Pharmacokinetics of a single, large dose of cholecalciferol

Mariam Ilahi, Laura AG Armas, and Robert P Heaney

ABSTRACT

Background: There is much interest in dosing vitamin D intermittently for patient convenience and long-term adherence.

Objective: The objective was to characterize the time course and response of 25-hydroxyvitamin D (calcidiol) to a large oral dose of cholecalciferol.

Design: One group (30 subjects) was supplemented with a single oral dose of 100 000 IU cholecalciferol. A second group (10 subjects) served as a control group to assess the seasonal change of calcidiol. Serum calcidiol concentrations were followed for 4 mo.

Results: Serum calcidiol rose promptly after cholecalciferol dosing from a mean (±SD) baseline of 27.1 ± 7.7 ng/mL to a concentration maximum of 42.0 ± 9.1 ng/mL. Seven percent of the supplemented cohort failed to achieve 32.1 ng/mL at any time point. The highest achieved concentration in any subject was 64.2 ng/mL. The control group had a nonsignificant change from baseline of −0.72 ± 0.80 ng/mL during 4 mo.

Conclusions: Cholecalciferol (100 000 IU) is a safe, effective, and simple way to increase calcidiol concentrations. The dosing interval should be ≤2 mo to ensure continuous serum calcidiol concentrations above baseline. This trial was registered at www.clinicaltrials.gov as #NCT00473239. Am J Clin Nutr 2008;87:688–91.

KEY WORDS Vitamin D, cholecalciferol, 25-hydroxyvitamin D, therapeutic use, calcidiol, hydroxycholecalciferol, calcium

INTRODUCTION

Vitamin D deficiency is a common problem (1, 2). Most vitamin D is obtained from the skin’s exposure to sunlight, with a limited amount from the diet (3). Supplements are used to improve vitamin D concentrations, but there are few data on what doses to give and how often to give them. Serum calcidiol, the functional indicator for vitamin D status, has a long half-life, so there is much interest in intermittent dosing for patient convenience and long-term adherence. Although single, large oral doses were studied, no one has determined the optimum dosing frequency. A small amount of data from prior studies have shown that a single large dose of vitamin D raises calcidiol concentrations (4–9). The doses used in those studies ranged from 50 000 to 240 000 IU, and calcidiol concentrations were measured at intervals of 10 d to 6 mo after dosing. Data show that those doses of vitamin D are clinically useful. Khaw et al (10) showed a decrease in parathyroid hormone after a single dose of 100 000 IU cholecalciferol (vitamin D3) in an elderly population, and Trivedi et al (11) showed a decrease in fractures with dosing of 100 000 IU cholecalciferol every 4 mo. However, no studies have measured the time course of serum calcidiol concentrations after a large oral dose of cholecalciferol. Thus, although a single large dose will clearly elevate serum calcidiol, the degree of elevation and its duration are unknown. It is also not known whether the response [ie, area under the curve (AUC)] is linearly related to dose. In our previous study, comparing the time course of ergocalciferol with cholecalciferol, we had noted that after a single dose of 50 000 IU cholecalciferol, calcidiol concentrations were still elevated 28 d after the dose (12). The current study was designed to assess the time course and response of serum calcidiol with a single oral dose of 100 000 IU cholecalciferol.

SUBJECTS AND METHODS

Setting and participants

The subjects were 40 healthy, community-dwelling, predominantly white men and women divided into 3 groups. The subjects did include 1 African American and 1 Pacific Islander.) A group of 20 older subjects (aged 61–84 y; 15 women, 5 men) and a group of 10 younger subjects (aged 27–47 y; 6 women, 4 men) were given a single large dose of cholecalciferol. A group of 10 subjects (aged 63–91 y; 9 women, 1 man) served as a concurrent untreated control group to assess the seasonal change of calcidiol. The subjects had limited sun exposure of <10 h/wk and daily milk consumption of <0.47 L (16 oz). We excluded subjects with reported granulomatous conditions, liver disease, kidney disease, or diabetes and subjects taking anticonvulsants, barbiturates, or steroids. Twenty-six of the 40 subjects were taking anticonvulsants, barbiturates, or steroids in any form. Twenty-six of the 40 subjects were taking calcium or multivitamin supplements that they continued to take throughout the study. Two control subjects did not complete the study because of travel to a sunny climate during the study months. All subjects were from Omaha, NE, and surrounding communities. Pertinent personal characteristics are set forth in Table 1. The project was approved by the Institutional Review Board of Creighton University, and all subjects gave written informed consent.

