

Advantages of adjusting the initial dose of intravenous calcitriol according to PTH levels

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Advantages of adjusting the initial dose of intravenous calcitriol according to PTH levels.

Background. To assess the usefulness of starting calcitriol therapy with a dose proportional to the degree of hyperparathyroidism, 141 patients from 28 centers were treated with intravenous calcitriol for 6 months. The aim was to achieve a final PTH between 125 and 250 pg/mL. Patients with serum PTH >250 pg/mL were included in the study and divided into 4 groups according to baseline PTH levels.

Methods. The study was completed by 100 patients, a third of which were treated strictly according to the protocol, labeled “compliers”; thus, calcitriol was started according to baseline PTH levels. Two thirds of patients, labeled “noncompliers,” showed one or more violation in the dosage regimen.

Results. After 2 months of treatment with calcitriol, 59% of the “compliers” and 35% of the “noncompliers” decreased their PTH levels >40% ($P = 0.022$), 70%, and 49%, respectively after 3 months of treatment. After 3 months of treatment, 67% of the “compliers” reached the target (PTH 125 to 250 pg/mL) in contrast with 23% of the “noncompliers” ($P < 0.001$). The number of hypercalcemic and hyperphosphatemic episodes was significantly lower in the “compliers” group ($P < 0.006$).

Conclusion. These results demonstrate several advantages when calcitriol therapy is started with a dose proportional to the severity of hyperparathyroidism.

Throughout recent years, knowledge of the factors and mechanisms that regulate bone metabolism, as well as the management of bone metabolic disorders of chronic renal failure have improved [1–4]. In spite of these advances, limitations still exist [5]. Many of these limitations became clear in a Spanish multicenter study on renal osteodystrophy recently carried out [6–9]. Some of the resulting problems were unforeseen, but were, at the same time, easy to correct, such as the necessity to start the treatment with vitamin D metabolites early, and also to finish such treatment as soon as possible in order to avoid the excessive suppression of the parathy-

roid function [8]. Other limitations revealed by this study which would have significant repercussions in clinical management include the need to adopt more homogeneous criteria relating to what the exact initial dose of vitamin D metabolites should be, as well as the need to quickly determine which patients do or do not respond to the treatment.

Guidelines from the Spanish Society of Nephrology [10] for the clinical management of renal osteodystrophy have reflected these results and transformed them into recommendations with the aim of improving the management of renal osteodystrophy, such as the use of calcitriol in doses proportional to the severity of secondary hyperparathyroidism. The aim of this study was to assess the effectiveness of calcitriol administered in doses proportional to the degree of secondary hyperparathyroidism and also to evaluate the adverse events found in using this strategy.

METHODS

The study was carried out on 141 dialysis patients treated in 28 hemodialysis centers in Spain, 41 (29%) of which did not finish the study due to the following causes: 25 due to incomplete protocol; 3 due to transplantation; 3 due to excessive suppression of parathyroid function; 4 due to repeated hyperphosphatemia; 2 due to death by cardiovascular events; 1 due to change of residence; 1 due to sepsis; 1 due to cerebral hemorrhage; and 1 due to surgical parathyroidectomy.

Of the 100 patients who completed the study, 42% were women and 58% were men (mean age 59 ± 16 years) with a mean time on dialysis of 52 ± 57 months. The most frequent calcium concentration used in the dialysate was 2.5 mEq/L (74%).

The initial criterion for inclusion in the study, and for the subsequent re-incorporation into the study after a temporary suspension of treatment, was to have PTH levels higher than 250 pg/mL. The aim was to achieve a

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Table 1. Initial dose of calcitriol and frequency of measurement of different biochemical parameters according to the initial levels of PTH

Group	Initial PTH pg/mL	Calcitriol dose 3 times per week μg	Frequency of PTH measurement	Frequency of Ca, P, Ca x P, and AP measurement
A + B	285–550	0.5–1	Monthly	Fortnightly
C	550–750	1.5	Fortnightly	Fortnightly
D	>750	2	Fortnightly	Fortnightly

final PTH between 125 and 250 pg/mL. The criteria for being initially excluded were PTH levels lower than 250 pg/mL, serum calcium levels higher than 10.5 mg/dL, serum phosphorus levels higher than 6 mg/dL, and a calcium x phosphorus product (Ca x P) higher than 60. The criteria for having a temporary break from the study were serum calcium levels higher than 11.2 mg/dL, serum phosphorus levels higher than 6.5 mg/dL, and a Ca x P product higher than 70 mg²/dL².

