The Effect of Long-Term Intravenous Calcitriol Administration on Parathyroid Function in Hemodialysis Patients

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ABSTRACT
Secondary hyperparathyroidism is common in dialysis patients. Intravenous calcitriol has proven to be an effective therapy for the reduction of parathyroid hormone (PTH) levels. However, the effect of i.v. calcitriol on parathyroid function, defined as the sigmoidal PTH-calcium curve developed during hypocalcemia and hypercalcemia, has not been evaluated during the prolonged administration of i.v. calcitriol. Six hemodialysis patients with marked secondary hyperparathyroidism, PTH levels greater than 500 pg/ml (normal, 10 to 65 pg/ml), were treated for 42 wk with 20g of i.v. calcitriol after each hemodialysis. Parathyroid function was evaluated before and after 10 and 42 wk of calcitriol therapy. Between baseline and 42 wk, the basal PTH level decreased from 890 ± 107 to 346 ± 119 pg/ml (P < 0.02) and the maximally stimulated PTH level decreased from 1293 ± 188 to 600 ± 140 pg/ml (P < 0.01). In addition, calcitriol administration significantly decreased PTH levels throughout the hypocalcemic range of the PTH-calcium curve. Although the slope of the PTH-calcium curve (with maximal PTH as 100%) decreased between baseline and 42 wk (P < 0.05), the set point of calcium did not change. Two patients with a decrease in both basal and maximally stimulated PTH levels after 10 wk of calcitriol, developed marked hyperphosphatemia between 10 and 42 wk; this resulted in an exacerbation of hyperparathyroidism despite continued calcitriol therapy. In conclusion, prolonged i.v. calcitriol administration is an effective treatment for secondary hyperparathyroidism in hemodialysis patients provided that reasonable control of the serum phosphate is achieved. In addition, the slope of the PTH-calcium curve may be a better indicator of parathyroid cell sensitivity than the set point of calcium.

Key Words: Parathyroid hormone, secondary hyperparathyroidism, serum calcium, serum phosphate, set point of calcium

Secondary hyperparathyroidism is common in maintenance hemodialysis patients (1-3). It is generally associated with a form of renal osteodystrophy (osteitis fibrosa), with bone histology characterized by increased cellular activity, with an increased bone formation rate, and with endosteal fibrosis (4-6). Treatment with oral or i.v. calcitriol has decreased parathyroid hormone (PTH) levels and improved bone histology (7-12). However, in studies with oral calcitriol, it is often difficult to determine whether the observed reduction in PTH levels was due to a direct suppressive effect of calcitriol or was secondary to the increase in serum calcium induced by calcitriol (7-9). Several studies have shown that i.v. calcitriol, administered thrice weekly at the end of each hemodialysis, reduced PTH levels independent of changes in the serum calcium concentration (10,11). In a recently published study of hemodialysis patients, we showed that 20g of i.v. calcitriol administered thrice weekly for 10 wk reduced basal PTH levels. In addition, an evaluation of parathyroid function, defined as the sigmoidal PTH-calcium curve developed during the induction of hypocalcemia and hypercalcemia, showed that treatment with calcitriol reduced PTH levels throughout the PTH-calcium curve. Despite a reduction in PTH levels, the set point of calcium (defined as the serum calcium concentration necessary to reduce the maximal PTH level by
dialyses and every 30 mm throughout the hemodi-
alysis treatment. Serum chemistries including total
PTH as well as total and ionized calcium was obtained
weekly throughout the study. At the start of the low-calcium
and high-calcium dialysis (dialysate calcium, 4 mEq/L) was performed
to induce hypocalcemia and maximally stimulate
PTH secretion. The following week, a high-calcium
(dialysate calcium, 1 mEq/L) was performed
secretion. The methodology for these studies have
dialysate calcium was reduced to 2.5 mEq/L to prevent
the development of hypercalcemia. If the serum calcium exceeded 10.5 mg/dL, the calcitriol
dosage was reduced. This was only necessary in one
patient in whom, after 38 wk, the calcitriol dose was
reduced to 1 µg after each hemodialysis. In another
patient, the calcitriol dose was increased after 3 wk,
to 3 µg after each hemodialysis. During the period of
the formal study (first 10 wk), the administration of
i.v. calcitriol was based on both the total calcium
concentration and a calcium times phosphate product
less than 70. In one patient, i.v. calcitriol was
withheld for 1 wk during the first 10 wk because of
a high calcium times phosphate product. However,
after completion of the formal study, the decision to
administer i.v. calcitriol was based only on the total
serum calcium concentration and, inadvertently, the
calcium times phosphate product was not used as a
criteria. After both 10 and 42 wk of calcitriol therapy,
parathyroid function was again evaluated with a low-
and high-calcium dialysis as previously described.

