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19-Nor-1-α-25-Dihydroxyvitamin D_2 (Paricalcitol) Safely and Effectively Reduces the Levels of Intact Parathyroid Hormone in Patients on Hemodialysis

KEVIN J. MARTIN,* ESTHER A. GONZÁLEZ,* MARY GELLENS,* L. LEE HAMM,† HANNA ABBOUD,‡ and JILL LINDBERG§

*Division of Nephrology, Saint Louis University, St. Louis, Missouri; †Section of Nephrology, Tulane University, New Orleans, Louisiana; ‡Division of Nephrology, University of San Antonio, Texas; and §Department of Nephrology, Ochsner Clinic, New Orleans, Louisiana.

Abstract. Paricalcitol (19-nor-1α-25-dihydroxyvitamin D_2), a new vitamin D analog developed for the treatment of secondary hyperparathyroidism, was evaluated in three double-blind, placebo-controlled, dose-escalating, randomized multicenter trials. A total of 78 patients (40 Paricalcitol injection, 38 placebo) achieved treatment phase eligibility, which included intact parathyroid hormone (iPTH) ≥400 pg/ml, normalized serum calcium levels between 8.0 and 10.0 mg/dl, and calcium × phosphorus product values less than 75. Study end points included a decrease in iPTH of at least 30% or a maximum of five dose escalations. After a 4-wk washout, paricalcitol or placebo was administered intravenously three times per week after dialysis for 12 wk. Study drug was started at a dose of 0.04 μg/kg and was increased by 0.04 μg/kg every 2 wk to a maximal allowable dose of 0.24 μg/kg or until at least a 30% decrease in serum iPTH was achieved. The dose of paricalcitol that decreased iPTH by at least 30% became the maintenance dose. Of 40 patients receiving paricalcitol, 27 (68%) had at least a 30% decrease in serum iPTH for 4 consecutive weeks, compared with three of 38 patients (8%) receiving placebo ($P < 0.001$). For patients who received 12 wk of treatment with paricalcitol, the levels of iPTH decreased significantly from 795 ± 86 to 406 ± 106 pg/ml ($P < 0.001$), whereas the values for PTH were 679 ± 41 pg/ml before and 592 ± 41 pg/ml after 12 wk of therapy in patients receiving placebo (P = NS). Also, there was a significant difference between treatment groups for the change from baseline PTH levels ($P < 0.001$). Paricalcitol treatment resulted in a significant reduction in serum alkaline phosphatase from 148 ± 23 U/L to 101 ± 14 U/L ($P < 0.001$) in patients treated for 12 wk compared with 120 ± 9 U/L to 130 ± 11 U/L (P = NS) in patients receiving placebo for 12 wk. Importantly, hypercalcemia did not occur before achieving target serum iPTH levels in any of the paricalcitol-treated patients. There was no significant difference for the change from baseline in serum phosphorus within or between treatment groups. There was no significant difference in adverse events between the paricalcitol and placebo-treated groups. These studies demonstrate that paricalcitol safely and effectively suppresses iPTH levels in hemodialysis patients. This second generation vitamin D analog may have a wider therapeutic window than current vitamin D preparations, and thus may allow reduction in PTH with less hypercalcemia.

Renal osteodystrophy, an early complication of renal insufficiency, encompasses numerous metabolic and morphologic abnormalities of bone (1). Secondary hyperparathyroidism is a major component of this disorder (1,2). Current therapy of the secondary hyperparathyroidism of chronic renal failure includes the use of vitamin D compounds such as calcitriol, reflecting the role of decreased levels of calcitriol in the pathogenesis of the altered parathyroid function (3–5). Calcitriol can decrease the synthesis and secretion of parathyroid hormone (PTH) by a direct effect on PTH gene transcription (6–9); in addition, calcitriol can facilitate the suppression of PTH by increasing intestinal calcium absorption with the resultant increase in serum calcium. Hyperphosphatemia, a persistent problem in chronic hemodialysis patients, can be further aggravated by doses of calcitriol that suppress PTH (10). The resulting hypercalcemia or hyperphosphatemia may limit the use of calcitriol therapy due to the increased risk of extraskeletal calcification.

