

# THE "D" VITAMINS

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## I. INTRODUCTION AND BIOSYNTHESIS

In a classical sense, vitamin D<sub>3</sub>, the form produced in animals, is not a true "vitamin" because it is produced in the skin from 7-dehydrocholesterol by UV radiation in the range 290 to 300 nm; 7-dehydrocholesterol is produced from cholesterol metabolism. Only when exposure to sunlight is inadequate does vitamin D<sub>3</sub> become a vitamin in the historical sense. Further, vitamin D<sub>3</sub> is now termed a provitamin because it requires hydroxylation by the liver and the kidney to be fully active.

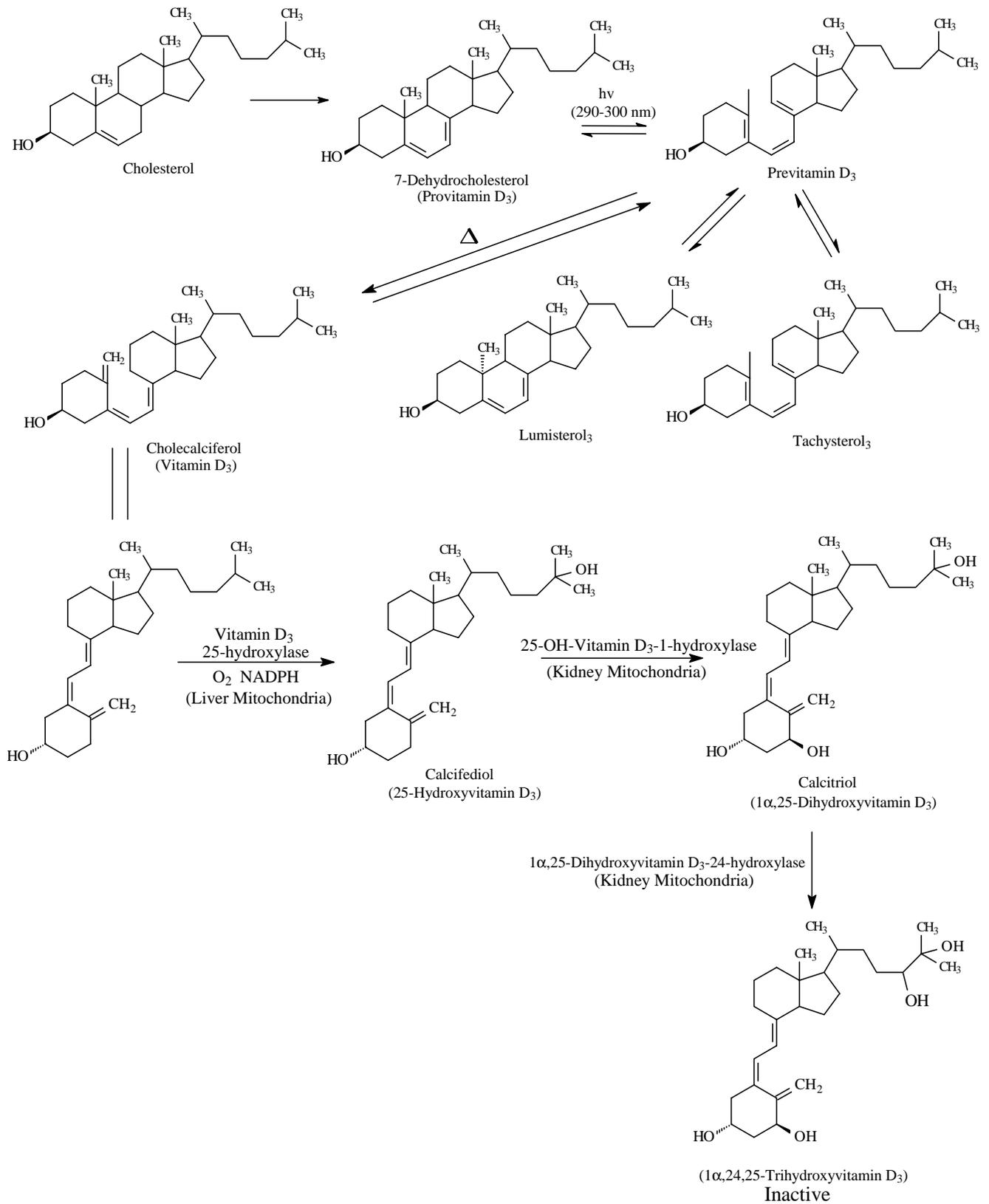
Upon UV irradiation, 7-dehydrocholesterol is converted rapidly to previtamin D<sub>3</sub> (Figure 1). Previtamin D<sub>3</sub> undergoes a slow thermal conversion to vitamin D<sub>3</sub> and the biologically inactive lumisterol<sub>3</sub> and tachysterol<sub>3</sub>. This provides a mechanism to prevent an overproduction of vitamin D<sub>3</sub> with an overexposure to sunlight, while providing a means for an adequate supply of the vitamin when exposure to sunlight is short. Excess exposure increases production of the inactive compounds. The slow conversion of previtamin D<sub>3</sub> to vitamin D<sub>3</sub> ensures adequate supplies when the exposure is brief. Further, lumisterol and tachysterol can be converted back to previtamin D<sub>3</sub>, thus serving as a reservoir. It has been estimated that a 10-minute exposure of just the uncovered hands and face suffices to produce sufficient vitamin D<sub>3</sub> (Figure 1).

