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Pharmacokinetics of daily versus monthly vitamin D_3 supplementation in non-lactating women

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Abstract

This study compared serum cholecalciferol and 25-hydroxyvitamin D [25(OH)D] concentrations over four weeks in healthy, non-pregnant, non-lactating females aged 18-40 years, who were randomized to oral cholecalciferol 5,000 international units (IU) daily for 28 days or a single dose of 150,000 IU. The study was conducted in Rochester, MN in March and April of 2010. We found no difference in mean 25(OH)D between treatment groups on study day 0 or day 28 ($p = 0.14$ and 0.28, respectively). The daily group had 11 more days of detectable serum cholecalciferol than the single-dose group ($p < 0.001$). There was no difference observed in cholecalciferol area under the curve (AUC_{28}) between groups ($p = 0.49$). However, The single dose group had a significantly greater mean 25(OH)D AUC_{28} compared with the daily group ($p < 0.001$).

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Recent epidemiologic data suggest the prevalence of vitamin D deficiency is increasing worldwide.[1,2] . Infant vitamin D status largely depends on maternal vitamin D status to prevent the clinical effects of vitamin D deficiency. Breast milk has limited vitamin D (~ 40 IU/L), which may predispose some breastfed infants to vitamin D deficiency, particularly those with dark skin or maternal deficiency at birth.[3] In the United States, it is recommended that all nursing infants receive 400 IU daily [4, 5].

The parent forms of vitamin D, cholecalciferol and ergocalciferol, cross directly from serum into breast milk, whereas 25(OH)D has limited transfer [6]. Breast milk vitamin D activity can be increased by supplementation with 2000-4000 IU daily [7]. However, the optimal dosing regimen to balance adherence and effectiveness is unclear.

The primary objective of this study was to compare the pharmacokinetics of daily cholecalciferol supplementation for 28 days with a single, large oral dose in healthy premenopausal female subjects. Our hypothesis was that daily supplementation would maintain detectable serum cholecalciferol levels (>12.5 nmol/L) longer than single dose supplementation. This would guide supplementation of young adult women and provide critical data for further studies regarding the optimal dosing regimen in lactating women supplementing breastfed infants.

Inclusion criteria for this prospective, randomized trial included non-pregnant, non-lactating women aged 18-40 years. Exclusion criteria included chronic diseases that may interfere with cholecalciferol absorption or distribution, baseline hypercalcemia or hyperphosphatemia, and travel south of 35°N parallel or indoor tanning in the 30 days prior to or during the study period. The study was conducted from March 9 to April 26, 2010 in Rochester, Minnesota (44°N parallel). Subjects were randomized to receive either cholecalciferol 150,000 IU orally once or 5000 IU orally daily for 28 days. Subjects were instructed to make no dietary changes, nor change their sunlight exposure during the study. Serum cholecalciferol, 25(OH)D, calcium, and phosphorus were measured on days 0, 1, 3, 7, 14, and 28. Serum vitamin D metabolites were measured by liquid chromatography-tandem mass spectrometry [8]. Assays for 25(OH)D were standardized against NIST reference material.

A t-test was utilized to compare serum calcium, phosphorus, 25(OH)D, cholecalciferol, and cholecalciferol area under the curve (AUC_{28}) between the two groups. Levels on days 1, 3, 7, 14, and 28 were compared with baseline values by paired t-test. Assuming a two-sided significance level of 0.05 with 80% power, 16 subjects per group were sufficient to detect a mean difference of one standard deviation and a 0.75 standard deviation change from baseline.

A total of 39 subjects were randomized, and the groups had similar characteristics at baseline (Table 1). In the 150,000 IU group, the mean (±SD) serum cholecalciferol peaked

on day 1 at 236.5 ± 58.3 nmol/L, dropped sharply by day 3, and continued to fall on day 7 (Table 2). On days 14 and 28, cholecalciferol was not detectable in 13 and 17 of 20 subjects, respectively. In the daily group, serum cholecalciferol was detectable in 10 subjects on day 3 with a mean concentration of 14.8 ± 12.2 nmol/L. The mean continued to increase and reached a plateau of 27.9 nmol/L by day 14. There was no difference in serum cholecalciferol AUC_{28} between the two treatment groups (p= 0.49). The daily group had significantly more days of detectable cholecalciferol than the 150,000 IU group (21.2 ± 6.0 days vs. 9.6 ± 7.6 days; p <0.001).