An analog of calcitriol that suppresses intact PTH (iPTH) levels, while having less impact on calcium and phosphorus metabolism, would be an ideal candidate for more effective control of the secondary hyperparathyroidism associated with end-stage renal disease. Among the recent advances in vitamin D research is the synthesis of new vitamin D analogs that have decreased calcemic effects, and thus may represent the next generation of vitamin D metabolites for clinical uses (11). *In vitro* studies and *in vivo* studies in rats indicate that 19-nor-1-α-25-dihydroxyvitamin D_2 (paricalcitol) can suppress iPTH levels as effectively as the now widely used parenteral calcitriol, but does not have as great an effect on serum calcium and phosphorus levels (12). Three phase III studies have been

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Correspondence to Dr. Kevin J. Martin, Division of Nephrology, Saint Louis University, 3635 Vista Avenue, St. Louis, MO 63110.
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completed comparing paricalcitol to placebo in patients with secondary hyperparathyroidism on maintenance hemodialysis, and the results of these studies are presented herein.

Materials and Methods

Patients

A total of 78 patients (40 men, 38 women) with a mean age of 54 ± 15 yr (range, 22 to 90) from 11 dialysis centers was studied in three identical double-blind, placebo-controlled, dose-escalating, randomized multicenter trials. All had end-stage renal disease and were maintained on intermittent hemodialysis three times per week. Patients were considered eligible for treatment if their intact PTH levels were ≥400 pg/ml, their normalized serum calcium was between 8.0 and 10.0 mg/dl, and their calcium × phosphorus product was less than 75. All calcitonin, dihydrotachysterol, and calcitriol treatment had been withdrawn at least 4 wk before the start of the treatment period. During the study, 40 patients received active drug and 38 patients received placebo. All patients gave informed consent to participate in the study that received the approval of the Institutional Review Boards of the study sites.

Study Protocol

This was a double-blind, placebo-controlled, randomized, multiinvestigator study to determine the safety and efficacy of paricalcitol compared with placebo. The study protocol is illustrated in Figure 1. If the patients were on calcitriol, it was discontinued, and 2 wk were allowed to elapse before entering the 2-wk baseline period. If no washout was required, the patients could enter the baseline period, during which PTH, calcium, and phosphorus were measured weekly. At this point, they were randomized into the placebo- or paricalcitol-treated groups, and the study continued for 12 wk. All patients were started on the initial dose of 0.04 μg/kg paricalcitol or were given placebo. The dose could be incremented by this amount at 2 weekly intervals if the decline in PTH was less than 30% of baseline, calcium was less than 11.5 mg/dl, and the calcium phosphate product was less than 75. The dose of drug was decreased by one dose level if PTH became less than 100 pg/ml or if hypercalcemia (>11.5 mg/dl) or an elevated calcium-phosphate product (>75) occurred. The dose was maintained if the decrement in PTH exceeded 30% and the patient was not hypercalcemic, with an acceptable calcium-phosphate product. All patients used calcium carbonate or calcium acetate as phosphate binders. No aluminum-based phosphate binders were used.

Data Collection

All chemistries and PTH determination were performed in a central laboratory (SCICOR, Covance, Indianapolis, IN), and PTH levels were determined by immunoradiometric assay. Chemistry variables, hematology variables, and adverse events were monitored for each patient to characterize the safety of treatment. Because for every 1 g/dl decrease in serum albumin there is a decrease in protein-bound calcium of 0.8 mg/dl, patients with an albumin below 4 g/dl had their total serum calcium normalized to an albumin of 4.0 g/dl. Normalized calcium values were used to calculate the calcium × phosphate product.

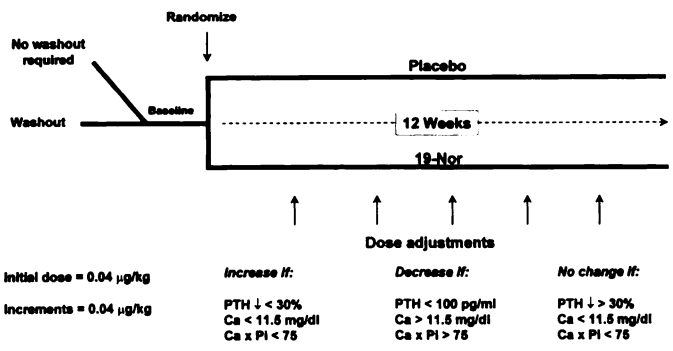

Figure 1. Diagrammatic representation of the study protocol. For a full description, see text.