The mechanism responsible for the movement of vitamin D<sub>3</sub> from the skin to the blood is not known. In the blood vitamin D<sub>3</sub> is bound primarily to a protein known as vitamin D-binding protein (VDBP). This protein selectively removes vitamin D<sub>3</sub> from the skin because it has low affinity for 7-dehydrocholesterol, previtamin D<sub>3</sub>, lumisterol and tachysterol (Figure 2).

Cholecalciferol (vitamin D<sub>3</sub>) does not perform its function, directly but must first be transformed by the liver and the kidney. The first step occurs in the liver by the enzyme vitamin D<sub>3</sub>-25-hydroxylase. This enzyme converts the provitamin to 25-hydroxyvitamin-D<sub>3</sub> (25-OH D<sub>3</sub>). This enzyme, requiring both molecular oxygen and reduced nicotinamide adenine nucleotide phosphate (NADPH), appears to be a cytochrome-P450 monooxygenase and is found in the endoplasmic reticulum and the mitochondria. The rate of this hydroxylation correlates with substrate concentration. The 25-OH D<sub>3</sub> thus, formed is the major circulating form of the vitamin bound to VDBP (Figure 1).

The epithelial cells of renal proximal convoluted tubules convert 25-OH D<sub>3</sub> to 1,25-OH D<sub>3</sub> by the enzyme 25-OHD 1 $\alpha$ -hydroxylase. The activity of this mitochondrial cytochrome P450 enzyme is controlled by 1,25-OH D<sub>3</sub> and parathyroid hormone as well as high concentrations of calcium and phosphate.

The second reaction of activation, 24-hydroxylation proceeds in the kidney, and this initiates inactivation. 1,25-OH D<sub>3</sub> can bring about the appearance of the 24-hydroxylase system that catalyzes its metabolic inactivation. The need for calcium stimulates parathyroid hormone secretion. Parathyroid hormone in turn suppresses the 24-



**Figure 1: Vitamin D biosynthesis, Activation and Inactivation**

hydroxylase and stimulates the  $1\alpha$ -hydroxylase system. When phosphate availability is below normal, the  $1\alpha$ -hydroxylase is stimulated and the 24-hydroxylase undergoes suppression.

## II. RECEPTOR BINDING AND PHYSIOLOGIC ACTIONS

As with vitamin A, most of the effects of vitamin D involve a nuclear receptor. The vitamin D receptor is a member of the steroid/thyroid hormone superfamily of receptors. When  $1\alpha,25$ -OH  $D_3$  binds to its receptor, the complex forms a heterodimer with an unoccupied RXR. This heterodimer subsequently binds to the regulatory regions on specific genes in target tissue. These regions are called vitamin D response elements (VDREs). The binding to VDREs can increase or decrease expression of genes. The proteins thus made carry out the functions of vitamin D.

The physiologic role of vitamin D is to maintain calcium homeostasis. Phosphate metabolism also is affected. Vitamin D accomplishes its role by enhancing the absorption of calcium and phosphate from the small intestines, promoting their mobilization from bone, and decreasing their excretion by the kidney. Also involved are parathyroid hormone and calcitonin.

