Guidelines for dosing of intravenous calcitriol in dialysis patients with hyperparathyroidism

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Abstract. Intravenous calcitriol has not been used appropriately in the treatment of secondary hyperparathyroidism (HPT) of dialysis patients. Initiation of calcitriol therapy late in severe HPT and inappropriate dosing of calcitriol are common causes of inadequate use of calcitriol. This paper gives general guidelines on the use of intravenous calcitriol and emphasizes the importance of appropriate control of serum phosphorous. The issue of dosing of calcitriol commensurate with the severity of the HPT are highlighted as essential for the complexion of a successful therapeutic attempt. In addition, maintenance dose of calcitriol varies according to the severity of the HPT at the time of initiation of therapy.

Key words: Dosing calcitriol; intravenous calcitriol; hyperphosphataemia; parathyroid hormone; secondary hyperparathyroidism

Introduction

Since the description that calcitriol, per se, has a direct inhibitory effect in the synthesis and secretion of parathyroid hormone (PTH), clinical studies have shown that intravenous (IV) calcitriol has a potent inhibiting effect on plasma PTH in dialysis patients [1–5]; and this effect is independent of the level of serum calcium concentration. Also, it appears that the peak serum concentration of calcitriol is the most important factor in determining the efficacy of IV calcitriol [6].

Over the last decade several studies have been published on the use of IV calcitriol in secondary hyperparathyroidism (HPT) [1–5]. However, at present there are no specific guidelines on the use of IV calcitriol. In general, there is uncertainty on the dose of calcitriol to be used in patients with HPT. In addition, there is controversy with regard to the need for and timing of parathyroidectomy. Also, the presence of soft tissue calcification and the increasing incidence of adynamic bone lesion have made the use of calcitriol more difficult and subject to more details. Some of the uncertainty may be due to the fact that IV calcitriol has been tried in groups of patients in whom the severity of HPT and dosing of calcitriol has varied greatly. Furthermore, until recently, there has not been a uniform way to assess the PTH response to IV calcitriol. The advent of the immunoradiometric assay for PTH has allowed for an accurate diagnosis and follow-up of patients with HPT.

The purpose of this presentation is to discuss guidelines on the use of IV calcitriol with special emphasis on dosing. What PTH concentration requires the administration of IV calcitriol? What are the factors determining the initial dose? When do we modify the initial dose and adjust it for long-term therapy? We will try to answer these questions based on the available data, as well as our own experience.

Data from previous clinical studies on the use of IV calcitriol are summarized in Table 1. From these studies, the following conclusions can be made. (1) Many studies have used IV calcitriol as the last therapeutic attempt. This is suggested by the high levels of PTH, serum Ca and duration of dialytic therapy. (2) The initial dose of calcitriol was variable, from 0.5 to 2.3 μg/dialysis. In general, a dose of 2 μg was more successful than doses less than 1 μg/dialysis. (3) Most failures to respond were due to an increased Ca × PO₄ product which resulted in a significant lowering of the dose [7]. (4) Few data are available regarding calcitriol dosing and even fewer in which doses greater than 2 μg were used. Fernandez et al. increased the dose sequentially in three patients: they received 2 μg, then 4 μg, then finally 6 μg; this regimen was successful in two patients [8]. (5) A dose of IV calcitriol of 2 μg was effective in most cases, as is shown by the percentage decrease of PTH. In some of these studies, the percentage decrease of PTH was not specified and the value noted has been extrapolated from the PTH decrease in absolute values. (6) The follow-up period was short in the majority of the studies, from 2 to 24 months. Thus, there are no follow-up data longer than 1 year.

