

Comparison of Daily, Weekly, and Monthly Vitamin D3 in Ethanol Dosing Protocols for Two Months in Elderly Hip Fracture Patients

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Background: Different dosing protocols have been used for vitamin D supplementation, but there has been a lack of comparative data among them.

Objective: Our objective was to determine whether the same cumulative dose of vitamin D3 produces different effects if it is given daily, weekly, or monthly.

Design: Women, age 81 ± 8 yr (\pm SD, $n = 48$), who had undergone surgery to repair hip fracture were randomized to vitamin D3-supplementation protocols at 1,500 IU daily, or 10,500 IU once weekly, or 45,000 IU once every 28 d. The primary outcome measure was the serum 25-hydroxyvitamin D [25(OH)D] concentration attained.

Results: Initially, serum 25(OH)D concentrations for daily, weekly, and monthly groups were, respectively, 15.13 ± 6.9 , 15.7 ± 10.1 , and 16.2 ± 10.1 ng/ml. By d 7, these had increased significantly in all the groups ($P < 0.001$). On the first day after the monthly dose, both serum 25(OH)D and serum 1,25-dihydroxyvitamin D had increased significantly ($P < 0.012$ each), whereas these did not change significantly on the day after daily or weekly doses. After 2 months, serum 25(OH)D with daily, weekly, and monthly dosing were, respectively, 33.2 ± 8.5 , 29.2 ± 8.9 , and 37.1 ± 10.3 ng/ml; there were no significant differences among these values.

Conclusions: Supplementation with vitamin D can be achieved equally well with daily, weekly, or monthly dosing frequencies. Therefore, the choice of dose frequency can be based on whichever approach will optimize an individual's adherence with long-term vitamin D supplementation. (*J Clin Endocrinol Metab* 93: 3430–3435, 2008)

In developed countries the frequency of hip fractures has been increasing by 1–3%/yr (1). Supplementation with vitamin D and calcium has lowered the risk of hip fracture (2). However, the adherence of elderly hip fracture patients with daily calcium and vitamin D supplements is low (3). For drugs for which the pharmacology is suitable, recent years have seen a shift away from daily dosing because patients prefer less frequent dosing and for which data consistently show better adherence (4, 5). The pharmacology of vitamin D is well suited to dose intervals longer than daily (6, 7).

Patients with osteoporotic hip fractures are candidates for antiresorptive therapy with bisphosphonates, drugs that are

most effective in patients with higher concentrations of serum 25-hydroxyvitamin D [25(OH)D] (8). A recent consensus concluded that to prevent fractures in older patients, the serum 25(OH)D concentrations should be higher than 30 ng/ml (75 nmol/liter) (9). Administration of a monthly dose of vitamin D starting during post-fracture hospitalization may provide a window of opportunity to establish higher vitamin D intake in patients. The pharmacology of vitamin D indicates a half-life suitable for weekly or monthly dosing (6, 7).

We wanted to determine whether the daily, weekly, or monthly use of the same cumulative dose of vitamin D3 would

0021-972X/08/\$15.00/0

Printed in U.S.A.

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doi: 10.1210/jc.2008-0241 Received February 1, 2008. Accepted June 2, 2008.

First Published Online June 10, 2008

Abbreviations: 1,25(OH)₂D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

produce similar biological responses. We were concerned that large intermittent, monthly doses of vitamin D might cause transient hypercalcemia because of a mass-action effect on the production of 1,25-dihydroxyvitamin D [1,25(OH)₂D] (10). A further objective was to characterize the efficacy of 1500 IU/d vitamin D in producing serum 25(OH)D serum concentrations higher than 30 ng/ml (75 nmol/liter).