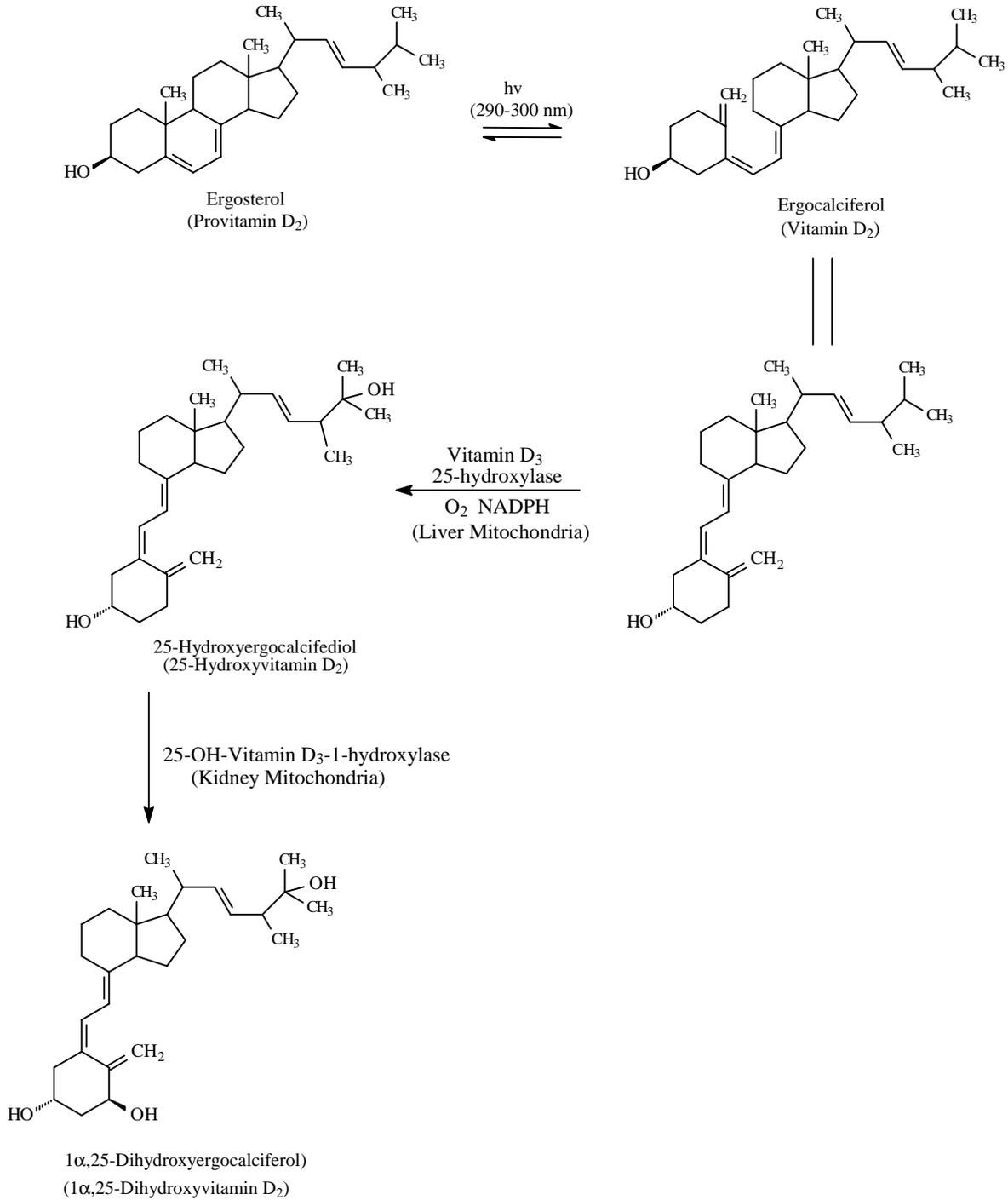
$1\alpha,25$ -OH  $D_3$  promotes  $Ca^{2+}$  intestinal absorption and increases  $Ca^{2+}$  renal reabsorption in the distal tubules and mobilization of  $Ca^{2+}$  from bone. The mechanism of action promoting  $Ca^{2+}$  transport in the intestine involves formation of a calcium-binding protein.  $1\alpha,25$ -OH  $D_3$  promotes availability of this protein. A calcium-dependent ATPase,  $Na^+$ , and the calcium-binding protein are necessary for the intestinal  $Ca^{2+}$ -transport process.  $1\alpha,25$ -OH  $D_3$  also promotes intestinal phosphate absorption, mobilization of  $Ca^{2+}$  and phosphate from bone, and renal reabsorption of  $Ca^{2+}$  and phosphate. Vitamin D deficiency results in rickets in infants and children as a result of inadequate calcification of bones. In adults, osteomalacia most often occurs during pregnancy and lactation. Rickets is rare in the United States due to fortification of foods. However, deficiencies in the elderly are the result of underexposure to sunlight.

Hypervitaminosis D may result from large doses of the vitamin or from a hypersensitivity to the vitamin. Early symptoms are associated with hypercalcemia, including fatigue, weakness, nausea, vomiting, vertigo, and bone pain. Prolonged hypercalcemia may result in calcium deposits in the kidneys, vessels, heart, lungs, and skin. Treatment includes withdrawal of the vitamin and a low-calcium diet with an increase in fluids.

