Regular Review

Therapeutic applications of vitamin D analogues

J REEVE

In the sunnier parts of the world a dietary intake of vitamin D is unnecessary,* but for most of us it is a true vitamin. Its dihydroxylated metabolite 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) is, however, a hormone synthesised in the kidney and borne by the bloodstream to distant target organs (gut, bone, and possibly the parathyroid glands) with a complex feedback mechanism regulating its rate of production.¹ None of the other vitamin D metabolites has yet been confidently assigned a hormonal role in man.

The unravelling of the interrelationships between vitamin D and its metabolites is one of the triumphs of recent medical research, and the stage has now been reached when treatment with synthetic metabolites of vitamin D is beginning to be available for several disorders. The major functional categories of endocrine disease are all represented among defects in the metabolism of 1,25(OH)₂D₃. Hormone deficiency may occur from failure of tubular cell function; impairment of feedback control may result in subnormal or excessive production; or the disorder may be due to unresponsiveness in the target organs.

Physiological considerations—Cholecalciferol (D₃) is formed in the skin under the influence of ultraviolet light.² Its precursors remain in situ because they are insoluble in water and do not bind to the circulating D-binding globulin³; but, once formed, D₃ is taken up into the circulation and is converted to its 25-hydroxylated form—(25(OH)D₃)—in the liver. This conversion is restricted, and the proportion of D₃ hydroxylated declines as more becomes available, so that production of 25(OH)D₃ is increased only 4-fold and 20-fold in response to increases in D₃ supply of 10-fold and 100-fold respectively.⁴ The result is a weak, but not negligible, inbuilt defence against overdosage with vitamin D.

25(OH)D₃ is, then, the principal circulating form of the vitamin, with a normal turnover of between three and four weeks.⁵ When given by mouth to patients with chronic renal failure 25(OH)D₃ has a weak direct action on calcium absorption of its own, roughly one-hundredth that of its metabolite 1,25(OH)₂D₃ and one-tenth that of 24,25(OH)₂D₃.⁶ Nevertheless, since 25(OH)D₃ circulates in concentrations about 30 times greater than those of 1,25(OH)₂D₃ and ten times greater than that of 24,25(OH)₂D₃, this action may be physiologically important. 25(OH)D₃ may also promote mineralisation of bone independently.⁷

The further metabolism of 25(OH)D₃ to 1,25(OH)₂D₃ and to 24,25(OH)₂D₃ occurs in the kidney. Neither metabolite is formed by any other tissue,^{8,9} except in pregnancy.¹⁰ The production rate of 1,25(OH)₂D₃ is closely regulated, not only

by its own concentration in the plasma, but also by the plasma concentrations of parathyroid hormone and calcium and by intracellular levels of phosphate.¹ 1,25(OH)₂D₃ is a potent stimulator of calcium absorption in physiological dosage and of bone resorption in slightly supraphysiological dosage.¹¹ Its turnover time in the plasma is about one day. The physiological function of 24,25(OH)₂D₃ is uncertain.¹² Its turnover time is much the same as that of 25(OH)D₃.¹³ When 1,25(OH)₂D₃ is given to normal man the production of 24,25(OH)₂D₃ increases.⁹

Some portion of the plasma D₃ may be metabolised through pathways other than the ones outlined above or excreted unchanged. There may be an enterohepatic recirculation of D₃ and its metabolites,¹⁴ though more recent studies have not confirmed this.¹⁵ Since in many patients with steatorrhoea absorption of vitamin D is only moderately impaired,¹⁶ the osteomalacia sometimes associated with malabsorption of fat has not been fully explained.

Vitamin D metabolites and analogues—For many years foods such as margarine have been fortified with ergocalciferol (vitamin D₂). The first available analogue of potency greater than the natural vitamin was dihydrotachysterol (DHT), though even this compound is 50-500 times less potent than 1,25(OH)₂D₃. DHT has a swifter onset and end of action than D₃ or 25(OH)D₃, and since it does not require a hydroxylation in the 1 position like 25(OH)D₃, treatment of "D-resistant" states became possible with dose levels of DHT little higher than those required to heal D-deficiency rickets or osteomalacia.