Patients and Methods

Patients

The study population comprised 48 women, aged 81 ± 8 yr (± SD), who had undergone surgery to repair hip fracture in the Department of Orthopedic Surgery at the Rambam Health Care Campus. Using a random-number table, patients were allocated to one of three identical cumulative doses of vitamin D₃, given as 1,500 IU daily, 10,500 IU once weekly, or 45,000 IU once every 28 d. The vitamin D₃ was crystalline U.S. Pharmacopeia grade (Sigma-Aldrich, St. Louis MO), dissolved in U.S. Pharmacopeia-grade ethanol at Mount Sinai Hospital. Vitamin D₃ content was confirmed to remain stable through the course of the study, both by UV spectroscopy, and HPLC assay as described previously (11–13). Each dose was given as 1 ml solution added to a drink. The protocol lasted a total of 56 d.

Blood was collected at baseline d 0, before the first dose, and at 24 h after the dose, 1 wk and 4 wk after the first dose; the same sampling sequence was repeated during the second month of therapy. Serum was analyzed for PTH, 25(OH)D, 1,25(OH)₂D, calcium, phosphorus, albumin, and creatinine concentrations. Laboratory evaluation of serum calcium and inorganic phosphate, creatinine, and albumin concentrations was performed using a Roche/Hitachi 747 biochemistry analyzer (Roche Diagnostics, Mannheim, Germany). Serum 25(OH)D and 1,25(OH)₂D were measured by RIA (DiaSorin, Stillwater, MN), and intact PTH was measured by immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA).

Statistical analysis

Tests of hypotheses relating to changes for repeated measures compared with a baseline value were performed using repeated measures ANOVA. *Post hoc* testing to determine specific values *vs.* baseline was done using conventional paired *t* tests, for which the α -decision point was adjusted downward to allow for multiple comparisons, using Holm's adjustment (14). Tests comparing mean values among more than two groups were performed using one-way analysis, followed by *t* test comparisons for which α -values were adjusted for multiple comparisons. This was to adjust for the three *t* tests comparing results at d 0 *vs.* the first day after the dose. To allow for nonlinearity, correlation between variables was performed using the Spearman nonparametric approach. The SPSS software package was used for statistical analysis (Release 13; SPSS, Inc., Chicago, IL).

Results

Baseline characteristics of the study participants are shown in Table 1. There were no differences in concomitant diseases or differences in concomitant medications among the three groups, and no differences in calcium and vitamin D supplementation regimens upon entering the study (Table 2).

The initial serum 25(OH)D concentration of study subjects was 15.7 ± 9.0 ng/ml (mean ± SD), and the initial mean values did not differ significantly among those allocated to the different dosing frequencies (Fig. 1). Based upon repeated measures

TABLE 1. Baseline characteristics of the study participants

Vitamin D regimen	Mean age ± SD	No. of previous fractures (%)	Concomitant diseases [No. (%)]									
			Cardiovascular	B12 deficient	Diabetes	Thyroid	Known osteoporosis	Joint	Parkinson's	Depression	Vision, hearing impairment	
Daily, no. 17	80.9 ± 8.7yr	4 (25)	16 (94.1)	2 (11.7)	5 (29.4)	1 (5.9)	1 (5.9)	1 (5.9)	2 (11.7)	0	2 (11.7)	7 (41.18)
Weekly, no. 16	81.0 ± 6.1yr	3 (18.7)	14 (87.5)	1 (6.3)	5 (31.3)	1 (6.3)	7 (43.7)	3 (18.8)	3 (18.8)	3 (18.8)	2 (12.5)	6 (37.5)
Monthly, no. 15	79.4 ± 6.8yr	2 (13.3)	15 (100)	4 (26.6)	4 (6.6)	3 (20)	4 (26.6)	0	1 (6.7)	1 (6.7)	1 (6.7)	11 (73.3)

TABLE 2. Concomitant medications used by study participants at baseline

Group dosing frequency (No.)	Calcium supplement			Vitamin D supplements			Diuretics	Antihypertensive	Sedatives	Anticonvulsants	Glucocorticoids	Antidepressant	Diabetes treatment	Anti-Parkinson
	600 mg/d	1200 mg/d	200 IU/d	400 IU/d	800 IU/d									
Daily (17)	2	2	2	1	1	1	5	11	7	1	1	2	4	0
Weekly (16)	5	3	3	0	0	0	2	10	6	0	0	2	3	2
Monthly (15)	3	3	1	1	0	0	5	13	4	0	2	1	2	1