Ergocalciferol (vitamin  $D_2$ ) is produced in plants from ergosterol upon UV irradiation. Vitamin  $D_2$  is the form most often used in commercial products and to fortify foods. Although different in structure, its biologic activity is comparable to that of vitamin  $D_3$  and must be bioactivated in a similar fashion (Figure 3). Ergosterol (precursor of  $D_2$ ) occurs naturally in fungi and yeast. Eggs and butter contain vitamin  $D_2$  (ergocalciferol) or  $D_3$  (cholecalciferol). Milk and bread are fortified with vitamin  $D_2$ -cholecalciferol is found in fish liver oils.

The gastrointestinal absorption of the vitamin Ds requires bile. Vitamin  $D_3$  may be absorbed better than vitamin  $D_2$ . The vitamin Ds enters the circulation through lymph chylomicrons. In the blood they are associated with vitamin D-binding protein (VDBP).

The 25-hydroxylated compounds are the major circulating metabolites. These may be stored in fats and muscle for prolonged periods. The 24-hydroxy metabolites are excreted primarily in the bile.



**Figure 3: Ergosterol and Vitamin D<sub>2</sub> metabolism**

The vitamin Ds are important in the therapeutics of hypoparathyroidism and of vitamin D deficiency. Ergocalciferol, cholecalciferol, and dihydrotachysterol are recognized by the *USP*. Although dihydrotachysterol has relatively weak antirachitic activity, it is effective and quicker acting in increasing serum  $\text{Ca}^{2+}$  concentrations in parathyroid deficiency. Dihydrotachysterol has a shorter duration of action; hence, it has less potential for toxicity from hypercalcemia.

Vitamin D receptors have been identified in tissue not normally associated with bone mineral homeostasis. Besides the intestines, kidneys, and osteoblasts, vitamin D receptors have been located in the parathyroid gland, the pancreatic islet cells, the mammary epithelium, and the skin keratinocytes. This has resulted in many investigational uses for vitamin D, including suppression of parathyroid hormone and treatment of colon and breast cancers and psoriasis. The previously mentioned investigational treatments require high doses of vitamin D. The resultant hypercalcemia and hypercalciuria limit the use of vitamin D natural metabolites. Vitamin D analogues with a decreased tendency to cause hypercalcemia and hypercalciuria are being developed and investigated. These analogues have low affinity for VDBP but retain high affinity for the vitamin D receptors. The only approved use of a vitamin D analogue is in the treatment of psoriasis with calcipotriene.

### III. VITAMIN D PRODUCTS

**Ergocalciferol, USP.** 9,10-Secoergosta-5,7,10(19),22-tetraden-3-ol (3,6,5z,7E,22E); vitamin D<sub>2</sub>; calciferol; activated ergosterol. One USP or International unit is 0.025  $\mu\text{g}$  of vitamin D<sub>3</sub>. Thus, 1  $\mu\text{g}$  equals 40 USP units. Because ergocalciferol is the least expensive of the vitamin D analogues, it is the preferred drug, unless the patient is unable to activate it. After irradiation, the steroid undergoes fission of ring B; therefore, it is known as a secosteroid. This is indicated name by the “9,10-seco” portion. The “ergosta” indicates the presence of 28 atoms in the carbon skeleton.

Ergocalciferol has a half-life of 24 hours (19 to 48 hours) and a duration of action of up to 6 months. After oral intramuscular administration, the onset of action (hypercalcemia) is 10 to 24 hours, with maximal effects seen 4 weeks, after daily administration.

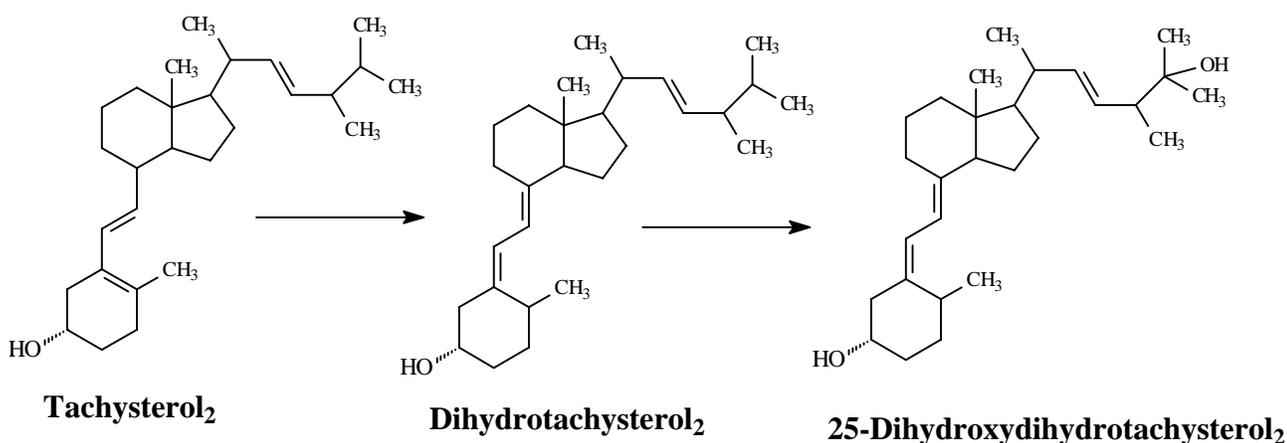
Vitamin D<sub>2</sub> is a white, odorless, crystalline compound that is soluble in fats and in the usual organic solvents including alcohol. It is insoluble in water. Vitamin D<sub>2</sub> is oxidized slowly in oils by oxygen from the air, probably through the fat peroxides that are formed. Vitamin A is much, less stable under the same conditions.

