Comparison of Effects of 1α-Hydroxy-Vitamin D₃ and 1,25-Dihydroxy-Vitamin D₃ in Man

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ABSTRACT The effects of short-term treatment with 1,25-dihydroxy-vitamin D₃ [1,25(OH)₂D₃] or 1α-hydroxy-vitamin D₃ [1α(OH)D₃] on intestinal absorption of ⁴⁰Ca were compared in 41 experiments in normals and 72 experiments in patients with chronic renal failure. 11 patients were studied a second time after treatment for 2-5 mo. Doses varied from 0.14 to 5.4 μg/day to establish dose-response relationships. Urinary calcium was monitored in normal subjects, nine of whom received a constant calcium intake on a metabolic unit. There was an increase in intestinal absorption of ⁴⁰Ca and urinary calcium in normals receiving 1,25(OH)₂D₃, 0.14 μg/day or greater, and 0.28 μg/day or greater augmented intestinal absorption of ⁴⁰Ca in both groups. The increase in urinary calcium to maximal levels was delayed during treatment with 1α(OH)D₃, 5-10 days vs. 2-5 days with 1,25(OH)₂D₃. Moreover, half times for urinary calcium to decrease to pretreatment levels after stopping treatment were greater after 1α(OH)D₃ (1.5-2.7 days) than 1,25(OH)₂D₃ (1.1-2.0 days). With long-term administration there was a progressive increase in intestinal absorption of ⁴⁰Ca in the patients receiving 1α(OH)D₃; this was not observed with 1,25(OH)₂D₃.

The pharmacologic differences between 1α(OH)D₃ and 1,25(OH)₂D₃ may be explained by the requirement for 25-hydroxylation of 1α(OH)D₃ before biologic effects occur; at low doses (< 1 μg/day), 1α(OH)D₃ competes with vitamin D₃ for 25-hydroxylation. With prolonged treatment or larger doses (>2 μg/day), 1α(OH)D₃ could accumulate and then be hydroxylated resulting in production of higher levels of 1,25(OH)₂D₃.

INTRODUCTION The naturally occurring hormonal form of vitamin D₃, 1,25-dihydroxycholecalciferol [1,25(OH)₂D₃],¹ and the synthetic analogue 1α-hydroxy-vitamin D₃ [1α(OH)D₃] have both been shown to be highly active in patients with advanced renal failure (1-7). [The synthesis of 1α(OH)D₃ has been accomplished with greater ease than that of 1,25(OH)₂D₃ and, it has been claimed that the former may become more readily available for clinical use.] Zerwekh et al. (8) suggested from data in rachitic chicks that 1α(OH)D₃ must undergo 25-hydroxylation before exerting its effects, while Toffolon et al. (9) proposed that this compound may act directly without subsequent metabolic conversion. The potencies of 1,25-(OH)₂D₃ and 1α(OH)D₃ were found to be equal in the vitamin D-deficient rat by Toffolon et al. (9) and in the rachitic chick by Haussler et al. (10), respectively. On the other hand, Holick et al. (11) found 1α(OH)D₃ to be about half as potent as 1,25(OH)₂D₃ in vitamin

¹ Abbreviations used in this paper: 1,25(OH)₂D₃, 1,25-dihydroxycholecalciferol; 1α(OH)D₃, 1α-hydroxy-vitamin D₃.


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D-deficient rats. Information which compares the relative potency and the onset and duration of action of 1,25-(OH)2D3 and 1α(OH)D3 in man is not available. In the present study, the actions of 1α(OH)D3 and 1,25-(OH)2D3 on intestinal calcium absorption were evaluated in normal subjects and in patients with renal failure. The present observations indicate that 1α(OH)D3 is less effective than 1,25(OH)2D3 at lower doses, has a slower onset of maximal effect, and may have a more prolonged duration of action after therapy is discontinued. These data provide indirect evidence that 25-hydroxylation of 1α(OH)D3 occurs before the excretion of a biologic effect in man.