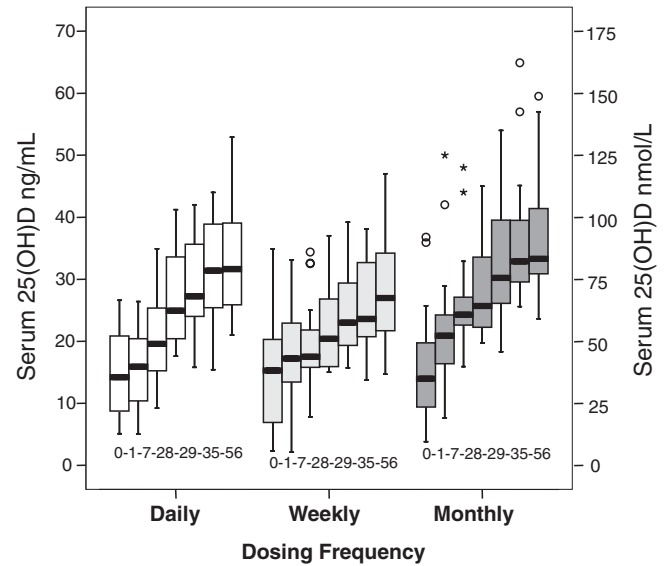


FIG. 1. Effects of the same cumulative dose of vitamin D3, equivalent to 1500 IU/d, but given once daily, once weekly, or once monthly (28 d), on serum 25(OH)D concentration in women followed up for hip fracture. Samples were taken on the number of days after the first dose of vitamin D, after baseline (d 0), as indicated by the numbers below the box plots. Each cluster of boxes shows results for samples taken repeatedly from the one group of patients. Boxes show quartile values; whiskers show the high and low, non-outlier values, whereas the open circles and stars are individual values determined by SPSS software as outliers. From d 7 onward, the serum 25(OH)D concentration was significantly higher than baseline for all groups.

ANOVA, serum 25(OH)D concentrations changed significantly by d 7, in all the groups ($P < 0.001$; Holm's $\alpha = 0.008$ for six comparisons vs. baseline). However, those patients taking the monthly dose (45,000 IU) exhibited a significant increase in concentration of serum 25(OH)D at 24 h after each dose ($P < 0.001$; Holm's $\alpha = 0.008$). Likewise, the *a priori* hypothesis of an increase after 24 h after dose in serum 1,25(OH)₂D was evident only in the monthly dose group ($P < 0.012$; Holm's $\alpha = 0.015$). The 1,25(OH)₂D change at 24 h after the dose was not statistically significant when the second monthly dose of vitamin D was administered. On neither occasion was there a significant elevation in serum calcium concentration at 24 h after the monthly dose. One patient in the daily dose group exhibited one instance of hypercalcemia.

Mean albumin-corrected calcium concentrations increased significantly in each of the groups between d 0 and 56 of the protocol but remained within the reference range. Mean serum PTH concentrations were significantly lower by the end of the study protocol in the weekly and the monthly dose groups (Table 3). The lack of a statistically significant decline in PTH for the daily dose group is consistent with the β -error expected, given the sample size of the individual groups. For all groups combined, PTH concentrations declined over the course of the study ($P = 0.003$).