**Cholecalciferol, USP.** 9,10-secocholesta-5,7,10(19)-trien-3-ol (3,8,SZ,7E); vitamin D<sub>3</sub>; activated 7-dehydrocholesterol. It occurs as white, odorless crystals that are soluble in fatty oils, alcohol, and many organic solvents. It is insoluble in water. Vitamin D<sub>3</sub> also occurs in tuna and halibut liver oils. It humans both vitamins have equal activity.

Vitamin D<sub>3</sub> exhibits stability comparable with vitamin D<sub>2</sub>. Epimerization of the -OH at C-3 in vitamin D<sub>2</sub> or D<sub>3</sub> Or conversion of the—OH at C-3 to a ketone group greatly

diminishes the activity but does not completely destroy it. Ethers and esters that cannot be cleaved in the body have no vitamin D activity. Inversion of the hydrogen at C-9 in ergosterol and other 7-dehydrosterols prevents the normal course of irradiation.

**Dihydratachysterol (Hytakerol®):** Also known as 9,10-Ergosta-5,7,22-trien-3-ol (3,6,5E,7E,10 $\alpha$ ,22E); dihydratachysterol<sub>2</sub>; dichysterol; DHT. Tachysterol is a by-product of ergosterol irradiation. Reduction of tachysterol led to dihydratachysterol. Dihydratachysterol occurs as colorless or white crystals or a white, crystalline, odorless powder. It is soluble in alcohol, freely soluble in chloroform, sparingly soluble in vegetable oils, and practically insoluble in water.



Dihydratachysterol has slight antirachitic activity. It causes an increase of the calcium concentration in the blood, an effect for which tachysterol is only one-tenth as active. In high doses, dihydratachysterol is more effective than the other analogues for the mobilization of calcium. Thus, it is used in hypoparathyroidism.

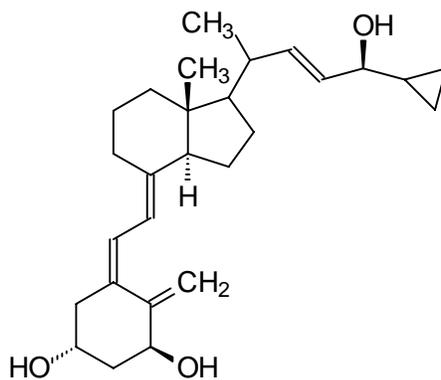
After oral administration, the onset of action is seen within hours. This fast onset of action is an advantage of this drug. Maximal activity is seen in 2 weeks after daily administration. Its duration of action is 2 weeks.

Dihydratachysterol is converted by hepatic enzymes to its active 25-hydroxylated metabolite. It does not require renal activation, for the hydroxy on ring A occupies the same position as that of the 1-hydroxyl in the activated forms of the vitamin Ds. 25-Hydroxydihydratachysterol<sub>3</sub> has weak antirachitic activity, but it is a more important bone-mobilizing agent and is more effective than dihydratachysterol<sub>3</sub>. Also, it is more effective in increasing intestinal calcium transport and bone mobilization in thyroparathyroidectornized rats. Its activity suggests that it may be the drug of choice in the treatment of hypoparathyroidism and similar bone diseases.

**Calcifediol, USP.** 9,10-Secocholesta-5,7,10(19)-trien-3,25-diol (3,6,5Z,7E); 25-hydroxy-cholecalciferol; 25-hydroxyvitamin D<sub>3</sub>. Calcifediol occurs as a white powder. It is practically insoluble in water and sensitive to light and heat. The half-life of calcifediol is 16 days (10 to 22 days). Its onset of action is seen within 2 to 6 hours, and its duration of action is 15 to 20 days. Calcifediol is indicated for patients receiving long-term renal dialysis.