METHODS

The effects of treatment for 7-12 days (short-term treatment) with 1α(OH)D3 and 1,25(OH)2D3 on intestinal calcium absorption and urinary calcium were studied in 41 experiments in 30 normal volunteers (26 males and 4 females). The ages ranged from 20 to 64 yr, with a mean of 41. Twelve studies in 6 subjects were carried out in the Metabolic Unit of the VA Wadsworth Hospital Center; the remaining 29 studies were undertaken in 24 reliable volunteers while they ingested their usual diets at home. Seventy-two studies of the effect of short-term treatment on calcium absorption were carried out in 35 patients with advanced renal failure (32 men and 3 women). The patients ages ranged from 20 to 69 yr, with a mean of 52. Eight patients were being treated triweekly with regular hemodialysis (dialysate calcium, 3.5 meq/liter). Endogenous creatinine clearances in those not requiring treatment with dialysis ranged from 5 to 24 ml/min, with a mean of 11 ml/min. These patients received their usual diets without dietary calcium supplements. Most were receiving multivitamin supplements providing 10 μg (400 IU) vitamin D3 per day. The uremic patients received aluminum hydroxide gel before and during this study. Seventeen studies were carried out on the Metabolic Ward and the remainder were done on an outpatient basis. Of the 113 studies currently reported, 35 have been previously reported (20 in normal subjects and 15 in azotemic patients) (2). Each subject was informed of the purpose and nature of the investigation and informed consent was obtained.

During short-term treatment, the 1α(OH)D3 or 1,25-(OH)2D3 was given by mouth each morning in 1.0 ml of 1:1:1, ethanol:1,2-propanediol for 8-12 days. Intestinal absorption of calcium was measured 2-6 wk before initiation of treatment and on the 7th through 12th day of treatment with the sterol. The daily quantities of each sterol given and the number of subjects treated at each dose are shown in Table I. In 14 studies, the 1,25(OH)2D3 was used chemically synthesized according to the method of Narwid et al. (12), (provided courtesy of Hoffman-LaRoche Inc., Nutley, N. J.); in the remaining studies, the 1,25(OH)2D3 utilized was prepared biosynthetically by previously described methods (13). Since there were no differences between the actions of 1,25(OH)2D3 prepared chemically or biosynthetically, the results are combined. Authentic 1α(OH)D3 was prepared from the prohormone as described elsewhere (14).

Six additional studies with 1,25(OH)2D3 and three with 1α(OH)D3 were carried out in normal volunteers admitted to the Metabolic Unit while they received constant daily diets according to methods previously reported (15). In these studies, daily urinary calcium was determined before and during treatment, and for periods up to 14 days after the agent had been discontinued, until the urinary calcium had returned to base-line levels. In all studies in the normal volunteers, 24-h urine samples were collected for 3 days before treatment and during the last 3 days of treatment.

Intestinal absorption of 45Ca was studied on two separate occasions in 10 uremic patients during treatment with either 1,25(OH)2D3 or 1α(OH)D3 for a more prolonged period. The first study was carried out after 8-12 days of treatment as described above (short-term treatment), and the second measurement of absorption was made after 2-5 mo of therapy (long-term treatment). The intestinal absorption of 45Ca was measured after a 12-h overnight fast by a previously described method (16), using a carrier providing 200 mg of calcium as the gluconate salt. Previous studies had shown that there was little variation in the fractional absorption of 45Ca when the same subject was studied on more than one occasion while ingesting the same diet. Urinary calcium was determined by atomic absorption spectrophotometry. Serum levels of calcium and phosphorus were also measured, but the factors influencing these parameters, such as the type and extent of skeletal disease and the severity of secondary hyperparathyroidism, are beyond the scope of the present report; these results and other clinical observations will form the basis for a subsequent communication. Statistical comparisons were made utilizing either t tests or analysis of variance according to standard techniques (17).

RESULTS

The absolute values for calcium absorption and urinary calcium during the control and treatment periods are shown in Table I. The pretreatment values for 45Ca absorption were lower in uremic patients than in normal subjects, consistent with our previous results (16); normal, 0.29±0.009 (SE) and chronic renal failure, 0.21±0.007. When normal subjects and uremic patients were considered separately, the pretreatment values for 45Ca absorption were not different in any group receiving the separate doses of either 1,25(OH)2D3 or 1α(OH)D3 (normal subjects, F = 0.30; and uremic patients, F = 0.37). Similarly there were no differences in pretreatment urinary calcium among the different dosage groups, F = 0.98. Because of differences in control 45Ca absorption between normal subjects and uremic patients and because of variation among individual subjects, the effects of 1,25(OH)2D3 or 1α(OH)D3 were expressed as the change in fraction of 45Ca absorption from control and treatment. These changes in 45Ca absorption in relation to the dose of either 1,25(OH)2D3 or 1α(OH)D3 are shown in Figs. 1 and 2 for normal subjects and patients with chronic renal disease, respectively. In normal subjects, 0.14 μg/day of 1,25(OH)2D3 increased 45Ca absorption, while 0.65 μg/day of 1α(OH)D3 had no significant effect. Moreover, the change in 45Ca absorption with 1,25(OH)2D3, 0.68 μg/day, was significantly greater than the change with 1α(OH)D3, 0.65 μg/day (P < 0.02). There was no difference between the effects