From the data obtained during dialysis-induced
hypocalcemia and hypercalcemia, individual PTH-
ionized calcium curves were constructed for each
patient at baseline (0 wk) and after 10 to 42 wk of
i.v. calcitriol. As we have done in previous studies
(13–15), composite PTH-calcium curves for each
group were compiled from the individual curves. For
the analysis of the PTH-calcium curve, the following
terms are defined and illustrated in Figure 1: maximal PTH was the highest PTH level which was ob-

METHODS

Six stable maintenance hemodialysis patients were
studied. These six patients were part of a larger group
of previously reported patients who had received i.v.
calcitriol for 10 wk (13). Although the original study
was completed after 10 wk, some of the patients
continued to receive i.v. calcitriol as part of the their
treatment. When it was learned that six patients had
been treated with i.v. calcitriol for 37 to 45 wk, it
was decided to reevaluate their parathyroid function.
Before the current treatment with calcitriol, these
patients had never received calcitriol or vitamin D
analogs. Patients were selected for i.v. calcitriol ther-
apy on the basis of a serum PTH level greater than
500 pg/mL and a serum aluminum level less than 50
µg/L. Patients were dialyzed for 3.5 to 4 h thrice
weekly throughout the study period. At the start
of the study, the six patients were taking aluminum-
containing antacids to bind phosphate. Between 10
and 42 wk, calcium carbonate was added as a phos-
phate binder. The amount of calcium prescribed was
similar in the six patients. All patients were male.
Their mean age was 55 ± 4 yr (range, 38 to 62 yr),
and the mean duration of dialysis was 32 ± 9 months
(range, 6 to 60 months).

To evaluate parathyroid function, a low-calcium
dialysis (dialysate calcium, 1 mEq/L) was performed
to induce hypocalcemia and maximally stimulate
PTH secretion. The following week, a high-calcium
dialysis (dialysate calcium, 4 mEq/L) was performed
to induce hypercalcemia and maximally inhibit PTH
secretion. The methodology for these studies have
been described in detail previously (13–15). Blood for
PTH as well as total and ionized calcium was obtained
at the start of the low-calcium and the high-calcium
dialyses and every 30 min throughout the hemodi-
alysis treatment. Serum chemistries including total
calcium, phosphate, and alkaline phosphatase were
obtained immediately before the study and at regular
intervals throughout the study.

After the baseline studies, patients were treated
with 2 µg of i.v. calcitriol at the end of each hemodi-
alysis for a mean duration of 42 wk (range, 37 to 45
wk). Throughout the remainder of the text, the mean
value of 42 wk will be used. During calcitriol therapy,
the dialysate calcium was reduced to 2.5 mEq/L to
prevent the development of hypercalcemia. If the
serum calcium exceeded 10.5 mg/dL, the calcitriol
dosage was reduced. This was only necessary in one
patient in whom, after 38 wk, the calcitriol dose was
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group were compiled from the individual curves. For
the analysis of the PTH-calcium curve, the following
terms are defined and illustrated in Figure 1: maximal PTH was the highest PTH level which was ob-