Because starting the treatment with an initial dose of calcitriol proportional to the severity of hyperparathyroidism had been recommended, study groups were created based on the PTH levels and the dose of calcitriol administered following the clinical guidelines of the Spanish Society of Nephrology (Table 1).

The frequency of biochemical analyses was programmed according to the degree of hyperparathyroidism. Monthly and/or fortnightly controls of PTH and fortnightly controls of the remaining parameters were carried out according to the severity of hyperparathyroidism (Table 1).

In all groups, the calcitriol dose was doubled if PTH dropped by less than 15%. In groups A, B, and C, the calcitriol dose was maintained if PTH dropped between 15% and 30% (except if alkaline phosphate fell by more than 25%, in which case the dose was reduced by 25%). If PTH dropped between 30% and 60%, the dose was reduced by 25%, and finally, if PTH dropped by more than 60%, the dose was halved. If a decrease of at least 15% in PTH was not observed after 3 increases in the calcitriol dose in groups A and B, or 2 increases in group C, the treatment was stopped.

In group D, if PTH fell between 15% and 45%, the same dose was maintained (except if alkaline phosphate fell by more than 25%, in which case the calcitriol dose was reduced by 25%), if PTH fell between 45% and 60% the dose was reduced by 25%, and if it fell by more than 60%, the calcitriol dose was halved. Only one increase of dose was permitted in group D. If, by doing this, a decrease in PTH was not observed, treatment was stopped.

The patients were first treated following the above scheme during 6 months. When the protocol was not followed correctly on one or more occasions, the patients were classified as “noncompliant,” compared to those who had correctly followed the protocol, classified as

“compliant.” Thus, the terms “compliant” and “non-compliant” do not qualify the behavior of the patient, but instead refer fundamentally to the adherence to the protocol by the nephrologists.

The statistical analysis was carried out using the statistical package SPSS 8.0 for Windows (SPSS, Inc., Chicago, IL, USA). The comparison between the beginning and the end of treatment was carried out using the paired-samples Student *t* test. The association between categorical variables was analyzed using Pearson’s chi-squared test. Changes were considered statistically significant if $P < 0.05$.

RESULTS

One hundred patients completed the full 6 months of the study; however, there were only 34 patients in whom the protocol was strictly implemented, while there were 66 patients in whom the protocol was implemented with one or more violations (fundamentally due to calcitriol prescription not following the protocol). Groups A and B were analyzed together.

The mean initial PTH for all patients was 771 ± 393 pg/mL, with no differences between the “compliant” and “noncompliant” groups. The evolution of serum PTH after 3 months of treatment in the different groups is shown in Figure 1. A decrease in the mean PTH was observed in all patients, both in the “compliant” and the “noncompliant” groups. Nevertheless, in the individual analysis, it was verified that all the “compliant” except one (2.9%) showed decreases in PTH, while in the “non-compliant” there was no homogenous response. There were even increases in PTH in 7 patients (11%).

After a month of treatment with intravenous calcitriol, 36% of the “compliant” and 24% of the “noncompliant” decreased their PTH levels more than 40% ($P = \text{NS}$). After 2 months of treatment, the figures were 59% and 35% ($P = 0.022$), and after 3 months, 70% and 49% ($P = 0.046$), respectively.

After 3 months of treatment, 67% of the “compliant” reached the objective of the study (PTH 125 to 250 pg/mL) in contrast with 23% of the “noncompliant” ($P < 0.001$) (Fig. 2). After 6 months of treatment, 82% of the “compliant” and 14% of the “noncompliant” reached the goal of the study ($P < 0.001$).