It appears that the use of bolus administration of IV calcitriol has significant advantages over other therapeutic approaches. First, experimentally, Reichel...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Baseline iPTH (pg/ml)</th>
<th>Baseline serum Ca (mg/dl)</th>
<th>Baseline serum P (mg/dl)</th>
<th>Average reduction of iPTH after therapy (%)</th>
<th>Initial/final dose (µg/dialysis)</th>
<th>Treatment withdrawal due to Ca × P &gt; 70</th>
<th>Treatment period (months)</th>
<th>Treatment duration (years)</th>
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<tr>
<td>Slatopolsky [9]</td>
<td>20</td>
<td>132 ± 20</td>
<td>4.1 ± 0.2</td>
<td>5.8 ± 0.3</td>
<td>70.1</td>
<td>0.5/4</td>
<td>None</td>
<td>2</td>
<td>—</td>
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<td>Andress [4]</td>
<td>5</td>
<td>172 ± 34</td>
<td>10.2 ± 0.1</td>
<td>5.8 ± 0.3</td>
<td>59.9</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>8.5 ± 5</td>
</tr>
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<td>Dunlay [2]</td>
<td>6</td>
<td>1468 ± 467</td>
<td>9.3 ± 0.2</td>
<td>7.8 ± 0.9</td>
<td>48.4</td>
<td>2/2</td>
<td>None</td>
<td>2–12</td>
<td>2.8 ± 0.5</td>
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<td>Rodriguez [5]</td>
<td>6</td>
<td>890 ± 107</td>
<td>8.7 ± 0.4</td>
<td>7.2 ± 1</td>
<td>71.1</td>
<td>2/2</td>
<td>None</td>
<td>2</td>
<td>2.6 ± 0.7</td>
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<tr>
<td>Oetinger [11]</td>
<td>97</td>
<td>624 ± 61</td>
<td>8.7 ± 0.2</td>
<td>5.3 ± 0.2</td>
<td>54</td>
<td>0.5–2/1.2</td>
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<td>2</td>
<td>3.5 (0.6–6)</td>
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<td>Sprague [12]</td>
<td>21</td>
<td>&gt; 4 × normal</td>
<td>8.9 ± 0.2</td>
<td>4.5 ± 0.2</td>
<td>29 ± 5</td>
<td>0.50/0.5/1–1</td>
<td>4</td>
<td>24</td>
<td>—</td>
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<tr>
<td>Gallieni [19]</td>
<td>Res: 58</td>
<td>793 ± 93</td>
<td>9.05 ± 0.09</td>
<td>5.0 ± 0.1</td>
<td>48.2</td>
<td>0.90/0.77</td>
<td>4</td>
<td>4</td>
<td>&gt; 6 months</td>
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<td>Italic. study</td>
<td>No ref: 18</td>
<td>642 ± 106</td>
<td>9.1 ± 0.1</td>
<td>4.6 ± 0.3</td>
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<td></td>
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<td>Malberti [13]</td>
<td>10</td>
<td>1069 ± 700</td>
<td>10.5 ± 0.6</td>
<td>4.65 ± 1.1</td>
<td>66.9</td>
<td>2/3.7</td>
<td>2</td>
<td>2–4</td>
<td>—</td>
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<td>Quarles [7]</td>
<td>9</td>
<td>932 ± 158</td>
<td>9.2 ± 0.2</td>
<td>6.5 ± 0.4</td>
<td>27</td>
<td>2.3 ± 2.1</td>
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<td>9</td>
<td>4.5 ± 0.9</td>
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<td>Cannella [3]</td>
<td>8</td>
<td>966 ± 160</td>
<td>9.2 ± 0.05</td>
<td>5.4 ± 0.3</td>
<td>80</td>
<td>2.1 ± 1.8</td>
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<td>Caravaca [22]</td>
<td>11</td>
<td>666 ± 280</td>
<td>9.4 ± 0.6</td>
<td>5.21 ± 1.2</td>
<td>14.6</td>
<td>1.05</td>
<td>None</td>
<td>2.5</td>
<td>7.3</td>
</tr>
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<td>Fernandez [21]</td>
<td>10</td>
<td>1.135 ± 436</td>
<td>10.1 ± 0.19</td>
<td>7.02 ± 1.3</td>
<td>80.6</td>
<td>2/1.4</td>
<td>5</td>
<td>18</td>
<td>6.7 ± 3/6</td>
</tr>
</tbody>
</table>

1 Mid-region/C-terminal antiserum (uleq/ml).
2 Ionized calcium (mg/dl).
3 Amino-terminal antiserum (normal range 8–24 ng/l).
4 Carboxy-terminal assay (normal range <10 mEq/l).
5 30 ng/kg body wt (corresponding to a total dose of 2.1 µg for a 70 kg subject).
6 In 3 patients the dose was increased sequentially to 6 µg. (After an 18 month follow-up, 5 patients were kept on treatment with lower maintenance doses than the initial ones).
7 Mean final dose 1.21 ± 0.79.
et al. showed suppression of PTH synthesis was greater with bolus administration of calcitriol as compared with continuous administration [6]. This was so despite the fact that after evaluating the sequential blood concentrations of calcitriol the area under the curve was greater in the group receiving continuous administration than the bolus. Second, in clinical studies, the peak serum calcitriol achieved with IV calcitriol was five to eight times greater than that with oral therapy [9]. Also, Slapolsky et al. noted that, in vitro, the inhibitory effect of calcitriol was dose dependent [9]. Furthermore, the clinical data suggest that IV calcitriol induced less hypercalcaemia and hyperphosphataemia than oral vitamin D analogues, which may be due to the bypassing of the intestinal mucosa. However, experimental data to confirm this are not available.

Initially, a marked decrease in PTH was noted after IV calcitriol; this occurred in the absence of an increase of serum Ca, suggesting a potent inhibitory effect of calcitriol on PTH synthesis and thus decreased bone resorption [2]; this in turn results in an influx of Ca on phosphorus back to the bone. Later, as the HPT is controlled, the maintenance of calcitriol therapy may increase gut absorption of Ca which in turn may increase serum Ca concentration.

Whether the administration of IV calcitriol leads to regression of parathyroid hyperplasia is not clear. It would appear that if, after renal transplantation, involution of the parathyroid hyperplasia occurs, a similar effect may be achieved after long-term administration of IV calcitriol. Preliminary clinical studies using various ultrasound techniques have noted a decrease in the parathyroid gland size after the administration of IV calcitriol [3]. In the experimental uraemic animal, the intraperitoneal administration of calcitriol resulted in enhanced cellular apoptosis of the parathyroid cells [10]. On the other hand, recent data suggest the possibility that the parathyroid may reach a size where monoclonal hyperplasia occurs, which in turn may lead to autonomous growth [11].

Guidelines for IV calcitriol dosing

A consensus conference on this subject, held in Orlando at the Annual Meeting of the American Society of Nephrology 1994, agreed that the most important parameter in determining the initial dose of calcitriol was the severity of the HPT. Also, it was agreed that the presence of PTH > 200 pg/ml was an indication for the commencement of IV calcitriol.

Mild–moderate HPT

It was agreed that the mild to moderate HPT group included mostly asymptomatic patients with PTH between 200 and 600 pg/ml. The initial dose of IV calcitriol should be 0.5–1 µg/dialysis. Although there are few data available on mild HPT, Sprague et al. convincingly showed that 0.5–1 µg/dialysis was effective in lowering PTH and was not associated with hypercalcaemia or hyperphosphataemia [12]. After a significant reduction in PTH, many patients were maintained on 0.5 µg/dialysis for 2 years; this occurred without any further increase or oversuppression of PTH.

Moderate–severe HPT

This is defined as PTH values between 600 and 1200 pg/ml. At this stage, it is advised to initiate therapy with 2–4 µg/dialysis. Available data suggest that such a dose controls most patients with moderate to severe HPT. Thus, Cannella et al. used 2–4 µg IV calcitriol in patients with a mean PTH of 900 pg/ml and were able to control the HPT, as well as decrease the size of the parathyroid gland [3]. Likewise, Malberti et al. achieved good control of the HPT using 2 µg/dialysis [13]. Also, they noted a shift of the PTH/Ca sigmoidal curve, as well as the set point of Ca towards the left. Similar observations were made earlier by Dunlay et al. in patients with a mean PTH of 900 pg/ml treated with 2 µg/dialysis [2].

Overt severe HPT

Once PTH is greater than 1200 pg/ml, the control of HPT is difficult. It appears that at this stage the severe diffuse hyperplasia may become nodular with lower numbers of vitamin D receptors (VDR) in the parathyroid glands. Studies by Fukuda et al. performed in parathyroidectomized glands showed that these nodules had decreased numbers of VDR [14]. They hypothesized that at this stage patients may become resistant to calcitriol. Of interest, none of their patients were treated with IV calcitriol prior to parathyroidectomy. However, recent data from Dressler et al. noted a good response to IV calcitriol in 17 patients with severe HPT [15]. A 92% reduction in PTH was achieved with a mean dose of IV calcitriol of 4 µg/dialysis; a maximum dose of 8 µg/dialysis was necessary in six patients with values ranging from 1200 to 1600 pg/ml; within 12 months PTH decreased to 300 pg/ml. By the end of the study, the dose of IV calcitriol was 1 µg/dialysis.

Since few data are available with regards to IV calcitriol therapy in patients with overt severe HPT, we evaluated prospectively 10 patients with PTH > 1200 pg/ml. The main goal was to test: (i) the possibility of resistance to IV calcitriol therapy; and (ii) calcitriol dosing commensurate with the severity of HPT. Finally, a major effort was placed on the control of hyperphosphataemia. Ten patients with a mean PTH of 1826±146 pg/ml were studied. Both patients and their closest relative were given a short dietetic course (1 week) by the renal dietitian on dietary P restriction and on the use of P binders. Within 2–3 weeks, the patients had reduced their serum P to < 6.5 mg/dL. Then, IV calcitriol was administered in dosage commensurate with PTH concentrations. Patients with PTH between 1200 and 1500 pg/ml received 2 µg/dialysis, patients with PTH > 1500 pg/ml initially received 4 µg/dialysis and patients with PTH > 1800 pg/ml were started on 4–6 µg/dialysis.
Within 1–2 weeks, plasma PTH was checked and if unchanged or increasing, the dose was increased by 2 µg/dialysis. Once PTH was in a decreasing trend, the dose was maintained and, if PTH decreased by 25–30%, the dose was reduced. Thereafter, the dose of calcitriol was reduced in a stepwise fashion. Patients were followed for a mean of 42 weeks (range 40–72 weeks). Calcitriol was not discontinued unless serum Ca > 12 mg/dl, Ca × P product > 70 mg/dl or serum P > 8 mg/dl. The biochemical data and calcitriol doses for the 10 patients are shown in Figure 1. Once the appropriate dose of IV calcitriol was reached, there was a dramatic decrease in PTH and by the end of the study the value was 211 ± 48 pg/ml. There were three episodes of hypercalcaemia in one patient. The dose of calcitriol had to be increased in seven patients. Figure 2 shows details for a representative dialysis patient in which the calcitriol dose was progressively increased. In this patient, once calcitriol dose was increased to 6 µg, PTH decreased dramatically. Surprisingly, in general, the maintenance dose of calcitriol, once PTH was < 300 pg/ml, was greater than expected (mean dose 1.2 µg/dialysis). An attempt to decrease the dose was invariably followed by a rapid increase in PTH (Figure 3). This most likely reflects
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Fig. 3. Note the significant increase in PTH which occurred in this patient once the dose of calcitriol was decreased to 1 µg. Note also how the dose has to be increased to 2 µg to achieve PTH inhibition.

Increased PTH
Direct?

Fig. 4. Diagrammatic representation of the negative side effects of hyperphosphataemia.

Complications of calcitriol therapy

Hypercalcaemia
The factors promoting hypercalcaemia as a consequence of calcitriol therapy are: (i) an increase gut absorption of Ca; (ii) improvement of the calcaemic response to PTH together with lack of PTH inhibition especially when low calcitriol doses are given; and (iii) the presence of aluminium bone disease.

At the consensus conference, it was agreed that it is desirable to maintain serum Ca concentration between 10 and 11.5 mg/dl. Such concentration was advised because in uraemic HPT there is a decreased sensitivity of the parathyroid cell to ambient serum Ca and the set point of Ca is shifted towards the right. Thus, a greater Ca concentration is required to inhibit PTH secretion. To minimize or avoid the hypercalcaemia, the first step is to use a dialysate Ca of 2.5 mg/dl. A greater dialysate Ca usually results in more hypercalcaemic episodes which in turn lead to a decrease in the dose of Ca binders and vitamin D therapy [16]. Furthermore, a recent study by Borrego et al. noted a shift of the set of point of Ca to the right when a dialysate Ca of 3.5 mg/dl was used [17]. The second step is to adjust the use of supplemental Ca and calcitriol to avoid a negative Ca balance which may occur with a dialysate Ca of 2.5 mg/dl. It is important to maintain predialysis serum Ca greater than 10 mg/dl, especially in lieu of new data showing that low serum Ca down-regulates VDR [18]. It is our experience that a large number of dialysis patients have serum Ca less than 9 mg/dl which may be suboptimal and be a factor in the aggravation of the HPT. In difficult cases of overt HPT with either hypercalcaemia or hyperphosphataemia, it may be necessary to decrease the Ca-containing binders, and for short periods to use aluminium-containing P binders alone or together with regular Ca-containing binders, until the Ca x PO4 product is < 70. In those cases in which there is "symptomatic" aluminium bone disease, deferoxamine therapy may be indicated.

Hyperphosphataemia
Since dietary P ingestion varies from 900 to 1200 mg/dl and the dialysis removal of P varies from 250 to 350 mg/dialysis, it is obvious that there is an obligatory positive P balance in our dialysis patients. In order of importance, the factors and steps necessary to control hyperphosphataemia are: (i) an appropriate dietary restriction of phosphorus; (ii) the correct use of P binders; and (iii) an adequate dialysis.

As we can see from Figure 4, hyperphosphataemia is not only an important factor in increasing the Ca x P product and increasing the risk for soft tissue calcification, but in addition it stimulates directly PTH secretion, thus worsening the HPT. Furthermore, a serum P > 8 mg/dl induces resistance to calcitriol-induced PTH inhibition. Thus, patients with significant hyperphosphataemia will not respond to high doses of IV calcitriol [19,20]. A recent randomized study by Quarles et al. evaluating IV calcitriol vs oral pulse therapy exemplified this point [7]. They treated patients with HPT with 2 µg of IV vs 2 µg oral calcitriol therapy. The patients' PTH concentrations were 932
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vs 902 pg/ml, respectively. By the end of the 38 period of observation, the PTH of both groups was > 600 pg/ml. There were greater than 50% episodes of hypercalcemia and 70% episodes of hyperphosphataemia. By the end of the study, the patients were receiving a much lower dose of calcitriol. The authors concluded that intermittent dosing of calcitriol was poorly tolerated and failed to control the HPT. It follows that it is essential to maintain the serum phosphorus less than 6.5 mg/dl.

In the treatment of hyperparathyroidism, it is important to emphasize three important points. First, a team effort approach is most important. The success in controlling hyperphosphataemia depends on a coordinated effort and the presence of a committed renal dietitian, dialysis nurse, social worker and nephrologist, all giving appropriate dietary education on P restriction and use of P binders to the patient. Second, the use of appropriate P binders is of paramount importance. It may be advisable to use Ca acetate in order to minimize the total amount of elemental Ca given to the patients. As mentioned earlier, the use of aluminium-containing P binders may be indicated for short periods of time. Third, it is essential to provide adequate dialysis therapy. Although the clearance of P decreased significantly after the second hour of dialysis, and the total amount of P removed with each dialysis is limited, adequacy of dialysis is necessary in the control of hyperphosphataemia.

Calcium + phosphorus product

In the interdialytic period, an excess of Ca and P may be deposited in soft tissues. Certain conditions may favour this process. These are conditions which may interfere with Ca influx into bone, such as adynamic bone lesion and aluminium bone disease.

It is accepted that the Ca x P product exceeding 70 increases the risk of soft tissue calcification. In general, the most common cause of a high product is hyperphosphataemia. Thus, again, control of hyperphosphataemia is essential to maintain this product within normal limits.

In the presence of massive tumoral calcifications, it may be advisable to perform manoeuvres which produce a negative Ca x P balance. Thus, Fernandez et al. were able to induce a significant negative Ca x P balance and dramatic shrinkage of tumoral calcinosis in a patient with severe hyperphosphataemia by using a dialysate Ca of 1 meq together with daily dialysis [21].

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References

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