Figure 1. A PTH-calcium curve from an individual patient is
presented, and the terms used for the analysis the PTH-
calcium curve are illustrated. Each of the terms is defined
in Methods.
served in response to hypocalcemia and which additional lowering of the serum-ionized calcium concentration did not further increase: \textit{minimal PTH} was the lowest PTH level during suppression by hypercalcemia and which an additional increase in serum-ionized calcium did not produce further inhibition; \textit{the slope of the sigmoidal PTH-ionized calcium curve} was calculated as the PTH concentration at maximal PTH minus the PTH concentration at minimal PTH divided by the difference between the serum-ionized calcium concentration at which maximal PTH and minimal PTH were observed; this slope, when the maximal PTH concentration is represented as 100\% should indicate the sensitivity of parathyroid cells (defined as the change in PTH for the change in ionized calcium) and should thus provide an appropriate comparison of groups with different absolute PTH concentrations; \textit{the set point of calcium} was the serum-ionized calcium concentration at which maximal PTH secretion was reduced by 50\%; \textit{the ionized calcium concentration at maximal PTH} was the serum-ionized calcium concentration at which maximal PTH was first observed; and \textit{the ionized calcium concentration at minimal PTH} was the serum-ionized calcium concentration at which minimal PTH was first observed. In addition to the above-illustrated terms, in this study, the \textit{basal PTH} was defined as the PTH level obtained immediately before the performance of the low-calcium dialysis and the \textit{basal ionized calcium} was the serum-ionized calcium concentration obtained immediately before the low-calcium dialysis. In all six patients, the basal PTH and basal ionized calcium concentrations were similar before the low- and high-calcium dialyses.

Intact parathyroid hormone was measured by the immunoradiometric assay (Allegro, Nichols Institute, San Juan Capistrano, CA). Validation of this assay in dialysis patients has been shown in previous studies (9,13–15). Normal values are 10 to 65 pg/mL. Serum-ionized calcium was measured with an ICA1 ionized calcium analyzer (Radiometer A/S, Copenhagen, Denmark). Serum phosphate, alkaline phosphatase, and total calcium were measured with a Technicon SMA II autoanalyzer (Technicon, Tarrytown, NY). Serum aluminum was determined by flameless atomic absorption spectrophotometry as previously described (16). Informed consent was obtained from each patient in a protocol approved by the Institutional Review Board.

Data were analyzed by \textit{t} test for paired comparisons and analysis of variance for repeated measures. Results are expressed as the mean ± SE.

**RESULTS**

In Table 1, the serum chemistries at 0, 10, and 42 wk are presented. The mean values provided represent the mean of three values before the start of calcitriol (0 wk), the mean of all values between 0 and 10 wk (10 wk), and the mean of all values between 10 and 42 wk (42 wk). Total serum calcium increased between 0 and 42 wk. The mean serum phosphate did not change during the course of the study. However, between 10 and 42 wk, two patients were notable because of poor control of their serum phosphate. During this interval in these two patients, the serum phosphate increased from 6.8 to 10.1 and from 9.6 to 11.3 mg/dL, respectively. Between 0 and 42 wk, the serum alkaline phosphatase decreased from 260 to 165 U/L, but this decrease was not significant despite a decline in five of the six patients. The exception was a patient who developed marked hyperphosphatemia.

In Table 2, the maximal, basal, and minimal PTH values are presented before and after 10 and 42 wk of calcitriol. Significant decreases in maximal and basal PTH levels were observed between 0 and 10 wk and between 0 and 42 wk, but not between 10 and 42 wk. However, if the two patients who developed marked hyperphosphatemia between 10 and 42 wk are excluded, significant decreases in the maximal (\(P = 0.035\)) and basal PTH (\(P = 0.024\)) levels were observed between 10 and 42 wk. No significant differences in the basal ionized calcium concentration, the ionized calcium concentration at maximal PTH, and the ionized calcium concentration at minimal PTH were observed; this was true even if the two patients who developed marked hyperphosphatemia were excluded. Although the ratio of basal to maxi-

<table>
<thead>
<tr>
<th>TABLE 1. Biochemical data before and after 10 and 42 wk of i.v. calcitriol$^a$</th>
<th>0 wk</th>
<th>10 wk</th>
<th>42 wk</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium (mg/dL)</td>
<td>8.78 ± 0.41</td>
<td>9.25 ± 0.29</td>
<td>9.57 ± 0.27$^b$</td>
<td>8.5–10.5</td>
</tr>
<tr>
<td>Serum Phosphate (mg/dL)</td>
<td>7.23 ± 1.0</td>
<td>7.25 ± 0.66</td>
<td>7.98 ± 0.95</td>
<td>2.5–4.5</td>
</tr>
<tr>
<td>Serum Alkaline Phosphatase (U/L)</td>
<td>260 ± 77</td>
<td>202 ± 46</td>
<td>165 ± 34</td>
<td>40–115</td>
</tr>
</tbody>
</table>

$^a$ Values are mean ± SE.