The 150,000 IU group showed a rapid rise in 25(OH)D concentration on day 1, which reached a peak value of 139.0 ± 26.0 nmol/L at day 7, and slowly declined thereafter (Table 2) . The 25(OH)D values on days 14 and 28 remained significantly above baseline values (p <0.001). The daily group had a gradual, almost linear increase in 25(OH)D concentrations, with no evidence of plateau at day 28. Beginning on day 3, 25(OH)D levels were significantly elevated above baseline values (p < 0.001). The highest observed 25(OH)D value was 130.5 nmol/L in the daily groups. Compared with the daily group, the 150,000 IU group had significantly higher values on every study day except days 0 and 28 (p = 0.14 and 0.28, respectively). The 150,000 IU group had a significantly greater mean 25(OH)D AUC_{28} compared with the daily group (1875.0 ± 481.2 nmol·d/L vs. 973.7 ± 312.5 nmol·d/L respectively; p <0.001).

There were no clinically important changes in serum calcium (> 3 mmol/L) or phosphorus (> 1.6 mmol/L) between treatment groups (Table 2). On days 3 and 7, serum calcium concentrations were higher than baseline (p = 0.028 and 0.003, respectively) in the 150,000 IU group, but remained within the normal reference range. The highest observed serum calcium was 2.6 mmol/L in both treatment groups. Asymptomatic increases in serum phosphorus from baseline were seen on days 1 and 7 in the 150,000 IU group (p = 0.004 and 0.015, respectively), and on day 14 in the daily group (p = 0.027). The highest observed serum phosphorus was 1.6 mmol/L in both treatment groups. The only reported potential adverse event was an increased interval between menses in one subject in the daily group.

This study compared the pharmacokinetics of a large, single dose of oral cholecalciferol to a daily dose in healthy, premenopausal females. The single dose (150,000 IU) produced peak cholecalciferol and 25(OH)D levels on days 1 and 7, respectively. The daily dose (5000 IU) produced peak cholecalciferol levels on day 7, and increasing 25(OH)D levels throughout the study duration. However, the cholecalciferol AUC_{28} was similar between groups. Compared with similar regimens in older subjects, the pharmacokinetics differed with lower peak serum cholecalciferol and higher 25(OH)D concentrations [9-10]. This is consistent with increased hepatic 25-hydroxylation in younger populations.

A single, large dose of vitamin D may improve adherence. Daily supplementation, however, resulted in significantly more days of detectable serum cholecalciferol, which may be more desirable when breastfeeding. However, this trial did not include lactating women nor did it measure breast-milk vitamin D metabolites, and the pharmacokinetics of vitamin D may be different in breastfeeding women. This study provides adequate pharmacokinetic

information for clinical trials in non-pregnant, pregnant, and lactating women to determine regimens that benefit both mothers and infants.

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Abbreviations

25(OH)D	25-Hydroxyvitamin D
IU	International Units
AUC_{28}	Incremental area under the curve

REFERENCES

1. Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, Orav JE, Ruifent L, Spiegelman D, et al. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. J Bone Miner Res. 2009; 24:935–942. [PubMed: 19113911]
2. Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat. 2010; 121(2):469–77. [PubMed: 19851861]
3. Weisberg P, Scanlon KS, Li R, Cogswell ME. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. Am J Clin Nutr. 2004; 80(6 Suppl): 1697S–705S. [PubMed: 15585790]
4. Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents. Pediatrics. 2008; 122(5):1142–1152. [PubMed: 18977996]
5. Ross, AC.; Taylor, CL.; Yaktine, AL.; Del Valle, HB. Dietary Reference Intakes for Calcium and Vitamin D. Food and Nutrition Board, Institutes of Medicine; Washington, DC: 2010.
6. Kovacs CS. Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies. Am J Clin Nutr. 2008; 88(2):520S–528S. [PubMed: 18689394]
7. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr. 2004; 80(6 Suppl):1752S–8S. [PubMed: 15585800]
8. Singh RJ. Quantitation of 25-OH-vitamin D (25OHD) using liquid tandem mass spectrometry (LC-MS-MS). Methods Mol Biol. 2010; 603:509–517. [PubMed: 20077103]
9. Ilahi M, Armas LA, Heaney RP. Pharmacokinetics of a single, large dose of cholecalciferol. Am J Clin Nutr. 2008; 87(3):688–91. [PubMed: 18326608]
10. Heaney RP, Armas LA, Shary JR, Bell NH, Binkley N, Hollis BW. 25-Hydroxylation of vitamin D3: relation to circulating D3 under various input conditions. Am J Clin Nutr. 2008; 87(6):1738–42. [PubMed: 18541563]