**Calcitriol.** 9,10-Secocholesta-5,7,10(19)-trien-1,3,25-triol ( $1\alpha,3,8,5Z,7E$ ); 1,25-dihydroxycholecalciferol; 1,25-dihydroxyvitamin D<sub>3</sub>. It occurs as colorless crystals that are insoluble in water. Since calcitriol does not require activation, an increase in calcium absorption is seen within 2 hours of administration. Its half-life is 3 to 8 hours, and its duration of action is 1 to 2 days. Calcitriol is the most active form of vitamin D<sub>3</sub>. It is indicated in patients receiving long-term renal dialysis or who cannot properly metabolize ergocalciferol.

**Calcipotriene.** 9,10-Secocholesta-5,7,10(19),22-tetraien-1,3,25-trio-1,24-cyclopropyl- ( $1\alpha,3,6,5Z,7E,22E,24S$ ); calcipotriol. Calcipotriene is a synthetic vitamin D<sub>3</sub> analogue indicated for topical application in the treatment of moderate plaque psoriasis. It has the same affinity for the vitamin D receptor as calcitriol, but its effect on calcium metabolism is 100 to 200 times less. Calcipotriene inhibits epidermal cell proliferation and enhances cell differentiation. It reduces cell numbers and total DNA content. Antiproliferative effects are caused by a reduction in the mRNA levels of a cellular oncogene associated with proliferation, c-myc. The mechanism resulting in differentiation changes is not completely known but involves the secondary messengers inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG).



Calcipotriene

#### IV. NEW VITAMIN D PRODUCTS

##### A. Paricalcitol (*Zemplar*®)

Hyperparathyroidism is a frequent complication of chronic renal failure and requires close monitoring and treatment to prevent the complications of renal osteodystrophy. Therapy includes prevention of hyperphosphatemia by the administration of phosphate binders (calcium carbonate or acetate) and the use of vitamin D compounds such as calcitriol. For patients on hemodialysis intravenous calcitriol achieves effective suppression of elevated parathyroid hormone (PTH) levels. However, hypercalcemia and/or hyperphosphatemia are frequent complications that limit the calcitriol therapy. The newly approved synthetic vitamin D analogue paricalcitol appears to represent a more effective agent to control secondary hyperparathyroidism associated with end-

stage renal disease since it suppresses intact PTH (iPTH) levels with less impact on calcium and phosphorus metabolism. Studies in animals suggest that paricalcitol and calcitriol have different dose-response profiles and mechanisms with respect to the regulation of intestinal vitamin D receptor (VDR) content, parathyroid gland growth and bone resorption. For example, while calcitriol and paricalcitol have nearly the same vitamin D binding protein affinity and circulating half-life, only calcitriol significantly upregulates the intestinal VDR content at therapeutic doses. Also at therapeutic levels paricalcitol reduces parathyroid gland weight while calcitriol does not. Finally plasma calcium and phosphorus levels are lower in animals treated with paricalcitol compared to those treated with the same dose of calcitriol. Overall, paricalcitol is approximately ten-fold less active than calcitriol in promoting calcium and phosphorus resorption from the bone.

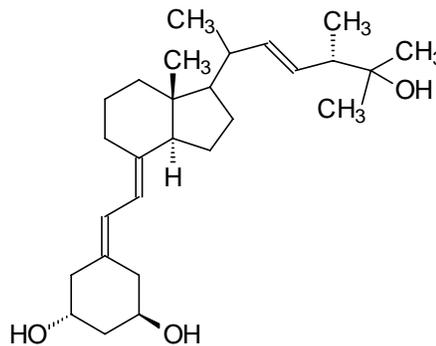
Paricalcitol has been shown to be safe and effective in reducing serum PTH levels in hemodialysis patients with secondary hyperparathyroidism associated with chronic renal failure. In general the side effect profile of paricalcitol is similar to that of calcitriol with the most common adverse reactions including nausea (13%), vomiting (8%), and edema (7%). Other adverse events observed in greater than 2% of the trial population included GI bleeding, pneumonia, chills, fever and flu, sepsis, lightheadedness, dry mouth, palpitation and miscellaneous cardiovascular and CNS effects. Of course, overdosage of paricalcitol may cause hypercalcemia with early symptoms including weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain and metallic taste. To avoid paricalcitol overdosing, serum calcium and phosphorus levels should be monitored closely. Paricalcitol doses should be reduced or therapy interrupted if symptoms of hypercalcemia are confirmed.

No specific drug interaction studies have been performed on paricalcitol. However, because of the risk of hypercalcemia in patients receiving paricalcitol, caution should be exercised when this drug is used in patients also receiving digoxin.