The elucidation over the last 10 years of the metabolic transformations undergone by D₃ has been followed by the synthesis of several of its metabolites.¹ 25(OH)D₃ may become available in the United States (approved name calcifediol), and 1,25(OH)₂D₃ is already available in the United States and some European countries (approved name calcitriol). In addition, the more easily synthesised analogue of 1,25(OH)₂D₃, 1α(OH)D₃ (approved name alfalcidol), is available in Britain and some other countries. Alfalcidol depends for its biological activity on its hydroxylation in the liver to 1,25(OH)₂D₃.

Substrate deficiency—Several disorders lead to substrate deficiency, which for preference should be treated with precursors of 1,25(OH)₂D₃, though theoretically effective treatment could be given with vitamin D, 25(OH)D₃, or 1,25(OH)₂D₃. Nevertheless, when the two former compounds are used the normal intrinsic mechanisms for regulating the rate of production of 1,25(OH)₂D₃ are activated, so automatically bringing the effectiveness of treatment to an optimum.

The most common cause of substrate deficiency in Britain is the combination of inadequate exposure to sunlight and a low intake of vitamin D in the diet. This combination is most prevalent among persons of Asian origin and among the elderly

*Vitamin D₃ is the naturally occurring form, cholecalciferol. Vitamin D₂, ergocalciferol, is simpler to manufacture and is used in the fortification of foodstuffs and some pharmaceutical preparations. They are biologically equivalent.

Outline of vitamin D metabolism in normal man. Only a small fraction of circulating vitamin D is eventually converted into $1,25(\text{OH})_2\text{D}_3$ in conditions of sufficiency, the remainder being converted into $24,25(\text{OH})_2\text{D}_3$ and other less active metabolic products, or excreted. Factors regulating $1,25(\text{OH})_2\text{D}_3$ production rate are described in the text.

and housebound. There is no place for treating these simple forms of vitamin D deficiency with anything other than the vitamin itself, in doses ranging from 10 to 100 μg (400 to 4000 IU) daily. This dosage may be partially achieved with dietary advice (margarine in the United Kingdom contains about 4 μg ergocalciferol in a normal daily ration of 50 g); by using a daily oral preparation (Ca and vitamin D tablets BPC, each containing 12.5 μg vitamin D_2); or by giving infrequent injections of calciferol (300 000 IU, 7.5 mg every three months). Epileptics receiving drug treatment seem to provide too little $25(\text{OH})\text{D}_3$ to the kidney and they may require larger doses, in the range 50–250 μg daily.

Patients with liver disease are said to convert D_3 to $25(\text{OH})\text{D}_3$ at a reduced rate. Current evidence suggests that this is not the mechanism for the osteomalacia associated with primary biliary cirrhosis, but reduced hydroxylation rates have been observed in some cases of alcoholic liver disease.¹⁷

Much work remains to be done on the indications for management of treatment with vitamin D and its metabolites in gastrointestinal disease, but the appropriate dose level of D is usually in the range of 100–300 μg (4000–12 000 IU) daily.¹⁸ Treatment with $1,25(\text{OH})_2\text{D}_3$, while of clinical interest,¹⁹ should become unnecessary as well as illogical in liver disease when $25(\text{OH})\text{D}_3$ becomes available for the management of those patients who cannot adequately hydroxylate D in the 25 position.

“Gland” failure—By far the most common cause of inadequate production of $1,25(\text{OH})_2\text{D}_3$ is chronic renal failure. Even so, as with other endocrine systems, a hereditary deficiency of the capacity to synthesise this hormone has been described.²⁰ In early chronic renal failure any tendency toward raised plasma concentration of phosphate and parathyroid hormone and a lowered one of calcium will produce a complex interaction of influences on the remaining tubular cells. Concentrations of $1,25(\text{OH})_2\text{D}_3$ begin to decline when the glomerular filtration rate falls below about 30 ml/min.²¹ There is no evidence that the vitamin D metabolites benefit the osteomalacia presumed to be caused by aluminium or other toxins.²²