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of 2.6–2.7 μg/day of the two sterols. The minimum quantity of 1,25(OH)2D3 necessary to augment absorption in patients with renal disease was 0.28 μg/day, whereas 1α(OH)D3 in a dose of 0.65 μg/day failed to augment 47Ca absorption. Also, the increment in 47Ca absorption was significantly greater in patients receiving 1,25-(OH)2D3 in a dose of 0.68 μg/day than with the equimolecular dose of 1α(OH)D3 of 0.65 μg/day (P < 0.01). A similar increase in 47Ca absorption was observed after administration of either agent at daily doses of 2.6 or 2.7 μg/day.

The changes in urinary calcium excretion paralleled those of calcium absorption in the normal subjects (Fig. 3). The administration of 0.14 μg/day of 1,25(OH)2D3 significantly enhanced urinary calcium excretion, whereas 0.65 μg/day of 1α(OH)D3 had no effect; 2.6–2.7 μg/day of the two compounds augmented urinary calcium to a similar degree. As with the change in 47Ca absorption, the increment in urinary calcium was greater with 1,25-(OH)2D3, 0.68 μg/day, than with 1α(OH)D3, 0.65 μg/day (P < 0.02). Daily measurements of urinary calcium in normal subjects receiving a constant dietary intake of calcium and 0.68–2.7 μg/day of 1,25(OH)2D3 or 2.6 μg/day of 1α-(OH)D3 may provide information about the appearance of a maximal effect of the sterol. With 1,25(OH)2D3, urinary calcium rose quickly and reached a plateau by the 2nd to 5th day of treatment. On the other hand, urinary calcium excretion continued to increase for as long as 6–9 days during treatment with 1α(OH)D3.

**Table I**

| Mean Values for Fractional 47Ca Absorption in Normal Subjects and Uremic Patients and for Urinary Calcium in Normal Subjects Treated with 1,25(OH)2D3 or 1α(OH)D3 |

<table>
<thead>
<tr>
<th>Daily dose (μg/day)</th>
<th>1,25(OH)2D3</th>
<th>1α(OH)D3</th>
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<tbody>
<tr>
<td>0.065</td>
<td>0.325</td>
<td>0.65</td>
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<tr>
<td>0.027</td>
<td>0.14</td>
<td>0.28</td>
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</tbody>
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<table>
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<tr>
<th>Fraction of 47Ca absorbed (mean±SE)</th>
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</thead>
<tbody>
<tr>
<td>Normal Control</td>
</tr>
<tr>
<td>1,25(OH)2D3</td>
</tr>
<tr>
<td>1α(OH)D3</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>1,25(OH)2D3</td>
</tr>
<tr>
<td>1α(OH)D3</td>
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<table>
<thead>
<tr>
<th>Urinary calcium excretion (mean±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Control</td>
</tr>
<tr>
<td>1,25(OH)2D3</td>
</tr>
<tr>
<td>1α(OH)D3</td>
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<tr>
<td>Treatment</td>
</tr>
<tr>
<td>1,25(OH)2D3</td>
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<td>1α(OH)D3</td>
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* At equivalent nanomole doses, the microgram quantities differ because of differences in molecular weight of 1α(OH)D3 and 1,25(OH)2D3, i.e., 400 and 416, respectively.

† The numbers in parentheses indicate the number of studies.
and the changes in fraction of $^{4}$Ca absorbed in normal subjects. Results are expressed as mean±SE; the symbols, $a^{1}$, $a^{2}$, and $a^{3}$, indicate values that are statistically different from control with $P$ values of <0.02, <0.01, and <0.001, respectively. (***) indicates a significant difference between the change in $^{4}$Ca absorption with 1,25(OH)$_{2}$D$_{3}$ and 1α(OH)D$_{3}$ ($P$ < 0.02).

