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Vitamin D Analogs: Actions and Role in the Treatment of Secondary Hyperparathyroidism

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Although calcitriol has been shown to have an important role in the pathogenesis of hyperparathyroidism, its use as a therapeutic agent often has been limited by calcemic and phosphatemic toxicity. Vitamin D analogs and the synthetic prohormones, with the potential to have lesser effects on calcium and phosphorus, have been introduced and shown to be effective therapeutic agents. Paricalcitol is used widely in the United States and may be associated with improved clinical outcomes. Further studies on the effects of these vitamin D sterols on the skeleton and further studies of potential differential effects on calcification processes will be forthcoming, and as the mechanisms of their lesser toxicity become understood, perhaps this will pave the way for a future generation of vitamin D analogs with even greater specificity for the suppression of hyperparathyroidism with lesser toxicity. *Semin Nephrol* 24:456-459 © 2004 Elsevier Inc. All rights reserved.

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It is well established that in the course of chronic kidney disease, impaired calcitriol production plays an important role in the pathogenesis of secondary hyperparathyroidism.¹⁻³ Calcitriol controls parathyroid cell growth and suppresses the synthesis and secretion of parathyroid hormone by decreasing the transcription of the parathyroid hormone (PTH) gene.⁴⁻⁷ Accordingly, the use of active vitamin D sterols is a reasonable part of the therapeutic plan for the management of the secondary hyperparathyroidism of chronic kidney disease. Although calcitriol has been shown to be effective in suppressing the levels of PTH in patients on dialysis, especially when administered intravenously,^{8,9} there is significant incidence of toxicity manifested by hypercalcemia and/or hyperphosphatemia, which can limit its use.^{10,11} These toxicities of calcitriol are the result of its effects to increase intestinal absorption of calcium and phosphate, as well as the ability to mobilize calcium and phosphate from bone. Obviously, the hypercalcemic toxicity of calcitriol may be facilitated if large amounts of calcium-containing phosphate binders also are used as part of the therapeutic plan. These toxicities may limit the ability to administer effective therapeutic doses of the sterol.

In an effort to decrease the toxicities of this therapy, vita-

min D analogs have been introduced, which may have lesser effects on calcium and phosphate absorption, but appear to retain the ability to suppress parathyroid hormone biosynthesis.¹² Currently, there are 3 vitamin D analogs and 2 synthetic prohormones that have been introduced for the treatment of secondary hyperparathyroidism. The structures of these vitamin D sterols are depicted in Figure 1.

Paricalcitol

This vitamin D analog, also known as 19-nor-1,25-dihydroxyvitamin D₂, was studied extensively and shown to be effective in suppressing PTH, with markedly lesser effects on increasing the levels of serum calcium or phosphorus.¹³ In experimental animals, paricalcitol effectively decreased the levels of PTH and was found to be 10 times less active than calcitriol in mobilizing calcium or phosphate from bone.¹⁴ Thus, this vitamin D analog could achieve a dissociation of the PTH suppressive effect of vitamin D from the calcemic and phosphatemic effects. The mechanism of this selectivity is not understood completely but it has been shown that, in contrast to the native hormone, calcitriol, paricalcitol does not up-regulate the vitamin D receptor in the intestine.¹⁵ This vitamin D analog has been studied in patients on hemodialysis and it effectively suppressed the levels of PTH with minimal effect on serum calcium or phosphorus levels.¹⁶ Paricalcitol is now in widespread use in the United States and can achieve excellent control of hyperparathyroidism.¹⁷ Although this vitamin D analog has lesser calcemic and phos-

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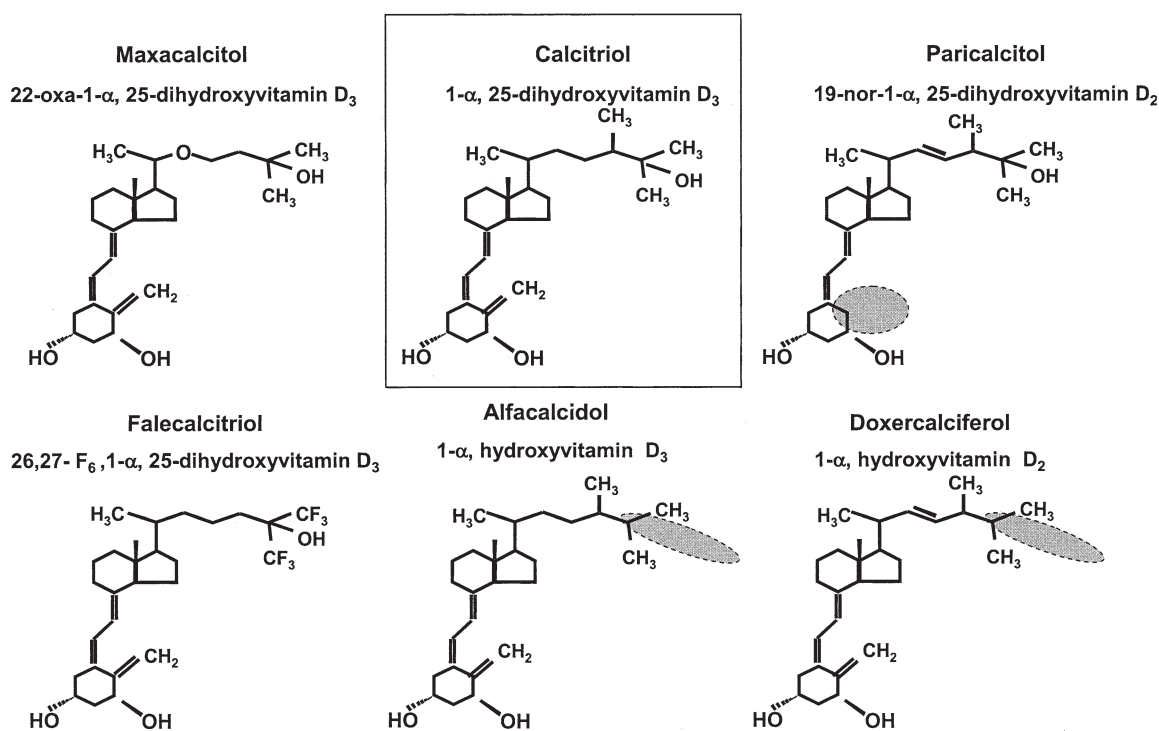