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TABLE 1
Demographic and intake data

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Weight</th>
<th>BMI</th>
<th>Calcium intake from supplements</th>
<th>Vitamin D intake from supplements</th>
<th>Milk intake</th>
<th>Baseline calcidiol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>y</td>
<td>kg</td>
<td>kg/m²</td>
<td>mg/dl</td>
<td>IU/dl</td>
<td>L</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Older (n = 20)</td>
<td>70.8 ± 5.62</td>
<td>71.6 ± 11.58</td>
<td>27.4 ± 6.27</td>
<td>535.7 ± 490.8</td>
<td>370.0 ± 245.2</td>
<td>0.28 ± 0.18</td>
<td>27.2 ± 8.4</td>
</tr>
<tr>
<td>Younger (n = 10)</td>
<td>37.9 ± 8.04</td>
<td>71.2 ± 20.9</td>
<td>24.3 ± 5.32</td>
<td>40.0 ± 84.3</td>
<td>80.0 ± 168.7</td>
<td>0.26 ± 0.16</td>
<td>26.8 ± 6.7</td>
</tr>
<tr>
<td>Control (n = 10)</td>
<td>71.1 ± 9.77</td>
<td>71.6 ± 13.3</td>
<td>27.8 ± 4.1</td>
<td>490.0 ± 417.5</td>
<td>325.0 ± 250.8</td>
<td>0.28 ± 0.15</td>
<td>27.7 ± 9.1</td>
</tr>
</tbody>
</table>

All values are x ± SD.

Design overview

Enrollment for this open-label study was conducted in October. Subjects in the older age group were randomly assigned sequentially, using previously generated random numbers, to groups receiving either 2 capsules each labeled to contain 50 000 IU (1.25 mg) cholecalciferol or no supplement (control group). All the subjects in the younger age group received 2 capsules each labeled to contain 50 000 IU (1.25 mg) cholecalciferol. [The vitamin D capsules were supplied by Tishcon Corp (Salisbury, MD). The product was assayed on August 29, 2006, and found to contain 56 220 IU cholecalciferol/capsule.] At the initial visit, each subject's height and weight were measured. Height was measured 3 times with the use of a Harpenden stadiometer (Seritex Inc, Carlstadt, NJ), and the average was used. Weight was measured 2 times with the use of a Health-O-Meter balance beam scale (Continental Scale Corp, Chicago, IL), and the average was used. The supplemented subjects had blood drawn on days 0, 1, 3, 5, 7, 14, 21, 28, 42, 56, 70, 84, 96, and 112 for serum calcidiol concentrations. Blood for serum calcium was drawn on days 0, 1, 3, 5, and 112. Intact parathyroid hormone was drawn on days 0 and 112. After the baseline blood was obtained, the subjects were observed while they took the assigned vitamin D supplement dose. The control group had blood drawn for calcidiol, calcium, and parathyroid hormone on day 0 and 112. All subjects had blood drawn between 0800 and 1120. All subjects had blood drawn for calcidiol, calcium, and parathyroid hormone on days 0 and 112. Serum calcidiol was measured by radioimmunoassay, with the use of the IDS kit (Nichols Institute, San Clemente, CA). The assay has an intraassay CV of 5.3–6.1% and an interassay CV of 7.3–8.2%. All calcidiol measurements for a given subject were assayed at the same time and with the same kit in the laboratory of the Creighton University Osteoporosis Research Clinic. Intact parathyroid hormone was measured by radioimmunoassay (DiaSorin, Stillwater, MN) in the laboratory of the Creighton University Osteoporosis Research Clinic. Calcium was measured by Roche Cobas Integra autoanalyzer (F Hoffmann-La Roche Ltd, Basel, Switzerland) in the medical laboratory of Creighton University.

Analytic methods

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Statistical methods

We estimated the sample size for our study from a previous study of calcidiol concentrations in a population of young, healthy subjects (12). Thirty subjects allowed us to measure a change in calcidiol of 4 ng/mL from baseline with a power of >90% and a P < 0.05.