Treatment of renal osteodystrophy with $1,25(\text{OH})_2\text{D}_3$ or $1\alpha(\text{OH})\text{D}_3$ will usually provide an encouraging response in symptomatic patients whose $1,25(\text{OH})_2\text{D}_3$ deficiency is accompanied by evidence of secondary hyperparathyroidism and a reduced plasma calcium concentration before treatment.^{23–25} In these “responsive” patients plasma concentrations of alkaline phosphatase and parathyroid hormone fall gradually to normal, though histological changes (osteitis

fibrosa and thickened osteoid seams) respond less dramatically.²⁴

What are the advantages of this form of hormone replacement treatment? The response in patients with symptoms is often gratifying, particularly in children.²⁵ Similar responses were, of course, seen before the advent of treatment with $1\alpha(\text{OH})\text{D}_3$ and $1,25(\text{OH})_2\text{D}_3$, but large doses of vitamin D had to be used and their effects were probably secondary to the weak actions of $25(\text{OH})\text{D}$ in mimicking $1,25(\text{OH})_2\text{D}_3$. Overdosage was associated with prolonged episodes of hypercalcaemia, which probably adversely affected the remaining renal function.²⁶ Dihydrotachysterol overdosage was associated with less prolonged episodes of hypercalcaemia than with treatment with D_3 , but $1,25(\text{OH})_2\text{D}_3$ and its analogue $1\alpha(\text{OH})\text{D}_3$ have the advantage over both. Nevertheless, reports have appeared implicating treatment with $1,25(\text{OH})_2\text{D}_3$ or $1\alpha(\text{OH})\text{D}_3$ in the accelerated decline of renal function.²⁷

Treatment with these compounds should therefore be reserved for those who have symptomatic osteodystrophy. Given facilities for frequent monitoring of the plasma calcium concentration (not less than once a month and preferably up to once weekly), treatment with 2.0–2.5 μg of $1,25(\text{OH})_2\text{D}_3$ or $1\alpha(\text{OH})\text{D}_3$ daily will usually obtain the best response.²⁴ Hypercalcaemia may occur early during treatment, particularly in adults with histologically pure osteomalacia who were normocalcaemic beforehand. The dose usually has to be reduced as the biochemical indices return towards normal.

Since $1,25(\text{OH})_2\text{D}_3$ increases the absorption of phosphate from the gut¹ the restoration of the plasma calcium concentration to normal carries with it the risk of metastatic calcification and a more rapid decline in remaining renal function²⁹ if the plasma phosphate concentration is not kept below 2.4 mmol/l by giving oral phosphate-binding agents. Any existing metastatic calcification should be reviewed radiologically at intervals to ensure that it is not increasing.

Inappropriate $1,25(\text{OH})_2\text{D}_3$ production rates—Almost certainly, the renal tubular cell has a subsidiary role to the parathyroids, so that in hypoparathyroid patients the production of $1,25(\text{OH})_2\text{D}_3$ is subnormal and calcium absorption falls as a consequence. This aggravates the risk of hypocalcaemia from reduced renal calcium conservation.

Recent studies have shown that $1,25(\text{OH})_2\text{D}_3$ and its analogue $1\alpha(\text{OH})\text{D}_3$ given in “replacement” doses can restore the plasma calcium concentration to normal and may be used instead of the large doses of D_3 used hitherto.^{29–31} Whether this substitution confers practical advantages remains to be determined³¹ and may depend on how much the patient’s requirements for D fluctuate with the two modes of treatment.

Interestingly, the opposite biochemical picture—inappropriately high $1,25(\text{OH})_2\text{D}_3$ secretion rates—may be seen in the hypercalcaemia associated with sarcoidosis.³²

Target organ resistance—There are two main target cells for $1,25(\text{OH})_2\text{D}_3$ —enterocytes and osteoclasts. Target organ resistance is far more common in the enterocytes: in coeliac disease, for example, the balance between calcium absorption and its endogenous faecal excretion is disturbed.³³ In such circumstances treatment should be directed at the primary disorder, but enough substrate must also be made available for the potentially raised production of $1,25(\text{OH})_2\text{D}_3$.