(Fig. 4). When treatment is discontinued in subjects receiving a constant diet, the decrement in urinary calcium towards the pretreatment rates of excretion may indicate the rate of decay of biologic response to the sterol. The differences in urinary calcium above the mean pretreatment values are shown in relationship to

FIGURE 2 Relationship between the daily dose of 1,25-(OH)$_{2}$D$_{3}$ (●) and 1α(OH)D$_{3}$ (▲) and the change in fraction of $^{4}$Ca absorbed in patients with chronic renal failure (CRF). Data are expressed as in Fig. 1; "a" indicates a value significantly different from base line with $P$ < 0.05; the designation, ***, indicates a difference between the increment in $^{4}$Ca absorption with 1,25(OH)$_{2}$D$_{3}$ and 1α(OH)D$_{3}$ ($P$ < 0.01).

FIGURE 3 Relationship between changes in urinary calcium excretion ($\Delta$ urinary Ca in milligrams per 24 h) and the daily doses of 1,25(OH)$_{2}$D$_{3}$ (●) and 1α(OH)D$_{3}$ (▲) in normal subjects. The data and symbols are expressed as in Figs. 1 and 2.

the time after stopping treatment in Figs. 5 and 6. In the subjects receiving 1,25(OH)$_{2}$D$_{3}$ urinary calcium fell on the first day with no treatment, and the change approximated a one-component, exponential decay; the half-life ($t_{1/2}$) for disappearance of effect on urinary calcium varied from 1.5 to 2.7 days (mean 1.5±0.15 days). In subjects treated with 1α(OH)D$_{3}$, urinary calcium did not fall until 2–4 days after the last day of therapy; and the subsequent $t_{1/2}$ for decay averaged 2.2±0.24 days, a value greater than that with 1,25(OH)$_{2}$D$_{3}$ ($P$ < 0.05).

Two subjects (A and B in Figs. 5 and 6) received both compounds; in A, the values for $t_{1/2}$ were 1.3 and 2.1 days with 1,25(OH)$_{2}$D$_{3}$ and 1α(OH)D$_{3}$, respectively; similar values in subject B for $t_{1/2}$ were 2.0 and 2.7 days, respectively.

The results of intestinal absorption of $^{4}$Ca in azo- temic patients after short-term and long-term treatment with 1,25(OH)$_{2}$D$_{3}$ or 1α(OH)D$_{3}$ are shown in Fig. 7. The change in fraction of $^{4}$Ca absorption between the study at 8–12 days (short-term) and 2–5 mo (long-term) of treatment with 1,25(OH)$_{2}$D$_{3}$ averaged 0.017±0.026, a value significantly less than the increment in absorption of 0.34±0.12 with 1α(OH)D$_{3}$ between 8–12 days and 2–5 mo ($P$ < 0.02).

DISCUSSION

The present data verify previous reports of the marked potency of both 1,25(OH)$_{2}$D$_{3}$ (1–3) and 1α(OH)D$_{3}$ (4–7) in patients with renal disease. The results also confirm that 1α(OH)D$_{3}$ (18) and 1,25(OH)$_{2}$D$_{3}$ (2) can augment the intestinal absorption of calcium in nor-

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normal man. Also a dose-response relationship for 1α-(OH)D₃ in uremic patients is reported together with additional information about dose-response relationships of 1,25(OH)₂D₃ in normal subjects and patients with renal failure. Responses of normal subjects to two doses of 1α(OH)D₃ is also reported.

The present observations in man demonstrate several differences between the pharmacologic properties of

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**Figure 4** Changes in urinary calcium in normal subjects receiving either 1,25(OH)₂D₃ or 1α(OH)D₃. (○) represent pre- or post-treatment values. For clarity, the rate of calcium excretion is plotted arbitrarily on the ordinate with the value on the first control day in milligrams per day shown for each subject.