Statistical Analyses

Descriptive statistics, including the frequency, mean, SEM, and minimal and maximal values, were generated for all primary variables of interest. All hypotheses tests were two-tailed, and P values < 0.05 were considered statistically significant. SAS was used to compute P values. Paricalcitol-treated patients were compared with placebo-treated patients using a one-way ANOVA for continuous variables, and Fisher exact test for categorical variables. Data are presented as mean ± SEM.

Results

The baseline characteristics of the study subjects are shown in Table 1. There were no significant differences observed between the placebo- and paricalcitol-treated groups.

Figure 2 illustrates the percent change from baseline of the levels of iPTH in the paricalcitol-treated and placebo groups. The dosage of paricalcitol is shown by the bars. According to protocol, dose increases occurred and reached a mean level of 0.12 ± 0.01 μg/kg. PTH levels decreased significantly in the paricalcitol-treated group, declining by approximately 60%

Table 1. Baseline characteristics[a]

Characteristic	Treated	Placebo
Gender		
male	21	19
female	19	19
Age		
mean ± SD	54 ± 14	54 ± 16
	(25 to 90)	(22 to 79)
Race		
white	4	6
black	35	27
Hispanic	1	5
Baseline chemistry	785 ± 66	745 ± 52
PTH (pg/ml)	(291 to 2076)	(320 to 1671)
normalized calcium	9.24 ± 0.1	9.06 ± 0.1
(mg/dl)	(7.2 to 10.4)	(7.8 to 10.7)
measured calcium	8.9 ± 0.1	8.7 ± 0.1
(mg/dl)	(6.9 to 10.6)	(7.6 to 10.5)
phosphorus (mg/dl)	5.86 ± 0.2	6.00 ± 0.3
	(3.7 to 10.2)	(2.8 to 8.8)

[a] Ranges are indicated in parentheses. There are no significant differences between the placebo- and paricalcitol-treated groups. PTH, parathyroid hormone.

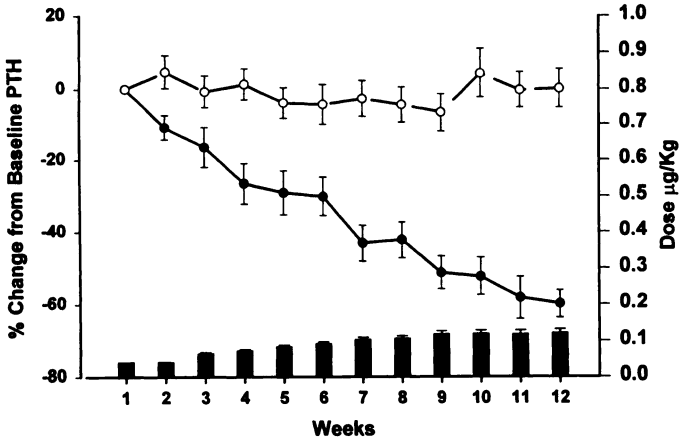

Figure 2. The changes in the levels of intact parathyroid hormone expressed as percentage change from baseline values during the study period in placebo-treated (○) and paricalcitol-treated (●) groups. The bars depict the doses of paricalcitol that increased according to protocol.

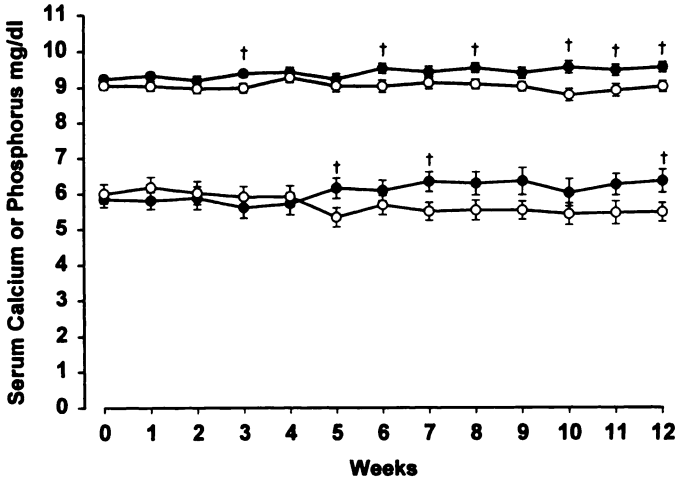

Figure 4. The values for normalized serum calcium (upper lines) and serum phosphorus (lower lines) during the 12 wk of study in placebo (○) and paricalcitol-treated (●) groups. $^{\dagger}P < 0.05$.