Several cases have now been described^{34,35} of inherited target organ resistance to $1,25(\text{OH})_2\text{D}_3$. These patients have raised serum concentrations of $1,25(\text{OH})_2\text{D}_3$ and are resistant to treatment with it. Some have alopecia.

Miscellaneous disorders—Vitamin D and its metabolites have been used to treat conditions in which there is less clear

evidence of disordered vitamin D metabolism. One example is the various forms of hypophosphataemic vitamin-D-resistant rickets. Traditional treatment has been phosphate supplements with or without large doses of vitamin D. When $1\alpha(\text{OH})\text{D}_3$ or $1,25(\text{OH})_2\text{D}_3$ is substituted for vitamin D, large doses (up to 6 $\mu\text{g}/\text{day}$) are required.³⁶ The only obvious advantage of such a switch is that biochemical abnormalities in the plasma may be brought back to normal more quickly.

Moderate reductions in plasma concentrations of $1,25(\text{OH})_2\text{D}_3$ have been found in primary osteoporosis. The simplest explanation is that this is a secondary feedback response to the imbalance between bone formation and resorption. Trials of treatment with $1\alpha(\text{OH})\text{D}_3$ and $1,25(\text{OH})_2\text{D}_3$ in osteoporosis have given mixed results.^{11 37-40} Overall, the effect on mineral balance seems so slight as to be of negligible benefit unless treatment is continued for many years. The combination of $1\alpha(\text{OH})\text{D}_3$ and oestrogen replacement therapy looks more promising,⁴⁰ but further results are awaited with interest.

In conclusion, it is worth re-emphasising that $1,25(\text{OH})_2\text{D}_3$, $1\alpha(\text{OH})\text{D}_3$, DHT, and vitamin D in large doses are hormones or hormone substitutes; whereas vitamin D and $25(\text{OH})\text{D}_3$ in daily doses of up to 200 μg require further well-regulated metabolic transformations for them to become active biologically, so that they may still be viewed as vitamins. Many of us are content for our patients happily and harmlessly to consume a range of vitamins far above their minimum requirements, because the "therapeutic ratio" for most vitamins is high. On the other hand, we are accustomed to prescribing replacement doses of hormones with care, taking every precaution to avoid producing the iatrogenic counterparts of the various diseases associated with hormone excess—which in the case of vitamin D given in large "hormonal" doses is still an all-too-common problem.⁴¹

J REEVE

Member of Scientific Staff, MRC Clinical Research Centre, and
Honorary Consultant Physician,
Northwick Park Hospital,
Harrow, Middx HA1 3UJ