$^b$ \(P < 0.05\) versus 0 wk.
TABLE 2. Parameters of the PTH-calcium curve before and after 10 and 42 wk of i.v. calcitriol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 wk</th>
<th>10 wk</th>
<th>42 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal PTH (pg/mL)</td>
<td>890 ± 107</td>
<td>483 ± 89&lt;sup&gt;a&lt;/sup&gt;</td>
<td>346 ± 119&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maximal PTH (pg/mL)</td>
<td>1293 ± 188</td>
<td>883 ± 126&lt;sup&gt;b&lt;/sup&gt;</td>
<td>600 ± 140&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Minimal PTH (pg/mL)</td>
<td>227 ± 51</td>
<td>158 ± 12</td>
<td>132 ± 27</td>
</tr>
<tr>
<td>Basal/Maximal PTH (%)</td>
<td>72 ± 9</td>
<td>55 ± 9</td>
<td>51 ± 8</td>
</tr>
<tr>
<td>Set Point of Calcium (mg/dL)</td>
<td>4.58 ± 0.17</td>
<td>4.54 ± 0.10</td>
<td>4.68 ± 0.23</td>
</tr>
<tr>
<td>Slope of PTH-Calcium Curve (%)</td>
<td>-168 ± 34</td>
<td>-176 ± 30</td>
<td>-90 ± 14&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ionized Calcium at Maximal PTH (mg/dL)</td>
<td>4.27 ± 0.18</td>
<td>4.27 ± 0.13</td>
<td>4.16 ± 0.23</td>
</tr>
<tr>
<td>Ionized Calcium at Basal PTH (mg/dL)</td>
<td>4.41 ± 0.17</td>
<td>4.43 ± 0.09</td>
<td>4.58 ± 0.29</td>
</tr>
<tr>
<td>Ionized Calcium at Minimal PTH (mg/dL)</td>
<td>4.91 ± 0.15</td>
<td>4.79 ± 0.10</td>
<td>5.10 ± 0.20</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are mean ± SE.
<sup>b</sup> P < 0.05 versus 0 wk.

The development of marked hyperphosphatemia in two patients appeared to negate the inhibitory effect of calcitriol on PTH secretion. This is illustrated in Figures 4A and B. Basal (Figure 4A) and maximal (Figure 4B) PTH levels decreased in all patients between 0 and 10 wk and continued to decrease in the four patients with reasonably controlled serum phosphate levels. However, in the two patients who developed marked hyperphosphatemia, patients 5 and 6, basal and maximal PTH levels increased between 10 and 42 wk. The mean serum phosphate and calcium values during this time period are shown for the six patients in Table 3. The serum phosphate levels ranged from 5.32 to 11.28 mg/dL and were considerably higher in patients 5 and 6. Similarly, the serum calcium levels were lower in patients 5 and 6.

DISCUSSION

The results of this study demonstrate that long-term administration of i.v. calcitriol effectively reduced PTH levels in hemodialysis patients with...
marked secondary hyperparathyroidism. Both basal and maximal PTH levels were reduced after 10 and 42 wk of calcitriol. In addition, calcitriol administration reduced PTH levels throughout the hypocalcemic range of the PTH-calcium curves. Calcitriol administration reduced the slope of the PTH-calcium curve even though the set point of calcium did not change. However, the results of this study also indicate that control of the serum phosphate is essential for calcitriol administration to effectively reduce PTH levels.

Although treatment with calcitriol for 42 wk did increase the total serum calcium concentration, the reduction of the dialysate calcium concentration to 2.5 mEq/L at the commencement of calcitriol therapy effectively prevented marked increases in serum calcium. At the end of the study, only one patient had a serum calcium concentration greater than 10.1 mg/dL; in this patient, the calcitriol dose was reduced after 38 wk to 1 μg after each hemodialysis. Optimal control of the serum phosphate was difficult to achieve in two patients. It is possible that through its effect on gut absorption of phosphate, calcitriol contributed to the elevation of serum phosphate (17). However, before the start of this study, these two patients had very high serum phosphate levels. Because lowering of the serum phosphate was achieved during the first 10 wk at a time when PTH was highest, it is likely that noncompliance was an important factor in these two patients, especially because control of the serum phosphate was not a problem in the other patients.

