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What is the optimal regimen for vitamin D?

JOHN CUNNINGHAM

Department of Nephrology, St Bartholomew's and the Royal London School of Medicine and Dentistry, Whitechapel, London, E1 1BB

What is the optimal regimen for vitamin D? The past 30 years have seen substantial advances in our understanding of the pathogenesis of the mineral, hormonal and skeletal disorders that comprise renal osteodystrophy. The introduction of calcitriol and alfacalcidol as treatments for this disorder in the early 1970s represented an enormous step forward in clinical practice, but unfortunately, the subsequent refinement of these therapies still leaves us well short of the ideal: hyperphosphatemia and hypercalcemia induced by the vitamin D metabolites, and failure to control parathyroid hyperplasia, all remain problematic. Novel pulsed regimens using alfacalcidol and calcitriol, while clearly effective, have not fulfilled initial high expectations of superiority in the context of comparative studies. New vitamin D metabolites, some of which have exhibited desirable selectivity in experimental settings with reduced tendency to raise phosphate and/or calcium while maintaining good control of the parathyroid glands, are now being evaluated. Of these, 22-oxacalcitriol, paricalcitol (19 nor-1,25 dihydroxyvitamin D_2) and doxercalciferol (1α-hydroxyvitamin D_2) have all shown high efficacy when compared with placebo, but so also did alfacalcidol and calcitriol in similar studies in the 1970s and 1980s. The results of randomized studies comparing the new vitamin D metabolites with current standard therapy (alfacalcidol or calcitriol) are either not yet available or show uncertain benefits in relation to hypercalcemia, hyperphosphatemia and hyperparathyroidism. The impact of these new metabolites on the increasing prevalence of low turnover bone disease is unknown, although experimentally there is evidence of potentially important differences at the level of the skeleton.

This review will approach the issue of optimal vitamin D treatment for patients with renal failure by considering, in order, the treatment objectives, relevant pathophysiology, the status and efficacy of current strategies, and finally the status and prospects for very recently developed and emerging strategies. Of necessity the review will therefore consider vitamin D metabolites that have been in clinical use for many years, as well as those that are only just beginning to enter the clinical arena.

TREATMENT OBJECTIVES

At a basic level, treatment objectives are quite easy to define and are given in Table 1. In essence, treatment aims to achieve and maintain a state of normal bone and mineral metabolism. This encompasses the metabolic and structural aspects of skeletal function, the physiological concentrations of the major mineral ions, the maintenance of appropriate circulating concentrations of the major calcium-regulating hormones (parathyroid hormone [PTH] and calcitriol), and finally, the prevention of abnormal parathyroid gland hyperplasia. Although fairly straightforward in concept, these objectives have nevertheless proved extremely elusive, and as a result the field has been associated with the development of a range of clinical strategies that, although in many ways effective, are far from perfect. In parallel with this has been an intense basic and clinical scientific effort aimed at the better understanding of the underlying pathophysiology of renal osteodystrophy. The main focus has been on 1) the skeletal abnormalities; 2) the abnormalities of calcium and phosphorus metabolism; 3) vitamin D bioactivation and action in relation to renal disease; and 4) parathyroid gland function and the biology of parathyroid hormone.

RELEVANT PATHOPHYSIOLOGY

Mineral ions and hormones

Changes to mineral ion concentrations and the calcium regulating hormones as renal function declines are driven principally by the combination of increasing impairment of the kidneys' ability to synthesize calcitriol, coupled with progressive impairment of phosphate excretory capacity. Both of these abnormalities lead directly and indirectly to increased parathyroid stimulation with resulting increases in the synthesis and secretion of PTH. The ensuing secondary hyperparathyroidism promotes phosphaturia and increased activity of the renal 25-hydroxyvitamin D 1α-hydroxylase, thereby tending to normalize plasma concentrations of, respectively, phosphate and calcitriol [1]. The price paid is significant, however, in that increased circulating PTH concentrations drive a range of unwanted effects on target organs, in particular the skeleton [2]. Furthermore, the unremitting parathyroid stimulation is associated with a sustained increase in mitotic activity with the development of parathyroid gland hyperplasia

Table 1. Therapeutic objectives

Maintenance of normal skeletal function
Metabolism
Bone turnover
Mechanical integrity
Maintenance of normal ECF mineral ion concentrations
Maintenance of appropriate parathyroid suppression
Optimal PTH
Prevention of hyperplasia

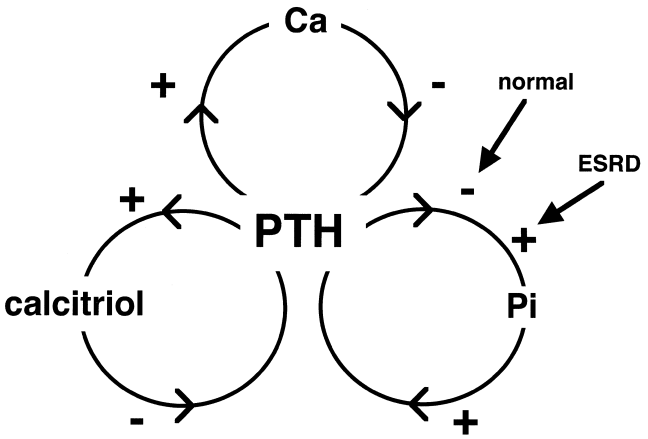

Fig. 1. Control of parathyroid activity by calcium, phosphate and calcitriol. In health, each of these modulators forms a negative feedback loop with PTH. In end stage renal disease the PTH–phosphate loop changes to positive feedback. Abbreviations are: PTH, parathyroid hormone; Ca, calcium; Pi, inorganic phosphate.

[3, 4]. This latter development is of great clinical importance. It is becoming increasingly clear that the kinetics of parathyroid cell division and apoptosis are such that, although hyperplasia can develop quite quickly, reversal by apoptosis is so slow as to be almost irrelevant clinically [4, 5]. The dynamic interactions between the parathyroids and the three principal modulators of parathyroid activity, namely, calcium, phosphate and calcitriol, are illustrated in Fig. 1. Note that in health each of the three modulators is part of a negative feedback loop, thereby favoring a damping function and maintenance of an appropriate steady state. In contrast, the presence of end-stage renal disease introduces a positive feedback loop. In this instance the normal action of PTH to promote phosphaturia and thereby decrease serum phosphate is sabotaged by the renal failure with the result that PTH serves to elevate serum phosphate by acceleration of phosphorus efflux from the skeleton. In addition to its three main modulators, parathyroid cell activity is also influenced by a considerable number of other processes, many of which are themselves a reflection of the lack of hormonal calcitriol synthesized by the kidney (Fig. 2). All of these are therefore potentially amenable to partial or complete correction during administration of exogenous calcitriol or related agents that act via the vitamin D receptor. The mechanisms whereby these major controllers influence the parathyroids has been the subject of intense study and is reviewed elsewhere in this supplement. Suffice to say, however, that calcitriol acts directly on the parathyroid glands to suppress PTH gene transcription and also parathyroid cell mitotic activity. In contrast, calcium and phosphate both regulate PTH synthesis by post-transcriptional effects on preproPTH mRNA. All three have powerful effects on parathyroid cell mitotic activity. Calcium in addition exerts minute to minute modulation of parathyroid hormone release via the extracellular calcium receptor.

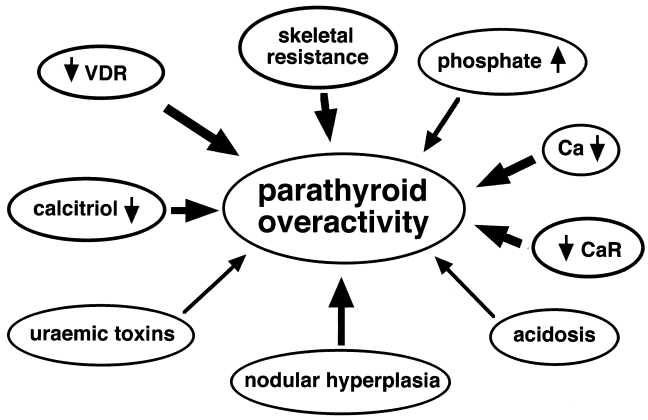

Fig. 2. Stimulatory inputs to parathyroid activity. Those depicted by the thick arrows are dependent directly or indirectly on the state of calcitriol sufficiency, and are therefore totally or partially correctable by calcitriol therapy. Abbreviations are: Ca, extracellular calcium concentration; CaR, extracellular calcium receptor; VDR, vitamin D receptor.

Bone

Hyperparathyroid bone disease was much the most common lesion seen in the early years of maintenance dialysis treatment and is characterized by increased activity of both osteoblasts and osteoclasts [6, 7]. Bone formation and resorption rates are thus increased and this may be recognized histologically by the presence of excessive amounts of osteoid with high mineralization activity (reflecting accelerated bone formation), and also by increased numbers of osteoclasts seen to be resorbing bone actively (reflecting increased bone resorptive rates).

The last decade has, however, seen the emergence of strikingly different bone lesions. In particular, adynamic bone (also designated aplastic bone disease or the adynamic bone disorder) is seen in increasing numbers of patients. This was first recognized in association with aluminum intoxication and characterized by striking reduction of cellular activity with deposition of aluminum at the mineralization front [8]. Subsequently, the effective removal of aluminum from the environment of the hemodialysis patient has not, as would have been ex-

pected, led to the disappearance of the adynamic bone lesion but instead has been temporally associated with a progressive increase in its prevalence [7]. The explanation for this is far from clear, but important associations include advanced age, the use of large amounts of calcium containing phosphorus binders, high calcium dialysate, coexistent diabetes mellitus and previous glucocorticoid therapy. These demographic factors have been increasingly in evidence over the past 10–15 years. Adynamic bone is usually, although not always, associated with relatively low PTH, in or just above the normal range or even subnormal in certain patients. In between these two extremes lies a group of patients who manifest normal bone turnover, and it is this that currently represents the best skeletal therapeutic target. In this group it is usual to see moderately elevated PTH concentration at 2–4 times the upper limit of normal on an intact PTH (1–84) assay, typically 100–200 pg/ml.

CURRENT STRATEGIES

The optimal use of vitamin D therapies cannot be considered in isolation, invariably being part of a broader attack on the derangements of uremia. Of crucial importance is the control of hyperphosphatemia; this remains difficult and unsatisfactory for large numbers of patients [9, 10]. Currently available dietary phosphate binders all suffer from relative lack of efficacy and weak action and most have potential or real toxicity. As a result many patients with advanced renal failure and those on dialysis are maintained in a state of moderate or severe hyperphosphatemia, with continued phosphate mediated drive to PTH synthesis and parathyroid cell hyperplasia [11]. This is of great importance in relation to calcitriol and other vitamin D therapies; it has become increasingly clear that poor phosphate control is a powerful predictor of unsatisfactory outcomes to vitamin D therapies. The first clinical use of 1α-hydroxylated vitamin D metabolites was in 1971 when Brickman et al showed effective elevation of calcium and reduction of PTH following the use of calcitriol [12]. Similar results with alfacalcidol were reported shortly thereafter [13] and these two agents quickly became established as the standard form of vitamin D therapy in patients with renal disease, as well as in some other vitamin D resistant syndromes. The main problem with these treatments has been their frequent failure to sustain the favorable early responses of the parathyroids and it is now clear that early suppression of PTH is often followed by subsequent breakthrough, increasing parathyroid hyperplasia and eventual parathyroidectomy in some patients. We have found that the enhanced parathyroid suppressibility by calcium that initially follows calcitriol therapy is not sustained, thereby providing a functional correlate with the poorly sustained clinical responses often seen (Fig. 3). Also counterproductive in this setting are the potent calcemic and phosphatemic actions of calcitriol and alfacalcidol, both of which substantially increase the intestinal absorption of both calcium and phosphorus. The development of hypercalcemia frequently limits the dose that can be used and the tendency to hyperphosphatemia is clearly disadvantageous in a clinical scenario where hyperphosphatemia is already a significant problem.

As a result of these limitations attempts have been made over the past 10 years to devise alternative schedules of administration that might prove more efficacious, in particular with the aim of selectively targeting the parathyroid glands for suppression without at the same time fueling hypercalcemia and hyperphosphatemia via the intestine and bone. Novel and somewhat unphysiological regimens for the administration of calcitriol and alfacalcidol were reported, initially by Madsen et al [14] and subsequently by Slatopolsky et al [15], both of whom studied the effect of intermittent intravenous dosing with calcitriol. These and subsequent studies appeared to show excellent clinical outcomes from intravenous dosing [16, 17] as did some reports of intermittent pulsed oral dosing [18, 19]. Unfortunately, a dispassionate review of the literature reveals that, although many studies have raised the possibility of enhanced efficacy of these new regimens, formal comparisons between intravenous or pulsed oral therapies on the one hand, and conventional daily oral therapies on the other, have revealed little or no clinical benefit either way [20, 21]. Nor have studies comparing alfacalcidol with calcitriol shown any important differences between the two, perhaps not surprising given that alfacalcidol is no more than a prodrug for calcitriol. The results of the first comparative studies published over 2 decades ago still hold true [22].