Bolus doses of 0.24 mcg/kg in CRF patients provides peak paricalcitol levels of 1850 pg/mL within 5 minutes. Plasma levels decrease rapidly within the first two hours after injection, and then decline in a log-linear manner with a mean half-life of about 15 hours. No accumulation of drug was observed after multiple dosing. Mean AUC, clearance and steady-state volume of distribution are 27,382 pg.hr/mL, 0.72 L/hr and 6 L, respectively. Plasma protein binding, in vitro, was >99.9%. Paricalcitol is eliminated primarily by hepatobiliary excretion with 74% of the dose recovered in feces and only 16% in urine. Several metabolites of undetermined structure have been detected in urine and feces and account more than 50% of the dose recovered. The effects of age and hepatic status on pharmacokinetics remains to be determined.

Paricalcitol is supplied as a 5 mcg/ml injection form in 1 or 2 ml single dose fliptop vials. The recommended initial dose is a 0.04 mcg/kg to 0.1 mcg/kg bolus dose no more than every other day during dialysis. The dose may be increased by 2 to 4 mcg at 2 to 4 week intervals if initial response is not satisfactory. Doses as high as 0.24 mcg/kg (16.8 mcg) have been safely administered. During any dose adjustment period, serum calcium and phosphorus levels should be monitored more frequently, and if an elevated calcium level or a Ca x P product of greater than 75 is noted, drug doses should be reduced immediately or therapy interrupted until

parameters are normalized. Drug therapy can be reinitiated at a lower dose after normalization of levels. Doses may need to be decreased as the PTH levels decrease in response to therapy. Thus, individualize incremental dosing and the manufacturer's literature should be consulted for dose titration. To ensure effectiveness of paricalcitol therapy, patients must adhere to a dietary regimen of calcium supplementation and phosphorus restriction. At present there are no adequate and well controlled studies in pregnant women. However, in animal studies high doses of paricalcitol there was a significant increase in fetal mortality linked to maternal hypercalcemia. Thus use of paricalcitol during pregnancy is advised only if the potential benefit justifies the potential risk to the fetus. Also, since it is not known whether paricalcitol is excreted in breast milk, caution should be exercised when paricalcitol is administered to nursing women.



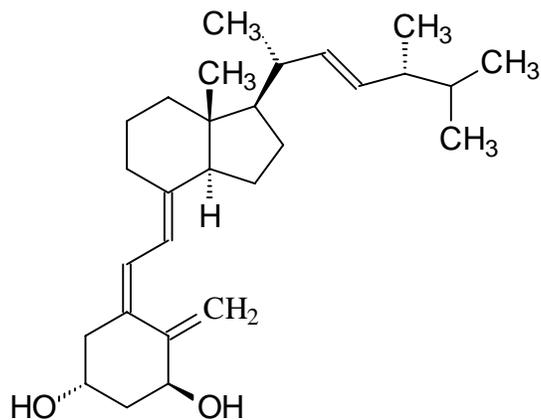
Paricalcitol

### **B. Doxercalciferol (Hectorol® - Bone Care International)**

In recent years there has been considerable interest in developing vitamin D analogues that have PTH suppressive actions comparable to calcitriol, but a lower incidence of hypercalcemia or hyperphosphatemia. Over the past several years two products with such properties have been introduced in the US, paricalcitol (Zemplar®) last year and doxercalciferol this year. Doxercalciferol is the 1 $\alpha$ -hydroxy analogue of ergocalciferol (Vitamin D<sub>2</sub>), the plant vitamin which yields hormones of activity comparable to calcitriol upon metabolic activation. Since it already contains a hydroxyl function at the 1-position, doxercalciferol requires oxidation by only hepatic (not renal) enzymes to yield an active hormone, 1 $\alpha$ ,25-dihydroxy vitamin D<sub>2</sub>. In animal models doxercalciferol is equipotent to most other vitamin D analogues in stimulating intestinal calcium transport, mobilizing calcium from bone and healing vitamin D-related disease states such as rickets. Furthermore, much higher doses of doxercalciferol are required to produce hypercalcemia, according to animal and human studies. At present it is not clear why doxercalciferol displays greater selectivity compared with calcitriol and other vitamin D products.