- ¹ DeLuca, H F, Vitamin D metabolism, *Clinical Endocrinology*, 1977, 7, suppl, p 1.
- ² Neer, R M, The evolutionary significance of vitamin D, skin pigment, and ultraviolet light. *American Journal of Physical Anthropology*, 1975, 43, 409.
- ³ Holick, M F, et al, The photo-biochemistry of vitamin D_3 in vivo in the skin, in *Vitamin D Basic Research and its Clinical Application. Proceedings of the IVth Workshop on Vitamin D*, Berlin, ed A W Norman et al, p 173. Berlin, de Gruyter, 1979.
- ⁴ Stamp, T C B, Haddad, J G, and Twigg, C A, Comparison of oral 25-hydroxycholecalciferol, vitamin D, and ultraviolet light as determinants of circulating 25-hydroxyvitamin D, *Lancet*, 1977, 1, 1341.
- ⁵ Haddad, J G, and Rojanasathit, S, Acute administration of 25-hydroxycholecalciferol in man, *Journal of Clinical Endocrinology and Metabolism*, 1976, 42, 284.
- ⁶ Brickman, A S, Llach, F L, and Coburn, J W, Preliminary report of biological actions of $24,25(\text{OH})_2\text{D}_3$ in normal man and patients with advanced renal failure, in *Vitamin D Basic Research and its Clinical Application. Proceedings of the IVth Workshop on Vitamin D*, Berlin, ed A W Norman et al, p 1085. Berlin, de Gruyter, 1979.
- ⁷ Bordier, P, et al, Vitamin D metabolites and bone mineralisation in man, *Journal of Clinical Endocrinology and Metabolism*, 1978, 46, 284.
- ⁸ Fraser, D R, and Kodicek, E, Unique biosynthesis by kidney of a biologically active vitamin D metabolite, *Nature*, 1970, 228, 764.
- ⁹ Taylor, C M, et al, The absence of 24,25-dihydroxycholecalciferol in anephric patients, *Clinical Science and Molecular Medicine*, 1978, 55, 541.
- ¹⁰ Lester, G E, Gray, T K, and Lorenc, R S, Possible extra-renal 25-OHD₃-1 hydroxylase activity in the pregnant rat, in *Vitamin D Basic Research and its Clinical Application. Proceedings of the IVth Workshop on Vitamin D*, Berlin, ed A W Norman et al, p 605. Berlin, de Gruyter, 1979.
- ¹¹ Marshall, D H, et al, The effect of 1α -hydroxycholecalciferol and hormone therapy on the calcium balance of postmenopausal osteoporosis, *Calcified Tissue Research*, 1977, 22, suppl, p 78.
- ¹² Russell, R G G, et al, Physiological and pharmacological aspects of 24,25-dihydroxycholecalciferol in man, in *Homeostasis of Phosphate and Other Minerals*, ed S G Maussry, E Ritz, and A Rapado, *Advances in Experimental Medicine and Biology*, p 487. New York, Plenum, 1977.
- ¹³ Stanbury, S W, and Mawer, E B, Physiological aspects of vitamin D metabolism in man, in *Vitamin D*, ed D E M Lawson, p 303. London, Academic Press, 1978.
- ¹⁴ Arnaud, S B, et al, 25-hydroxyvitamin D_3 : Evidence of an enterohepatic circulation in man, *Proceedings of the Society for Experimental Biology and Medicine*, 1975, 149, 570.
- ¹⁵ Mawer, E B, The role of the liver in the control of vitamin D metabolism, in *Vitamin D Basic Research and its Clinical Application. Proceedings of the IVth Workshop on Vitamin D*, Berlin, ed A W Norman et al, p 553. Berlin, de Gruyter, 1979.
- ¹⁶ Krawitt, E L, Mawer, E B, and Davies, M, Absorption of vitamin D and 25-OH vitamin D in patients with intestinal malabsorption, in *Vitamin D Basic Research and its Clinical Application. Proceedings of the IVth Workshop on Vitamin D*, Berlin, ed A W Norman et al, p 975. Berlin, de Gruyter, 1979.
- ¹⁷ Stanbury, S W, and Mawer, E B, personal communication.
- ¹⁸ Sitrin, M, Meredith, S, and Rosenberg, I H, Vitamin D deficiency and bone disease in gastrointestinal disorders, *Archives of Internal Medicine*, 1978, 138, 886.
- ¹⁹ Long, R G, et al, Parenteral 1,25-dihydroxycholecalciferol in hepatic osteomalacia, *British Medical Journal*, 1978, 1, 75.
- ²⁰ Prader, A, Kind, H P, and DeLuca, H F, Pseudovitamin D deficiency (vitamin D dependency), in *Inborn Errors of Calcium and Bone Metabolism*, ed H Bickel and J Stern, p 115. Lancaster, MTP Press, 1976.