The side effects of the treatment (hypercalcemia, hyper-

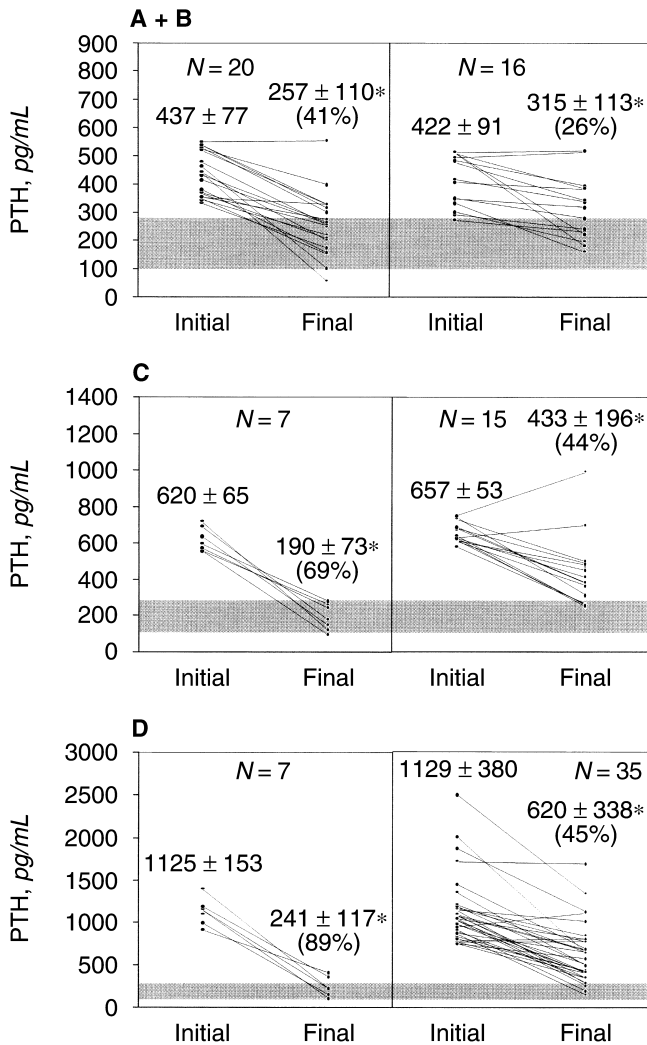


Fig. 1. Evolution of PTH after 3 months of treatment in the “compliant” and “noncompliant” in the 3 groups of patients. Gray boxes indicate the limits of PTH considered the goal of the study (125 to 250 pg/mL). The percentage of PTH decrease is shown in parentheses. **P* < 0.002 compared with the initial PTH.

phosphoremia, or both) were noted in 25% of the “compliant,” and in 57% of the “noncompliant” (*P* < 0.006).

DISCUSSION

Moderate and severe cases of secondary hyperparathyroidism still have a high percentage of treatment failure when using vitamin D metabolites. In a Spanish multicenter study carried out on 10,724 dialysis patients, a lack of homogeneity was noted in the initial doses of intravenous calcitriol used according to the degree of hyperparathyroidism [6]. Despite the fact that 71% of the centers considered that the correct form of administering calcitriol was to use a dose proportional to the severity of secondary hyperparathyroidism, they did not use this strategy from the beginning of treatment. The most com-

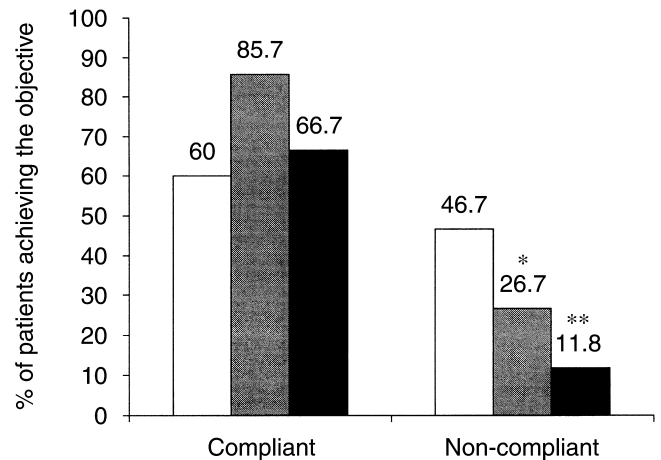


Fig. 2. Percentage of patients reaching the objective of the study (PTH 125 to 250 pg/mL) after 3 months of treatment in the different groups of patients. **P* < 0.025 and ***P* < 0.003, respectively.

mon practice was to initiate treatment with a calcitriol dose independent from the initial serum PTH levels. In fact, 77% of the patients received 1 µg 3 times per week as initial dose, and the dose was not initially adjusted according to PTH levels [11, 12]. This commonly used strategy requires a progressive increase of the dose, which in turn increases the intestinal absorption of calcium and phosphorous, frequently producing hypercalcemia and hyperphosphatemia before the desired PTH response is obtained.

In order to obtain a more rapid response with fewer side effects, the administration of calcitriol based on baseline PTH levels has been recommended [13–15]. However, until this study, the published data referred to the use of this strategy in severe and protracted cases of secondary hyperparathyroidism, but not in all forms of secondary hyperparathyroidism.

We believe that all forms of secondary hyperparathyroidism should be managed by dosing calcitriol according to baseline PTH levels as it has been proposed by the Spanish Society of Nephrology [10]. Throughout the course of this study and after finishing the 6-month period, we became aware of the high number of protocol violations. Furthermore, we realized that following, or not strictly following, the protocol meant important differences in the final results. Thus, the patients were divided into 2 groups, the “compliant” and “noncompliant,” with the aim of analyzing the differences in the results according to the adherence to the protocol for the doctor in charge of the study.

A decrease in the PTH levels was noted in the “compliant” as well as the “noncompliant,” but in the “compliant,” the response was always better, more pronounced, and much more homogeneous. The global analysis showed that after 3 months, 67% of the 34 patients who

complied strictly with the protocol achieved the objective (PTH 125 to 250 pg/mL), in contrast with the 23% of the 66 patients who did not comply with the protocol. Moreover, in the two groups with higher PTH (C and D), the percentage of “compliers” who reached the target of the study after 3 months of treatment was significantly higher (Fig. 2). These results were even better after 6 months of treatment [16]. Therefore, the advantages of adhering more strictly to the protocol were more evident in groups C and D. These findings were expected, as the milder forms of secondary hyperparathyroidism will respond more easily to any form of treatment, while more severe forms will need a more careful management strategy, as has been suggested by other authors [15].

Thus, a clinically relevant outcome of our study was that the “compliers” showed a faster and greater response than the “noncompliers.” At any given point in the study, the “noncompliers” needed a longer time period of treatment to achieve the $\geq 40\%$ reduction in PTH levels, and after 3 months of treatment, the percentage of “noncompliers” who achieved the goal of the study was 3 times lower than the “compliers” (23% vs. 67%).

Another important advantage of using this strategy was that there was a lower incidence of hypercalcemic and hyperphosphatemic episodes in the “compliers,” despite the total dose of calcitriol administered in the 6-month period being similar for both groups, with a mean of $76 \pm 36 \mu\text{g}$ and $74 \pm 39.5 \mu\text{g}$, respectively [16]. The “noncompliers” had twice the number of occurrences of side events (56% vs. 25%), a relevant difference which reinforces the need to follow the recommended strategies more strictly [10].

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APPENDIX

Caldial Study Group: Participating Centers

Ávila: H. Ntra. Sra. Sonsoles; J. Martín; *Cádiz:* Centro periférico Cílu. Jerez: M.L. Alcalá; H. del SAS. Jerez: R. Pérez; *Castellón:* H. General; F. Maduell; *Nefroplana:* A. Bernat; *Nefrovall;* Vall D’Uxo: M.A. Jiménez; *Ciudad Real:* H. Alcázar de S. Juan; J.M. Garrancho; M. Arrant; *A Coruña:* H. Juan Cardona de El Ferrol; J. Calviño; L. Bolaños; R.J. Mouzo; H. Juan Canalejo de Coruña; F.J. Moncalián; *Granada:* H. Clínico San Cecilio; J. Hervás; *Guipúzcoa:* H. Aranzazu. S. Sebastián: J. Arrieta; *Huelva:* H. Juan Ramón Jiménez; F. Fernández; *Jaén:* H. Gral Especialidades; C. Sánchez; *Madrid:* Fundación Hospital de Alcorcón; E. Gruss; H. 12 de Octubre; M. Praga; H. Ramón y Cajal; M. Fernández;

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