**Figure 5** Dissipation of biological effect of 1,25(OH)₂D₃ as measured by the return of urinary calcium excretion toward pretreatment levels in normal subjects. The changes in urinary calcium (Δ urinary Caₜ), shown on a log₁₀ scale, represent the difference between the observations on each post-treatment day and the mean pretreatment rate of excretion. The regression lines were calculated by the method of least squares (17). The arrows indicate the last day of treatment with the sterol. The designations, A and B, refer to subjects who received both 1,25(OH)₂D₃ and 1α(OH)D₃ (Fig. 6).

**Figure 6** Dissipation of biological effect of 1α(OH)D₃ as measured by the return of urinary calcium excretion toward pretreatment levels, in normal subjects. The data are shown as in Fig. 5.

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1,25(OH)\(_2\)\(\text{D}_3\) and 1\(\alpha\)(OH)\(\text{D}_3\); thus, 1\(\alpha\)(OH)\(\text{D}_3\) is less potent than 1,25(OH)\(\text{D}_3\) at doses below 1 \(\mu\)g/day, but equally potent at doses above 2.0 \(\mu\)g/day. The onset of maximal action, as judged by the increment in urinary calcium, is more gradual with 1\(\alpha\)(OH)\(\text{D}_3\) than 1,25(OH)\(\text{D}_3\), and the duration of effect disappeared at a slower rate after 1\(\alpha\)(OH)\(\text{D}_3\) was discontinued than observed with 1,25(OH)\(\text{D}_3\). In addition, observations in azotemic patients given the compounds for several months suggest that there may be a progressive or cumulative effect of 1\(\alpha\)(OH)\(\text{D}_3\) compared to 1,25(OH)\(\text{D}_3\). The last observation is similar to that of Catto et al. (5), who noted a progressive increase in calcium absorption in two of three uremic patients receiving a constant dose of 1\(\alpha\)(OH)\(\text{D}_3\) for 9–10 wk.

Our observations in man of the relative potencies of 1\(\alpha\)(OH)\(\text{D}_3\) and 1,25(OH)\(\text{D}_3\) are in agreement with results of Holick et al. (19), who gave rats either 1\(\alpha\)(OH)\(\text{D}_3\) or vitamin \(\text{D}_3\) daily for 7 days. The 1\(\alpha\)(OH)\(\text{D}_3\) was 2–5 more potent than vitamin \(\text{D}_3\) compared to their previous data showing 1,25(OH)\(\text{D}_3\) to be 5–10 times more potent than vitamin \(\text{D}_3\) (20).

In contrast, other data obtained in vitamin D-deficient rats and chicks have indicated that 1\(\alpha\)(OH)\(\text{D}_3\) is at least as potent as 1,25(OH)\(\text{D}_3\); Haussler et al. (10), and Cork et al. (21) found 1\(\alpha\)(OH)\(\text{D}_3\) to be equally or slightly more active than 1,25(OH)\(\text{D}_3\) in chicks. Toffolon et al. (9) found the two sterols to be equally effective in stimulating calcium transport in very young rats, while Pechet and Hesse reported that 1\(\alpha\)(OH)\(\text{D}_3\) was more effective than 1,25(OH)\(\text{D}_3\) in mobilizing skeletal calcium in rats (22). Toffolon et al. reported 1\(\alpha\)(OH)\(\text{D}_3\) and 1,25(OH)\(\text{D}_3\) to have equally rapid appearance of action after a single dose; on the basis of these data, they suggested that 1\(\alpha\)(OH)\(\text{D}_3\) acted directly without subsequent metabolic conversions (9).

A number of studies comparing the effects of 1\(\alpha\)(OH)\(\text{D}_3\) and 1,25(OH)\(\text{D}_3\) in vitro support the contention that 1\(\alpha\)(OH)\(\text{D}_3\) must undergo metabolic conversion, presumably to 1,25(OH)\(\text{D}_3\), before exerting its effect. Thus, Procsal et al. (23) found 1\(\alpha\)(OH)\(\text{D}_3\) to bind 1/800th as avidly to the chick intestinal-cytosol-chromatin receptor system for 1,25(OH)\(\text{D}_3\) as did 1,25(OH)\(\text{D}_3\), itself; Zerwekh et al. (8) found the binding affinity of 1\(\alpha\)(OH)\(\text{D}_3\) to be 1/100th to 1/1,000th as great as 1,25(OH)\(\text{D}_3\). Since the two sterols were equally active in vivo, it was suggested that 1\(\alpha\)(OH)\(\text{D}_3\) undergoes rapid 25-hydroxylation to 1,25(OH)\(\text{D}_3\) before exerting its action. Moreover, only 1,25(OH)\(\text{D}_3\), as identified by the competitive binding assay, was found associated with chick intestinal chromatin after treating intact birds with 1\(\alpha\)(OH)\(\text{D}_3\) (8). Reynolds et al. (24) found 1\(\alpha\)(OH)\(\text{D}_3\) to be 1/100th as active as 1,25(OH)\(\text{D}_3\) in promoting bone resorption when the compounds were added to explants of mouse calvaria, in vitro. In contrast, the compounds were nearly equal in potency when they were given in vivo before the evaluation of bone resorption, in vitro.