AUC of serum calcidiol increments was calculated by the trapezoidal method individually for each subject, and the resulting AUC values were aggregated for descriptive statistics. AUC is the integrated blood concentration over time. The other standard pharmacokinetic markers [time to reach maximum concentration (T\text{max})] and concentration maximum (C\text{max})] were also recorded individually for each participant, and these values were aggregated as well. MICROSOFT OFFICE EXCEL, version 2003 (Microsoft Corporation, Redmond, WA), or SPSS, Version 14 (SPSS Inc, Chicago, IL), was used for statistical calculations.

RESULTS

Serum calcidiol rose promptly after cholecalciferol dosing from a mean (±SD) baseline of 27.1 ± 7.7 ng/mL to a C\text{max} of 42.0 ± 9.1 ng/mL (Figure 1). The mean C\text{max} rise from baseline was 14.9 ± 5.1 ng/mL. The peak occurred at 7 d (median T\text{max}), and the serum concentration declined approximately linearly thereafter. Mean values no longer significantly different from baseline were reached by 84 d, and the mean calcidiol concentration also fell below 32.1 ng/mL by 84 d.

Figure 2 expands the early portion of the time course and displays the dispersion around the mean values as ±1 SD, thus giving a visual indication of the spread of the individual values. Two points stand out: 1) 1 SD below the mean extends <32.1 ng/mL even at the T\text{max} (7% of our participants never reached 32.1 ng/mL) and 2) 1 SD above
DISCUSSION

Trivedi et al (11) showed that dosing with 100 000 IU cholecalciferol every 4 mo reduced osteoporotic fractures, but those investigators supplied no information on optimal dosing frequency, because the time course of the response in their subjects was not measured. Similarly, Wigg et al (13) recently reported that 100 000 IU every 3 mo worked well to improve vitamin D nutrition in a residential care setting, but they, too, provide no data on time course and no information about how long the induced rise in serum calcidiol lasted. Thus, neither study, although using intermittent 100 000 IU doses, provides the information needed to devise an optimal dosing regimen. The present study is the first to do so. As shown in Figure 1, mean values had fallen below the desirable 32.1 ng/mL concentration by ≈70 d. Thus, clearly, a 121-d dosing schedule, as was used by Trivedi et al (11), does not provide continuous support of optimal calcidiol concentrations. Even the 90-d schedule used by Wigg et al (13) is probably suboptimal.

We saw that in several of our subjects even this large dose did not raise their calcidiol concentrations >32 ng/mL. Distinguishing features of these subjects were their low baseline calcidiol concentrations (between 15 and 18 ng/mL) and 1 subject was African American. We did not note any relation between baseline calcidiol concentrations and incremental response to treatment. A significant inverse correlation was observed of calcidiol concentrations and incremental response to treatment. We addressed this issue by comparing the AUC developed for this dose to our previously reported study of a single dose of 50 000 IU cholecalciferol (12). Figure 3 makes that comparison graphically. Because the earlier study had data for only 28 d, AUC values for both studies had to be calculated for that time period. In addition, because the earlier study had enrolled only younger subjects and because the present study showed that the time course for the 2 age groups differed somewhat, it was necessary to use only the data from the younger subjects in the present study for this comparison. As is visually evident in the figure, the mean AUC for the present 100 000-IU dose is just about twice that for the 50 000-IU dose. Further, both doses, as referred to in this analysis, are for the labeled content. As noted earlier, the measured content of the preparation used in this study was ≈12% higher than labeled, and a similar departure occurred with the earlier study. When suitable correction is made for the actually ingested doses, the AUC values for the 2 differ by a factor of almost exactly 2-fold. Hence, one can reasonably infer that other doses will probably produce results that can be calculated from these 2 studies. Briefly, the 2 studies show that an
confirm the apparent difference in responses between the different age groups. Further studies, with larger numbers of subjects, would be needed to determine whether this is a true difference.

Our study highlights that 100,000 IU cholecalciferol is a safe, efficient, and cost-effective means to increase calcidiol concentrations in the elderly. From this study we can safely recommend 100,000 IU cholecalciferol dosed every 2 mo in persons with moderate baseline calcidiol concentrations. However, in those persons with baseline calcidiol concentrations < 20 ng/mL, even this large dose will not adequately raise their calcidiol concentrations.

The author’s responsibilities were as follows—MI: collected data and prepared the manuscript; LAGA: designed the study, collected and analyzed data, and prepared the manuscript; RH: designed the study, analyzed data, and prepared the manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES