

# Vitamin D Analogs for the Management of Secondary Hyperparathyroidism

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Secondary hyperparathyroidism is a common complication of kidney disease which begins early in its course and generally progressively worsens as kidney function decreases. A series of detailed investigations over the last three decades have indicated that the major pathogenetic factors involved in the generation of secondary hyperparathyroidism are phosphate retention as a consequence of decreased kidney function and decreased ability of the diseased kidney to produce the active vitamin D sterol, calcitriol<sup>1,2</sup>. Both of these factors acting independently or together with their effects on the levels of serum calcium, contribute in a major way to the generation and maintenance of hyperparathyroidism. It has also been well established that the consequences of hyperparathyroidism are important with regard to skeletal and extraskeletal effects, and thus, it is generally

accepted that hyperparathyroidism needs to be controlled. Therapy for the control of secondary hyperparathyroidism is directed at these major pathogenetic factors, and accordingly, it is reasonable to target the problem of phosphate retention by controlling hyperphosphatemia, and the impaired calcitriol production by using vitamin D sterols as part of the approach to the management of this disorder.

Initial attempts at treatment focused upon the native hormone, calcitriol, and detailed investigations have shown that calcitriol has several direct effects on parathyroid function<sup>3,5</sup>, including direct suppression of PTH gene transcription, direct regulation of parathyroid vitamin D receptor, regulation of parathyroid cell proliferation, increased expression of the calcium-sensing receptor, and under some circumstances, alterations in the setpoint for calcium. These

direct effects of calcitriol on the parathyroid provide a sound rationale for the inclusion of calcitriol in the treatment regimen. However, the principal effect of calcitriol in the body is to increase intestinal calcium absorption, which can lead to an increase in serum calcium<sup>6</sup>. It has also been well established that calcitriol increases the absorption of phosphorus from the intestine and can contribute to hyperphosphatemia<sup>7</sup>. The combination of increased calcium absorption and increased phosphorus absorption could therefore facilitate extraskeletal calcifications, which, although common in this patient group, are clearly undesirable. Accordingly, efforts were undertaken to try to minimize the toxicity of calcitriol in this regard, while maintaining the beneficial effects on parathyroid function.

The early attempts to minimize the toxicity of calcitriol involved investigation into the effect of intermittent administration, which was shown in experimental animals, by Reichel and others, to have a benefit over more constant administration in terms of suppression of parathyroid function<sup>8</sup>. In the United States, intermittent intravenous administration is the most commonly utilized regimen for the administration of active vitamin D sterols. Further efforts were then undertaken to try to evaluate structural alterations of the calcitriol molecule which might retain the desirable effects on parathyroid function, while minimizing the effects from the levels of calcium and phosphorus in the serum. Several lines of investigation in experimental systems have provided background information that the dissociation of these calcemic and phosphatemic effects from other effects of vitamin D sterols was indeed possible by structural alterations of calcitriol<sup>9</sup>. Accordingly, five vitamin D sterols have been introduced for the purposes of the control of secondary hyperparathyroidism which are listed in Table 1.

## **VITAMIN D PROHORMONES, ALFACALCIDOL AND DOXERCALCIFEROL**

The vitamin D prohormones, 1- $\alpha$ -hydroxyvitamin D<sub>2</sub> (doxercalciferol) and 1- $\alpha$ -hydroxyvitamin D<sub>3</sub> (alfacalcidol) are also in clinical use, the latter has been widely used in many parts of the world for many years. These two sterols have been investigated in detail in experimental animals and were shown to be equivalent in their abilities to increase the absorption of calcium and phosphorus from the intestine of experimental animals<sup>10</sup>. These sterols were also equivalent in raising serum calcium<sup>11</sup>. However, when administered at high dosage, it was clear that the sterol based upon the vitamin D<sub>2</sub> structure appeared to have lesser toxicity, presumably as a result of alternate degradative pathways for the vitamin D<sub>2</sub> structure<sup>11</sup>. Further investigations in the experimental settings showed that in the therapeutic range, 1- $\alpha$ -hydroxyvitaminD<sub>2</sub> and 1- $\alpha$ -hydroxyvitaminD<sub>3</sub> were equivalent in their ability to increase calcium, increase serum phosphorus, and to decrease PTH<sup>12</sup>. Accordingly, no selectivity for PTH suppression is demonstrable for these vitamin D sterols. Intravenous intermittent administration of 1- $\alpha$ -vitamin D<sub>2</sub> has been studied in patients on hemodialysis in a similar fashion to studies with paricalcitol (see below), and the results of these studies show that while there is effective suppression of PTH, there is also a significant calcemic and phosphatemic effect of 1- $\alpha$ -hydroxyvitaminD<sub>2</sub><sup>13</sup>.

## **CALCITRIOL ANALOGS, MAXACALCITOL AND FALECALCITRIOL**

Two of these calcitriol analogs, maxacalcitol and falecalcitriol, are based on the vitamin D<sub>3</sub> structure and are in use in Asia. Maxacalcitol, or 22-oxa-calcitriol, has an oxygen inserted at

**Table 1** – Synthetic Vitamin D Sterols Used for the Treatment of Secondary Hyperparathyroidism

Synthetic Compound	Parent Compound	Compound Activity	Availability in the U.S.
Paricalcitol	Vitamin D <sub>2</sub>	Active hormone	Yes
Doxercalciferol	Vitamin D <sub>2</sub>	Pro-hormone	Yes
Alfacalcidol	Vitamin D <sub>3</sub>	Pro-hormone	No
Maxacalcitol	Vitamin D <sub>3</sub>	Active hormone	No
Falecalcitriol	Vitamin D <sub>3</sub>	Active hormone	No

position 22 and results in a decreased affinity for the vitamin D receptor and for vitamin D binding protein<sup>14,15</sup>. The latter results in a very rapid clearance from plasma and may account for its lesser calcemic and phosphatemic effects. Falecalcitriol has fluorine substituted at carbons 26 and 27 and results in a very prolonged biological action<sup>16</sup>. This analog has been shown to effectively suppress PTH in limited clinical studies<sup>17</sup>.

### CALCITRIOL ANALOG, PARICALCITOL

19-nor-1,25-dihydroxyvitamin D<sub>2</sub>, paricalcitol was investigated in great detail in experimental animals by Slatopolsky and others, who showed in a series of studies that paricalcitol was less calcemic and was also markedly less phosphatemic than the native hormone, calcitriol, in experimental animals<sup>18,19</sup>. Studies designed to investigate the mechanism of this dissociation of calcemic and phosphatemic characteristics revealed that paricalcitol appeared not to induce the vitamin D receptor in the intestine, while the native hormone, calcitriol, demonstrated the characteristic marked induction of vitamin D receptor<sup>20</sup>. Accordingly, it is possible that the lesser ability of paricalcitol to increase absorp-

tion of calcium and phosphorus in the intestine is the result of the failure to increase the vitamin D receptor in intestine. Paricalcitol, however, was quite efficacious in decreasing the levels of PTH in experimental animals<sup>18</sup>, and based on these results, clinical trials were conducted in patients on hemodialysis. Paricalcitol administered intermittently and intravenously to patients on hemodialysis demonstrated a marked decrease in PTH levels with minimal changes on calcium and phosphorus in serum<sup>21</sup>. It was only when PTH levels were suppressed to levels that were regarded as excessively low (close to 100 pg/ml in the intact PTH assay), that any hypercalcemia was evident<sup>22</sup>. Further clinical studies under less rigorous conditions revealed satisfactory reduction of parathyroid hormone values, with calcium and phosphorus remaining stable over prolonged periods of time<sup>23</sup>. Additional studies were then undertaken in patients to see if the relative selectivity of paricalcitol could also be demonstrated in patients as it was in experimental animals. Accordingly, clinical studies revealed that approximately the same ratio of paricalcitol to calcitriol, 3:1 and 4:1 was required to suppress PTH in patients<sup>22,24</sup>. This dose range was similar to the dose range found in experimental animals. Additional studies by Coyne and others demonstrated that approxi-

mately eight times more paricalcitol was required than calcitriol to produce equivalent calcemic effects<sup>25</sup>, similar to the 10 fold difference that was seen in experimental animals. Studies by Sprague and others also demonstrated a lesser phosphatemic ability of paricalcitol compared to calcitriol, demonstrating that many of the same characteristics of this vitamin D analog were evident in the patients, as were seen in experimental animals, and provided a sound rationale and support for its use in patients<sup>26</sup>. Accordingly, paricalcitol now accounts for more than 90 percent of intravenous vitamin D sterol use in the United States.

#### **ARE THERE SIGNIFICANT DIFFERENCES BETWEEN VITAMIN D STEROLS?**

It is important to know if the structural alterations in the calcitriol molecule outlined above, designed to decrease toxicity, actually translate into improved clinical outcomes for patients. In this regard, retrospective studies in patients on hemodialysis by Teng *et al.* appear to reveal a survival advantage in patients treated with paricalcitol as compared to the native hormone, calcitriol<sup>27</sup>. The precise mechanism of this apparent survival advantage cannot be elucidated from these studies, but suggests that the analogs may behave differently from the native sterol. Support for this concept also comes from *in vitro* studies, in which Cardus and others have shown that calcitriol is a growth factor for vascular smooth muscle cells in culture, whereas paricalcitol does not have this effect<sup>28</sup>. Additional studies by Hirata *et al.* in Japan have shown a marked dissociation between calcitriol and 22-oxacalcitriol with regard to vascular calcification<sup>29</sup>.

These experimental observations suggest that the analogs and the native sterol may be-

have differently, and the implications of these findings is that much further work needs to be done to try to define the differences between vitamin D sterols, and to understand the mechanisms of their effects, so that perhaps other more selective analogs can be devised based upon these findings. When doxercalciferol is compared with paricalcitol in experimental animals, there is a clear therapeutic advantage for paricalcitol over doxercalciferol<sup>30</sup>, again, emphasizing that not all analogs or vitamin D sterols have a similar spectrum of effects. At the present, it would be appropriate to consider that all vitamin D sterols should not be considered alike, but we should take particular note of which particular sterol is being investigated.

#### **CLINICAL CONSIDERATIONS FOR VITAMIN D ANALOGS**

Clinical practice guidelines recently introduced provide stringent targets for PTH control and concomitant biochemistries that are very difficult to meet in the current era of practice<sup>31,32</sup>. While epidemiologic studies are beginning to provide support for these aggressive practice guidelines, in the interim, it is clear that in order to meet these therapeutic goals, the least toxic vitamin D sterols will be required, if we are to make significant progress in achieving these goals. Accordingly, vitamin D sterols that are in any way less calcemic or phosphatemic would appear to be beneficial in this regard, and hopefully, in future years, with increased research *in vivo* and *in vitro*, even more selective analogs will be developed which will lead to newer and better therapeutic agents to help in the control of hyperparathyroidism.

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