Table 1

Comparison of Baseline Characteristics between Treatment Groups

Characteristic	150,000 IU Once n = 19	5,000 IU Daily n = 20
Age (yrs)	26.11 (21 – 35)	25.8 (21 – 35)
Weight (kg)	64.1 (50.4 – 96.1)	63.4 (50.8 – 93.1)
Height (cm)	165.4 (154.4 – 174.9)	166.9 (155.1 – 177)
BMI (kg/m^2)	23.4 (19 – 23.4)	22.8 (18.6 – 33.5)
Pulse (bpm)	75.8 (56 – 112)	72.8 (49 – 103)
Systolic BP (mm Hg)	111.8 (95 – 138)	115.9 (93 – 146)
Diastolic BP (mm Hg)	66.3 (50 – 80)	65.5 (45 – 88)
Race: White	89%	90%
Asian	5%	5%
Other	5%	5%

***Displayed as mean value (range) or proportion (%)**

Table 2

Serum Cholecalciferol, 25-hydroxyvitamin D, Calcium, and Phosphorus According to Vitamin D_3 Dose

Serum Cholecalciferol ± SD (nmol/L)

	Day 0	Day 1	Day 3	Day 7	Day 14	Day 28	AUC_{28}
150,000 IU Once	10.3 ± 9.9	236.5±58.3*#	73.6 ± 18.8*#	23.6 ± 13.3*	9.6 ± 5.4	7.1 ± 2.5	700.9 ± 226.4
5,000 IU Daily	6.6 ± 1.7	9.4 ± 7.6	14.8 ± 12.2*	27.1 ± 9.0*	27.9 ± 7.4#	27.9±15.6*#	651.5 ± 216.4

Serum 25-Hydroxyvitamin D ± SD (nmol/L)

	Day 0	Day 1	Day 3	Day 7	Day 14	Day 28	AUC_{28}
150,000 IU Once	64.0 ±21.7	110.0±28.5*#	133.5±29.3*#	139.0±26.0*#	137.5±25.5*#	122.0±24.8*	1875.0 ± 481.2#
5,000 IU Daily	70.1 ±21.9	73.1±22.6*	79.5 ±22.6*	91.2 ± 22.9*	108.5 ± 28.0*	130.5±25.1*	973.7 ± 312.5

Serum Calcium ± SD (mmol/L)^

	Day 0	Day 1	Day 3	Day 7	Day 14	Day 28
150,000 IU Once	2.3 ± 0.1	2.4 ± 0.1	2.4 ± 0.1*	2.4 ± 0.1*	2.4 ± 0.1	2.4 ± 0.1
5,000 IU Daily	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1

Serum Phosphorus ± SD (mmol/L)%

	Day 0	Day 1	Day 3	Day 7	Day 14	Day 28
150,000 IU Once	1.2 ± 0.1	1.3 ± 0.1*	1.2 ± 0.1	1.3 ± 0.1*	1.2 ± 0.1	1.2 ± 0.2
5,000 IU Daily	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.2	1.3 ± 0.2	1.3 ± 0.1*	1.2 ± 0.1

*p-value < 0.05 when compared with baseline value

#p-value < 0.05 when compared with other treatment group

^hypercalcemia > 3.0 mmol/L

%hyperphosphatema > 1.6 mmol/L