NEW VITAMIN D METABOLITES

The realization that vitamin D metabolites exhibit a range of biological actions that extend far beyond those connected with bone and mineral metabolism, in many cases associated with powerful anti-proliferative and pro-differentiation effects, has raised the possibility that these agents may be used in malignancy and other diseases associated with excessive cell turnover [23]. Clinical and basic scientists, and the pharmaceutical industry, have together mounted an intensive search for structurally modified vitamin D metabolites that may selectively act upon some target tissues at the expense of others. In the field of cancer, a desirable profile would be a vitamin D metabolite able to act via the vitamin D receptor on the relevant malignant cells, but not acting to the same degree on traditional calcemic target tissues. By analogy other agents might confer the major advantage of enabling effective parathyroid suppression with les-

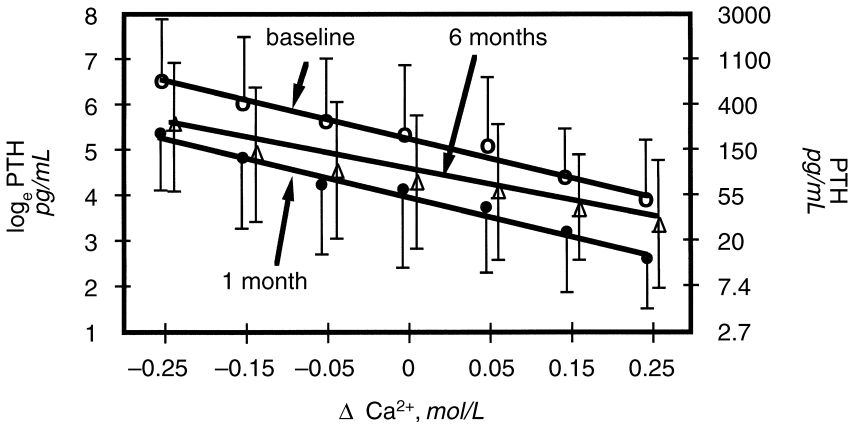

Fig. 3. Effect of calcitriol therapy on parathyroid sensitivity to extracellular calcium. Patients were given pulse oral calcitriol. Although after one month a marked increase in parathyroid suppression was seen, this was not fully sustained when re-tested after six months of calcitriol therapy. Abbreviations are: PTH, parathyroid hormone; Ca^{++}, increment or decrement of extracellular calcium ion concentration.

sened or absent risk of hypercalcemia and of hyperphosphatemia. A number of these agents are at varying stages of clinical development and one of them already has a product license in some countries.

22-Oxacalcitriol

22-Oxacalcitriol (OCT), first described in the late 1980s, was subsequently shown experimentally to exhibit profound suppression of bovine parathyroid cells *in vitro*, with little or no calcemia in intact and uremic rats. Parathyroid suppressing potency was similar to that of calcitriol whereas calcitriol at equivalent doses resulted in profound hypercalcemia [24]. Further studies in uremic dogs yielded broadly similar results. Unfortunately it is clear from early clinical studies that, despite the very promising experimental profile, OCT is certainly not devoid of calcemic effects in dialysis patients. Thus in a large study conducted in Japan, PTH suppression was effective and dose dependent, but substantial numbers of patients experienced hypercalcemic episodes [25]. No comparative studies with calcitriol or alfacalcidol have yet been undertaken and so, although it is clear that OCT is effective in the context of renal hyperparathyroidism, it is not yet clear whether OCT has any therapeutic advantages over current standard therapy.