from the baseline values, a decrease that exceeded the target decrement of 30%. A decrease in PTH by >30% was achieved in 87% of the patients at some point during the study period.

Figure 3 illustrates the absolute values for the levels of iPTH at baseline and at follow-up in the patients who received placebo treatment for 12 wk (left panel). Mean PTH values were 680 ± 45 pg/ml (range, 320 to 1505) before treatment and 592 ± 41 pg/ml (range, 340 to 1314) after 12 wk, values that were not statistically different. In contrast, the right panel shows the absolute values for the levels of iPTH at baseline and at follow-up after 12 wk of therapy with paricalcitol. The mean PTH value in this group at the start of therapy was 795 ± 86 pg/ml (range, 291 to 2076), which decreased to a mean value of 406 ± 106 pg/ml (range, 40 to 2388), a difference that was highly significant ($P < 0.001$).

Figure 4 illustrates the serum calcium and phosphorus values in placebo- and paricalcitol-treated patients. The mean serum calcium did not change in the placebo group (9.06 ± 0.1 mg/dl at baseline and 9.02 ± 0.15 mg/dl at the end of the study). In the paricalcitol-treated group, mean serum calcium was 9.24 ± 0.12 at baseline and 9.56 ± 0.15 mg/dl at the end of the study, a small but statistically significant increase ($P < 0.02$) within the normal range. The mean serum phosphorus value did not change significantly during the study in either group, and was 6.00 ± 0.26 mg/dl at baseline compared with 5.48 ± 0.27 mg/dl at the end of the study in the placebo group (NS). In the paricalcitol-treated group, phosphorus values were 5.86 ± 0.24 mg/dl at baseline compared with 6.35 ± 0.32 mg/dl at study end (NS). However, statistical differences were apparent between the two groups at several periods during the study, as shown in Figure 4. Occurrences of elevations of calcium × phosphate product were relatively few, although more common in the paricalcitol-treated group (45 of 395 determinations) than in control subjects (16 of 412 determinations), but were easily corrected by adjustment of phosphate binders.

Table 2 depicts the absolute number of episodes of elevations of serum calcium that occurred during the study in both groups. Of 414 determinations of serum calcium in the paricalcitol-treated group, only 27 ever exceeded 10.5 mg/dl. Only eight episodes occurred that exceeded 11.0 mg/dl, three episodes were greater than 11.5 mg/dl, and there were only two instances in which serum calcium exceeded 12 mg/dl. In the placebo group, there were 14 episodes of serum calcium

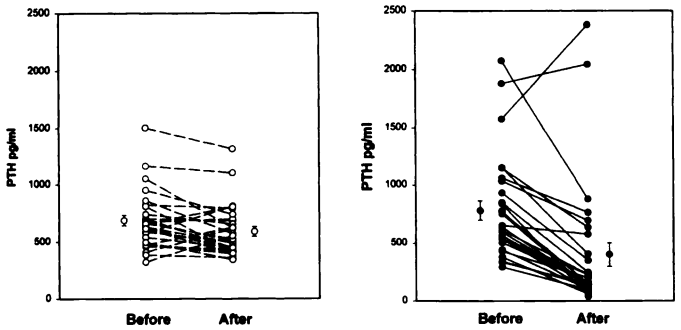

Figure 3. The absolute values for intact parathyroid hormone (PTH) before and after 12 wk of study in the placebo group (○, left panel) and in the paricalcitol-treated group (●, right panel). The mean values ± SEM are shown by the symbols that are offset from the data points. The decrease in the values in the paricalcitol-treated group are significant ($P < 0.001$).

Table 2. Episodes of increases in serum calcium during treatment[a]

Serum Calcium	>10.5 mg/dl	>11.0 mg/dl	>11.5 mg/dl	>12.0 mg/dl
Paricalcitol (n = 401)	27	8	3	2
Placebo (n = 417)	14	4	0	0

[a] n = number of determinations.

greater than 10.5 mg/dl; three greater than 11 mg/dl; and none greater than 11.5 mg/dl.

Figure 5 illustrates the changes in alkaline phosphatase and placebo in paricalcitol-treated groups. There was a significant decrease in serum alkaline phosphatase in the paricalcitol-treated group from baseline to follow-up after the 12 wk of therapy, from 148 ± 23 to 101 ± 14 U/L ($P < 0.001$), whereas no such change occurred in those on placebo for 12 wk (120 ± 9 U/L *versus* 130 ± 11 U/L; P = NS). There was also a significant difference between treatment groups for the change from baseline in alkaline phosphatase levels ($P < 0.001$).

Discussion

The therapy of hyperparathyroidism in patients with advanced renal failure includes the use of calcium-based phosphate binders such as calcium carbonate or calcium acetate to supplement dietary phosphorus restriction, as well as the use of vitamin D metabolites such as calcitriol (4). Although this therapy has been shown to be effective in achieving the suppression of elevated levels of PTH, hypercalcemia is a frequent complication (13). Similarly, because calcitriol also increases the absorption of phosphorus at the level of the intestine (10), hyperphosphatemia also often occurs such that the calcium phosphorus product may exceed 70 with the attendant risks of precipitation of calcium phosphate at extraskeletal sites, including soft tissues and the vasculature. Accordingly, it would be highly desirable to dissociate the effects of vitamin D on calcium and phosphorus absorption from the effects of vitamin D metabolites on the parathyroid. In this regard, analogs of vitamin D have been developed that have less calcemic activity than calcitriol and retain many of the effects of calcitriol on other cellular functions (11). One such analog, 19-nor-1-α-dihydroxyvitamin D_2 (paricalcitol), has been shown *in vitro* to achieve suppression of PTH that is comparable to that seen with calcitriol (12). *In vivo*, this compound was found to be less calcemic than calcitriol and was effective in suppressing elevated levels of PTH in uremic rats (12). Interestingly, this vitamin D analog was also found to be less phosphatemic than calcitriol. These results suggested that this agent might have some advantage over the currently used vitamin D metabolites. Therefore, it was important to confirm these findings in patients, because if the results were similar, then this vitamin D analog might be an improvement over calcitriol for the therapy of hyperparathyroidism.

The present studies were designed to test paricalcitol in patients with established hyperparathyroidism maintained on regular hemodialysis for safety and efficacy in double-blind, placebo-controlled multicenter trials. The results of these studies reveal that paricalcitol was effective in achieving suppression of elevated levels of PTH. PTH values decreased progressively and declined by more than 50% of the initial values over the course of the 12 wk of study. Importantly, mean serum calcium values remained within the normal range throughout the study, and there were only occasional transient elevations of serum calcium above the upper limit of normal in some patients. The few hypercalcemic episodes that occurred were all associated with a >70% decrease in PTH levels. Calcium carbonate and calcium acetate were the phosphate binders used in the studies. Aluminum-based phosphate binders were not used. Interestingly, serum phosphorus values also did not change significantly compared with the baseline values, al-

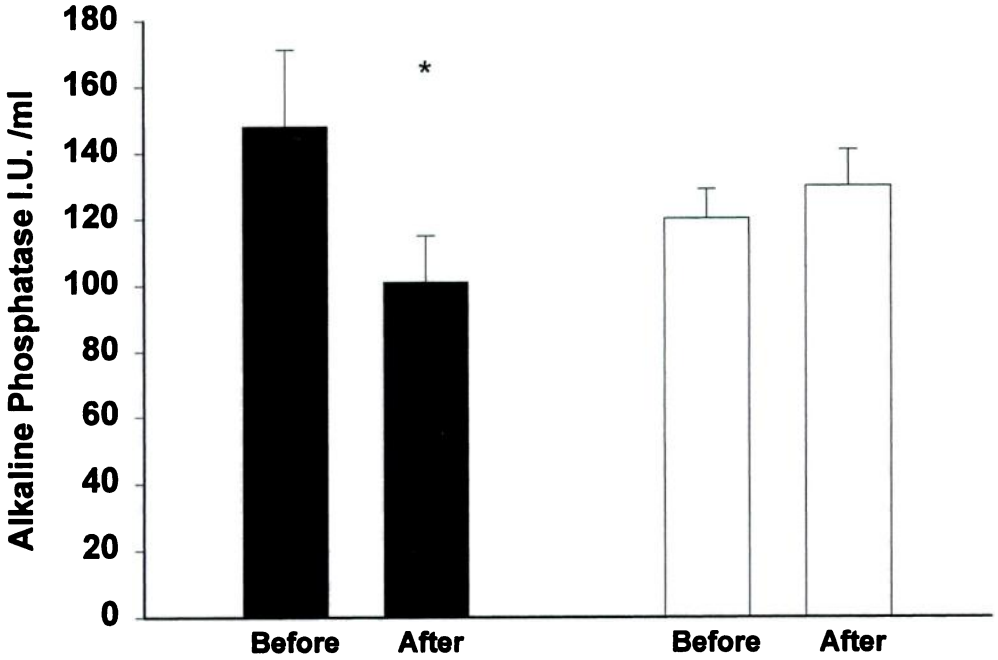

Figure 5. Changes in alkaline phosphatase before and after 12 wk of therapy in paricalcitol-treated patients (■) and in the placebo group (□). The decrease in the paricalcitol-treated group after 12 wk of therapy is significant (*$P < 0.001$).

though they tended to be slightly higher in the paricalcitol-treated group than in the group receiving placebo. Occurrences of elevations of calcium × phosphate product were relatively few, although were more common in the paricalcitol-treated group (45 of 395 determinations) than in control subjects (16 of 412 determinations), but were easily corrected by adjustment of phosphate binders so that therapy could be continued. The therapy was well tolerated, and no increase in side effects could be attributed to the paricalcitol therapy. It is important to emphasize, however, that the duration of the therapy was relatively short, and therefore one cannot conclude that disturbances of calcium and phosphorus may not become more common during prolonged therapy. Additional studies will be required to evaluate the long-term effects of therapy.

The mechanism for the decreased calcemic and phosphatemic effects of this vitamin D analog compared with calcitriol while maintaining the effect of suppression of PTH is not fully understood. Because both agents bind to and activate the vitamin D receptor, a variation in the effects on different organs would not be anticipated. One explanation for this variation would be a difference in pharmacokinetics. Thus, 22-oxacalcitriol, which also is less calcemic than calcitriol, is cleared rapidly from the circulation because of markedly decreased binding (more than 250 times less than calcitriol) to vitamin D-binding protein (DBP). Because the affinity of paricalcitol is only slightly (3 times) less than calcitriol for DBP binding, a difference in clearance does not occur (14). The possibility that altered affinity for the vitamin D receptor might account for the different biological effects must also be considered. Binding to the vitamin D receptor is 3 times less for paricalcitol than calcitriol, whereas binding of oxacalcitriol is 10 times less (A. Brown, personal communication), differences that do not appear to be large enough to explain the observed effects (11). Neither of these alterations explains the differences between organs, *e.g.*, the preservation of a robust effect on the parathyroid but a markedly decreased effect on the intestine. Preliminary evidence also indicates that paricalcitol may be less potent in causing mobilization of calcium from bone than calcitriol (15). Thus, at the present time, the mechanism for the difference in paricalcitol action is not clear. Additional studies are required to elucidate the mechanisms involved in the apparently favorable clinical effects of paricalcitol on the parathyroid while the effects on intestine and possibly bone are decreased. Other "less calcemic" vitamin D analogs that are being evaluated in clinical trials, such as 22-oxacalcitriol (16) and 1-α-(OH)-vitamin D_2 (17), also require further study, because the mechanisms of selectivity of their actions may differ from that of paricalcitol.

In summary, paricalcitol therapy was well tolerated with minimal side effects. It effectively decreased PTH by approximately 60% over the study period of 12 wk. It did not result in hypercalcemia, and mean serum phosphate values did not increase significantly. Therefore, it is suggested that this second generation vitamin D analog may have a wider "therapeutic window" than calcitriol and may be a preferable agent for the control of hyperparathyroidism in patients with end-stage renal disease on hemodialysis.

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