Doxercalciferol is indicated for the treatment of secondary hyperparathyroidism in end-stage renal disease. The dose of doxercalciferol must be individualized and based on intact parathyroid hormone (iPTH) levels with monitoring of serum calcium and serum phosphate levels. In one of the largest trials in patients with moderate-to-severe

hyperparathyroidism doxercalciferol doses of 10 micrograms (mcg) three times weekly (after dialysis initially), followed by dose adjustments, were found to maintain serum PTH levels of 150-300 pg/mL in most patients. Final doses ranged from less than 2.5 to 28 mcg per hemodialysis. Therapy was administered for a total of 16 weeks and patients received phosphate binders (calcium carbonate or acetate) to maintain serum phosphorus levels of less than 2.2 mmol/L. In another study a doxercalciferol dose of 4 mcg daily was comparable in efficacy and safety to 10 mcg three times weekly. In an 8-week, double-blind continuation of two open label studies, patients continuing on doxercalciferol maintained their reduced levels of iPTH, whereas iPTH rose again in patients taking placebo. In most studies mean increases in serum calcium have been modest during therapy (usually about 0.2 mmol/L), although episodes of asymptomatic hypercalcemia increased compared to pretreatment. Mild hyperphosphatemia also occurred, but did not appear to affect reductions in PTH. Although there are no studies directly comparing doxercalciferol with calcitriol or alfacalcidol, it appears that hypercalcemia and hypercalciuria may occur less frequently and be less severe with doxercalciferol than with alfacalcidol or calcitriol. Intravenous doxercalciferol is under investigation and data from preliminary phase III data suggest efficacy comparable to oral administration in secondary hyperparathyroidism. Doxercalciferol also is currently under investigation in postmenopausal osteoporosis. Trials to date suggest that the drug produces significant and dose-related increases in serum osteocalcin, suggesting stimulation of osteoblastic activity without altering hydroxyproline excretion (lack of



Doxercalciferol

effect on bone resorption) and renal function. Hypercalciuria was not evident at doses less than 5 mcg/day, but did occur at higher doses. Serum calcium increased with 4 mcg daily only, and clinically significant hypercalcemia was not observed at any dose.

The primary adverse reactions associated with doxercalciferol therapy are hypercalcemia, hypercalciuria, hyperphosphatemia, edema, headache, malaise. The incidence of hypercalcemia is reported to be less than that observed for calcitriol or alfacalcidol and usually can be controlled by dose reduction. Withdrawal of treatment due to hypercalcemia or hypercalciuria was required only rarely in clinical trials. In several trials, renal function, assessed by creatinine clearance and blood urea nitrogen (BUN), was not significantly affected in patients receiving up to 10 mcg of doxercalciferol.

The absorption of doxercalciferol could be reduced by cholestyramine and mineral oil since these products are reported to interfere with the absorption of other fat soluble vitamins. Patients receiving doxercalciferol should not use calcium, magnesium, or phosphorus-containing drug products (antacids) or supplements. Although not specifically studied to date, drugs that induce or inhibit hepatic enzymes have the potential to alter the rate of doxercalciferol bioactivation and this may necessitate dosage adjustments.

Doxercalciferol is rapidly absorbed from the GI tract and converted to the pharmacologically active form,  $1\alpha, 25$ -dihydroxyvitamin  $D_2$ , by hepatic cytochrome enzymes. Another minor metabolite,  $1\alpha, 24$ -dihydroxyvitamin  $D_2$  also forms. Peak blood levels of the  $1\alpha, 25$ -dihydroxyvitamin  $D_2$  metabolite occur at 11 to 12 hours after repeated oral doses of 5 to 15 mcg. The active metabolite has a half-life of 32 to 37 hours. Hemodialysis causes a temporary increase in  $1\alpha, 25$ -dihydroxyvitamin  $D_2$  mean concentrations, probably due to volume contraction. The active metabolite is not removed from blood during hemodialysis.

Doxercalciferol is manufactured as 2.5 microgram gelatin capsules which may be stored at 68 to 77°F. The optimal dose of doxercalciferol must be carefully determined for each patient. The recommended initial dose is 10 mcg administered 3 times weekly at dialysis (approximately every other day). The initial dose may then be adjusted as needed in order to lower blood PTH into the range of 150-300 pg/ml. The dose may be increased at 8-week intervals by 2.5 mcg if PTH is not lowered by 50% and fails to reach the target range. The maximum recommended dose is 20 mcg administered 3 times a week at dialysis for a total of 60 mcg/week. The administration of doxercalciferol should be suspended if PTH falls below 100 pg/ml. It may be restarted one week later at a dose that is at least 2.5 mcg lower than the last administered dose. During titration, PTH, serum calcium, and serum phosphate levels should be monitored weekly. If hypercalcemia, hyperphosphatemia, or a serum calcium times serum phosphate product ( $Ca \times P$ ) > 70 is noted, immediately suspend the drug until these parameters are appropriately lowered, and then restart the drug at a dose that is  $\leq 2.5$  mcg. Doxercalciferol should be used with caution in renally impaired patients, patients with renal osteodystrophy with hyperphosphatemia (potential for metastatic calcification), pregnancy and patients using concurrent medications that affect bone or calcium metabolism. Doxercalciferol is contraindicated in patients with recent hypercalcemia or hyperphosphatemia, or in cases of hypervitaminosis D.