- ²¹ Slatopolsky, E, et al, The pathogenesis of secondary hyperparathyroidism in early renal failure, in *Vitamin D Basic Research and its Clinical Application. Proceedings of the IVth Workshop on Vitamin D*, Berlin, ed A W Norman et al, p 1209. Berlin, de Gruyter, 1979.
- ²² Ward, M K, et al, Newcastle bone disease, in *Vitamin D Basic Research and its Clinical Application. Proceedings of the IVth Workshop on Vitamin D*, Berlin, ed A W Norman et al, p 835. Berlin, de Gruyter, 1979.
- ²³ Coburn, J W, et al, The renal osteodystrophies: clinical features in patients classified by histologic features and their response to treatment with 1,25-dihydroxyvitamin D_3 , in *Vitamin D Basic Research and its Clinical Application. Proceedings of the IVth Workshop on Vitamin D*, Berlin, ed A W Norman et al, p 1217. Berlin, de Gruyter, 1979.
- ²⁴ Kanis, J A, et al, Treatment of renal bone disease with 1-hydroxylated derivatives of vitamin D_3 , *Quarterly Journal of Medicine*, 1979, 48, 289.
- ²⁵ Chesney, R W, et al, Increased growth after long-term oral 1α 25-hydroxyvitamin D_3 in childhood renal osteodystrophy, *New England Journal of Medicine*, 1978, 298, 238.
- ²⁶ Hossain, M, Vitamin-D intoxication during treatment of hypoparathyroidism, *Lancet*, 1970, 1, 1149.
- ²⁷ Christiansen, C, et al, Deterioration of renal function during treatment of chronic renal failure with 1,25-dihydroxycholecalciferol, *Lancet*, 1978, 2, 700.
- ²⁸ Ibels, L S, et al, Preservation of function in experimental renal disease by dietary restriction of phosphate, *New England Journal of Medicine*, 1978, 298, 122.
- ²⁹ Davis, M, Effects of 1,25-dihydroxycholecalciferol on calcium and phosphorus metabolism in hypoparathyroidism, *Calcified Tissue Research*, 1977, 22, suppl, p 68.
- ³⁰ Lewin, I G, Papapoulos, S E, and O'Riordan, J L H, 1α -hydroxyvitamin D_3 in the long-term management of hypoparathyroidism and pseudohypoparathyroidism, *Clinical Endocrinology*, 1977, 7, suppl, p 203.
- ³¹ Heyburn, P J, and Peacock, M, The management of hypoparathyroidism with 1α -hydroxyvitamin D_3 , *Clinical Endocrinology*, 1977, 7, suppl, p 209.
- ³² Papapoulos, S E, et al, 1,25-dihydroxycholecalciferol in the pathogenesis of the hypercalcaemia of sarcoidosis, *Lancet*, 1979, 1, 627.
- ³³ Melvin, K E W, et al, Calcium metabolism and bone pathology in adult coeliac disease, *Quarterly Journal of Medicine*, 1970, 39, 83.
- ³⁴ Brooks, M H, et al, Vitamin-D-dependent rickets type II: resistance of target organs to 1,25-dihydroxyvitamin D, *New England Journal of Medicine*, 1978, 298, 996.
- ³⁵ Liberman, U A, et al, End organ resistance to $1,25-(\text{OH})_2\text{D}_3$ —an hereditary congenital syndrome, *Calcified Tissue International*, 1979, 27 (no 91), suppl, p A23.
- ³⁶ Russell, R G G, et al, Clinical uses of 1,25-dihydroxycholecalciferol, in *Vitamin D Basic Research and its Clinical Application. Proceedings of the IVth Workshop on Vitamin D*, Berlin, ed A W Norman et al, p 1099. Berlin, de Gruyter, 1979.
- ³⁷ Davies, M, Mawer, E B, and Adams, P H, Vitamin D metabolism and the response to 1,25-dihydroxycholecalciferol in osteoporosis, *Calcified Tissue Research*, 1977, 22, suppl, p 74.
- ³⁸ Haas, H G, et al, Efficacy of $1,25(\text{OH})_2\text{D}_3$ in postmenopausal osteoporosis, *Calcified Tissue International*, 1979, 27 (no 55), suppl, p A14.
- ³⁹ Riggs, B L, Gallagher, J C, and DeLuca, H F, Osteoporosis and age-related osteopenia: evaluation of possible role of vitamin D endocrine system in pathogenesis of impaired intestinal calcium absorption, in *Vitamin D Basic Research and its Clinical Application. Proceedings of the IVth Workshop on Vitamin D*, Berlin, ed A W Norman et al, p 107. Berlin, de Gruyter, 1979.
- ⁴⁰ Marshall, D H, and Nordin, B E C, The effect of 1α -hydroxyvitamin D_3 with and without oestrogens on calcium balance in postmenopausal women, *Clinical Endocrinology*, 1977, 7, suppl, p 159.
- ⁴¹ Davies, M, and Adams, P H, The continuing risk of vitamin-D intoxication, *Lancet*, 1978, 2, 621.