patients. For these same reasons, we do not know what would happen with the opposite conversion, that is to say, switching from alfacalcidol to calcitriol, but we believe that it is necessary to perform controlled conversion studies in order to decrease the uncertainty in therapeutic response.

## ACKNOWLEDGMENTS

To the Bone and Mineral Metabolism Department for its collaboration in reviewing the writing of this study.

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