Treatment with i.v. calcitriol reduced basal and maximally stimulated PTH levels as well as PTH levels throughout the hypocalcemic range of the PTH-calcium curve. We and others have shown that i.v. calcitriol for up to 10 wk decreased hypocalcemia-stimulated PTH secretion (10,11,13). Longer studies have shown that both oral and i.v. calcitriol reduced basal PTH levels (8,9,12). However, in these studies, it is often difficult to separate the effect of calcitriol from that produced by the increase in the serum calcium concentrations. In the study presented here,
calcitriol treatment did not significantly reduce basal and maximally stimulated PTH levels between 10 and 42 wk. However, in Figure 4, it can be ascertained that the two patients (patients 5 and 6) who developed marked hyperphosphatemia during this interval had increases in their basal and maximally stimulated PTH levels that affected the comparisons. If these two patients are excluded, then significant reductions in basal and maximally stimulated PTH levels were observed in the remaining patients. Similarly, between 10 and 42 wk, PTH values in the hypocalcemic range of the two PTH-calcium curves were significantly lower with the exclusion of these two patients.

Studies in renal failure have established that hyperphosphatemia exacerbates the magnitude of secondary hyperparathyroidism (18-20). One mechanism is that hyperphosphatemia produced skeletal resistance to the calcemic action of PTH (21,22). Little information is available about whether marked hyperphosphatemia directly affects PTH secretion. Despite the presumed presence of high circulating levels of calcitriol, basal and maximal PTH levels increased between 10 and 42 wk in the two patients with marked hyperphosphatemia. The mean serum phosphate levels in these two patients exceeded 10 mg/dL and were more than 2 mg/dL greater than those of any of the other patients. Thus, even though calcitriol is known to directly inhibit PTH production (23–25) and may also improve the calcemic response to PTH (26,27), it did not counteract the stimulus for hyperparathyroidism induced by marked hyperphosphatemia.

An important finding in the study presented here was that the slope of the PTH-calcium curve decreased between 0 to 42 wk, whereas the set point of calcium for the three PTH-calcium curves did not change. The set point is often presented as a marker of the sensitivity of the parathyroid gland to calcium (11,28,29). However, it is our belief as well as that of others (30) that the slope of the PTH-calcium curve (with maximal PTH represented as 100% to provide an assessment of PTH production per parathyroid cell) is a better indicator of the sensitivity of the parathyroid cell. Thus, sensitivity would represent the change in PTH production for the change in serum calcium concentration. We believe the set point may be a better indicator of the serum calcium level at which PTH secretion is stimulated. The results of the study presented here serve to support these concepts. Although treatment with calcitriol for 42 wk decreased maximally stimulated PTH from 1,293 to 600 pg/mL, the set point increased minimally. However, during the same time, the slope of the PTH-calcium curve significantly decreased. Our interpretation of these findings is that the sensitivity of parathyroid cells (PTH production for the change in serum calcium) decreased, whereas the serum calcium concentration at which PTH was stimulated did not change.

In summary, six hemodialysis patients with marked secondary hyperparathyroidism were treated after each hemodialysis with high-dose i.v. calcitriol for 42 wk. Both basal and maximal PTH levels, in addition to PTH levels throughout the hypocalcemic range of the PTH-calcium curve decreased significantly. Calcitriol treatment decreased the slope of the PTH-calcium curve but did not alter the set point. Finally, two patients who developed marked hyperphosphatemia after an initial response to calcitriol had exacerbation of their hyperparathyroidism despite continued calcitriol therapy. In conclusion, i.v. calcitriol is an effective treatment of secondary hyperparathyroidism in hemodialysis patients provided that reasonable control of the serum phosphate is achieved. In addition, the slope of the PTH-calcium curve may be a better indicator of parathyroid sensitivity than is the set point of calcium.

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Calcitriol and Parathyroid Function