Figure 1 The structures of the native hormone, calcitriol (outlined box), compared with the synthetic vitamin D sterols used for the treatment of secondary hyperparathyroidism. Note that paricalcitol and doxercalciferol have the vitamin D₂ side-chain structure.

phatemic actions than calcitriol, hypercalcemia still can be encountered, especially if PTH is suppressed to low levels.¹⁸ Clinical studies have shown a similar therapeutic profile in patients to that seen in experimental animals. Thus, the relative potency to suppress PTH compared with calcitriol is similar to the findings in experimental animals.¹⁸ The effect of paricalcitol to mobilize calcium from bone is considerably less than calcitriol and again these observations are similar to the findings in experimental animals.¹⁹

Finally, in a comparative study between paricalcitol and calcitriol, there were less episodes of severe hyperphosphatemia in the patients treated with paricalcitol.²⁰ Recent studies have addressed the question of whether this apparent lesser calcemic and phosphatemic actions of paricalcitol translates into improved patient outcomes. In this regard, Teng et al²¹ performed a retrospective study of a large dialysis database and found an apparent survival benefit in favor of paricalcitol-treated patients, which could not be accounted for by adjustment for any known comorbidities. These observations, although retrospective, may suggest that the improved therapeutic profile with paricalcitol, compared with the native hormone, might be beneficial. Further studies would be helpful in confirming these observations.

22-Oxacalcitriol

22-oxacalcitriol is a vitamin D analog based on the vitamin D₃ structure. The structural modification of insertion of an oxygen in the 22 position results in a decreased binding affinity of 22-oxacalcitriol for the vitamin D receptor, as well as for

vitamin D-binding protein.²²⁻²⁴ The decreased binding to vitamin D-binding protein results in a very rapid clearance from the circulation. This phenomenon potentially may account for the apparent lesser toxicities of this vitamin D analog in terms of increasing calcium and phosphorus levels. This vitamin D sterol effectively suppresses PTH and has been studied in experimental animals and is now in clinical use in Asia.^{25,26} Recent studies in experimental animals show that this vitamin D analog also may have the potential to result in lesser toxicity, as shown by the absence of calcification of the heart and blood vessels of uremic animals, as compared with those treated with calcitriol.²⁷ This vitamin D sterol also has been shown to have favorable effects in ameliorating the effects of PTH on bone.^{28,29}

Falecalcitriol

Falecalcitriol is a vitamin D analog that has the substitution of hydrogen with fluorine at carbons 26 and 27. This modification results in prolonged biological activity owing to decreased metabolism of the vitamin D analog.³⁰ In limited clinical studies, this analog also has been shown to effectively suppress hyperparathyroidism and is currently in clinical use.³¹

Vitamin D Prohormones

The vitamin D prohormones, 1- α -hydroxyvitamin D₃ (alfacalcidol) and 1- α -hydroxyvitamin D₃ (doxercalciferol) are also in clinical use for the therapy of hyperparathyroidism. 1- α -hydroxyvitamin D₂ has been in clinical use for a number

of years and is used widely outside the United States.³²⁻³⁶ This vitamin D sterol becomes 25-hydroxylated in the liver after entry into the circulation and, therefore, becomes 1, 25-dihydroxyvitamin D₃. This sterol has been shown to have similar activity to calcitriol and is available both orally as well as intravenously.

1- α -hydroxyvitamin D₂ is a similar prohormone, but based on the vitamin D₂ structure. This also becomes 25-hydroxylated in the liver to become 1-25-dihydroxyvitamin D₂. In studies in experimental animals there appears to be lesser toxicity associated with vitamin D₂ compounds, especially when administered at very high doses.³⁷ It is not clear how this apparent decrease in toxicity is mediated because in experimental animals there appears to be little evidence that this sterol is less calcemic or phosphatemic than its vitamin D₃ counterpart.³⁸ It has been proposed that the apparent lesser toxicity of high doses may be owing to metabolism to 1,24-dihydroxy vitamin D₂, which may have lesser calcemic effects compared with the native hormone.³⁹ This vitamin D sterol is also in clinical use and is available in both oral and intravenous forms. Clinical studies have shown that this vitamin D sterol can effectively suppress PTH levels in patients on hemodialysis, although there was significant incidence of hypercalcemia and/or hyperphosphatemia during the clinical trials.^{40,41}

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