Paricalcitol

Paricalcitol (19-nor-1,25-dihydroxyvitamin D_2) has been developed following initial indications of a reduced tendency to raise calcium and phosphorus in experimental animals. Paricalcitol was found to suppress PTH *in vitro* and *in vivo* in a dose dependent fashion and, at relevant doses, to be essentially devoid of calcemic and phosphatemic actions [26]. Paricalcitol also exhibited other actions expected of a vitamin D-like compound, inhibition of PTH gene transcription and of parathyroid cell mitotic activity [27]. Many of the early experimental studies were conducted with calcitriol as the comparitor, and these results suggested that paricalcitol should bring substantial clinical benefits.

Over the past 2 years placebo controlled clinical studies have been published and these have confirmed paricalcitol as an effective treatment for hyperparathyroidism in these patients. The studies have shown good suppression of PTH concentrations with apparently reduced tendency to increase calcium or phosphate [28]. These studies were, however, placebo controlled and there are as yet no full publications in relation to the comparative studies (paricalcitol vs. calcitriol) that have been completed recently. However, initial reports of these are suggesting that both paricalcitol and calcitriol suppress PTH with equal efficacy, although the suppression by paricalcitol at the doses used was somewhat brisker. Calcemic episodes appear to have been broadly similar in the two groups. Thus the comparative studies undertaken so far appear likely to indicate that paricalcitol confers no important clinical benefit over calcitriol, at least when used according to these early protocols. It is possible, however, that the more rapid PTH reduction in the paricalcitol-treated patients is indicative of an excessively large dose of this agent having been chosen and that, with suitable modification to dosing, hypercalcemic episodes could be reduced significantly. Further studies will be needed to clarify this point.

1α-Hydroxyvitamin D_2

This compound, generic name doxercalciferol, is the vitamin D_2 equivalent of alfacalcidol. It has been widely assumed that the metabolism of alfacalcidol and 1α-hydroxyvitamin D_2, which are, respectively, the cholecalciferol and ergocalciferol derivatives of parent vitamin D, would lead to the formation of similar quantities of biologically equivalent 1,25-dihydroxyvitamin D metabolites. This now appears not to be the case. Alfacalcidol (1α-OH D_3) is 25-hydroxylated in the liver to form calcitriol, the natural hormonal form of vitamin D_3. In contrast 1α-OH D_2 is

metabolized to produce both 1,25-dihydroxyvitamin D_2 and also 1,24S-dihydroxyvitamin D_2 in roughly equal amounts [29]. The 1,24S compound has been shown to be an extremely potent antiproliferative agent with minimal calcemic properties and is currently undergoing evaluation in a variety of oncological test beds. Its effects on PTH are as yet unknown. Initial studies in hemodialysis patients have shown 1α-hydroxyvitamin D_2 to be an effective suppressor of secondary hyperparathyroidism with minimal hypercalcemia or hyperphosphatemia [30]. Comparative studies with calcitriol or alfacalcidol have not yet been completed and it remains unclear as to whether this agent will represent a significant therapeutic advance. Nevertheless, the generation of the 1,24S-dihydroxyvitamin D_2 metabolite raises the possibility of qualitatively and/or quantitatively different therapeutic responses from those of alfacalcidol and calcitriol.

CONCLUSIONS

Although an enormous effort has gone into the identification of new vitamin D regimes and new vitamin D metabolites as therapies in patients with renal osteodystrophy, the clinical gain over the past 25 years has been modest. Certainly the placebo-controlled studies of the newer metabolites, and of the pulsed regimens of the more traditional metabolites, have shown high efficacy. This is, nevertheless, very reminiscent of the results seen in the 1970s when calcitriol and alfacalcidol were first used in patients with renal disease [12, 13]. There is an urgent need for proper comparisons with current best therapy (using alfacalcidol or calcitriol as the comparitor) to see whether any of the new metabolites are significantly better. So far the evidence that they are is relatively thin, although it is to be hoped that with further refinement of dosing regimens some of the new metabolites may prove to have a significant clinical edge. Until this happens, however, there appears to be little justification for moving away from current best therapy with alfacalcidol or calcitriol. With these tried and tested agents the choice of regimen appears to be relatively unimportant with respect to clinical outcomes, although may be much more so with regard to convenience of delivery and/or national reimbursement practices.

Reprint requests to Dr. John Cunningham, Department of Nephrology, St Bartholomew's and the Royal London School of Medicine and Dentistry, Whitechapel, London, E1 1BB United Kingdom.

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