The duration of action of 1\(\alpha\)(OH)\(\text{D}_3\) and 1,25(OH)\(\text{D}_3\) has received little attention in animal studies. Haussler et al. (10) found 1\(\alpha\)(OH)\(\text{D}_3\) and 1,25(OH)\(\text{D}_3\) to be equally active 40 h after their administration to chicks, and Toffolon et al. found the agents to have similar actions 14 h after giving a single dose to very

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young rats (9). The present studies in normal man indicate both a delayed appearance of maximal action after the daily administration of 1α(OH)D₃ and a slower dissipation of effect after the cessation of therapy than were observed with 1,25(OH)₂D₃.

The observations of potency and of onset and duration of action of 1α(OH)D₃ compared to 1,25(OH)₂D₃ in man may be explained by the necessity that 1α(OH)D₃ must undergo 25-hydroxylation to 1,25(OH)₂D₃ before exerting its effect. Both normal subjects and uremic patients would be expected to have adequate quantities of vitamin D₃, and exogenous 1α(OH)D₃ and endogenous vitamin D₃ may compete for the same hepatic (or intestinal [8]) 25-hydroxylase. Our suggestion of a requirement in man for hepatic hydroxylation of 1α(OH)D₃ before the onset of its biological action is consistent with the recent report of Fukushima et al. (25). They obtained unequivocal evidence that radioactive 1α(OH)D₃ was rapidly converted to 1,25(OH)₂D₃ in an isolated, perfused rat liver system.

With treatment of patients with low doses of 1α-(OH)D₃ or during the first few days of therapy, 25-hydroxylation of vitamin D₃ may be favored over that of 1α(OH)D₃. Hence, 1α(OH)D₃ is less potent than 1,25(OH)₂D₃. During continued treatment with 1α-(OH)D₃ or with the administration of larger doses, its plasma or tissue level may increase, and sufficient 25-hydroxylation may occur to produce the resultant biologic action. The augmentation of 4Ca absorption observed after continued long-term treatment with 1α(OH)D₃ could be accounted for by the accumulation of increased body stores of the sterol and its continued 25-hydroxylation. Moreover, the 25-hydroxylation of 1α(OH)D₃ probably occurs continuously with persistent production of 1,25(OH)₂D₃. The turnover rates of plasma and tissue pools of 1,25(OH)₂D₃ are probably quite rapid (26), and it is likely that wide fluctuations of plasma and tissue concentrations of 1,25(OH)₂D₃ occur during treatment with single daily doses of exogenous sterol.

The observation that 1α(OH)D₃ produces a rapid action and has the same potency as 1,25(OH)₂D₃ in vitamin D-deficient rats (9) or chicks (10) after the administration of a single dose may be explained by a greater activity of 25-hydroxylase in the vitamin D-deficient state, or because there is no vitamin D₃ present to compete for the cholecalciferol-25-hydroxylase. On the other hand, it should be pointed out that both 1,25(OH)₂D₃ and 1α(OH)D₃ are effective in man at doses that are at least two orders of magnitude lower than those used in the rat (9) or chick (10).

The present study was not carried out to compare the therapeutic efficacy or safety of 1,25(OH)₂D₃ and 1α-(OH)D₃. However, the progressive increase in 4Ca absorption in uremic patients receiving 1α(OH)D₃ for several months, both in the present study and in that of Catto et al. (5), suggests that a danger of “vitamin D intoxication” could exist during prolonged treatment with 1α(OH)D₃. Clearly, there is a need for further observations of the long-term actions of both 1α(OH)D₃ and 1,25(OH)₂D₃ before either agent enters widespread clinical use.

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