To characterize the effect of initial 25(OH)D concentration on the concentration attained at d 56, we pooled all subjects in the study and stratified them according to the initial concentration of 25(OH)D (Fig. 2). The increase in 25(OH)D correlated inversely with initial serum 25(OH)D concentration (Spearman nonparametric $P = 0.002$). Of the six patients in whom serum

TABLE 3. Effect of dosing frequency and of 8-wk vitamin D supplementation on serum 25(OH)D, PTH, and albumin-corrected calcium concentration for each treatment protocol

	Daily regimen	Weekly regimen	Monthly regimen
25(OH)D (ng/ml)			
Basal	15.13 ± 6.9	15.7 ± 10.1	16.2 ± 10.1
Final	33.2 ± 8.5 ^a	29.2 ± 8.9 ^a	37.1 ± 10.3 ^a
1,25(OH) ₂ D (pg/ml)			
Basal	26.8 ± 14.0	28.0 ± 15.7	33.5 ± 24.0
Final	37.9 ± 15.4 ^a	38.7 ± 10.4 ^a	46.0 ± 20.1 ^a
Serum albumin-corrected calcium (mg/dl)			
Basal	9.25 ± 0.66	9.22 ± 0.41	9.27 ± 0.63
Final	9.76 ± 0.36 ^a	9.78 ± 0.39 ^a	9.7 ± 0.33 ^a
PTH (pg/dl)			
Basal	38.46 ± 18.85	50.83 ± 33.08	42.34 ± 17.51
Final	36.45 ± 22.36	31.50 ± 9.32 ^a	28.47 ± 11.17 ^a

Values are expressed as mean ± SD.

^a Statistically significantly different from concentration at baseline, based on significant analysis of variance, followed by *post hoc* paired *t* test values, with α adjusted according to Holm's procedure.

25(OH)D was less than 10 ng/ml, the 8-wk protocol with 1500 IU/d produced a 50% likelihood of a 25(OH)D more than 29 ng/ml. Of the 25 patients with serum 25(OH)D 10–20 ng/ml, the protocol produced a 56% likelihood of a 25(OH)D more than 29 ng/ml. Of the 17 patients with serum 25(OH)D more than 20 ng/ml, the protocol produced an 82% likelihood of a 25(OH)D more than 29 ng/ml.

Discussion

For decades, various dose intervals for vitamin D supplementation or treatment have been in use, including annual injections, a pill every fourth month, as well as monthly, weekly, and daily

doses (15–17). Basic pharmacology principles suggest that the circulating half-life is a suitable dosing interval for a drug (18). Because vitamin D and 25(OH)D exhibit half-lives in the body that are in the order of months and weeks, the daily administration of vitamin D is probably unnecessary (6). However, vitamin D is not like a normal drug because it is activated by enzymes that do, in the short-term, function *in vivo* as if their substrate concentration is below the Michaelis constant of the enzyme (10, 19). In other words, it was thought that a large ingested dose of vitamin D could potentially cause an acute increase in serum 1,25(OH)₂D concentration. This has been shown in the rat (10, 19), and we hypothesized that a large dose of vitamin D given to a human might also produce a transient increase in serum 1,25(OH)₂D concentration, and if so then that might transiently increase serum calcium.

A transient increase in serum 1,25(OH)₂D concentrations did occur the first day after the initial 45,000 IU dose of vitamin D3 but was not accompanied by hypercalcemia. In further agreement with what had been observed in the rat, the subsequent large vitamin D dose did not produce a statistically detectable increase in 1,25(OH)₂D. The other feature distinguishing the monthly approach to giving vitamin D was that there was a significant increase in serum 25(OH)D on the day after the dose.

Aside from the expected initial differences in serum 25(OH)D and 1,25(OH)₂D among the groups, there were no significant longer-term differences between dosing regimens. This finding differs from a recent report by Chel *et al.* (16), in which daily, weekly, and monthly dosing approaches were compared using different vitamin D formulations for each dosing interval. Chel *et al.* (16) reported an increase in 25(OH)D with monthly dosing that was only about half what they observed with daily or weekly dosing. We suggest that their lower monthly administration efficacy was due to the use of a powdered vitamin D supplement that, unlike their pills for daily or weekly doses, may not have been completely consumed by their patients. By contrast, an advantage of our approach to the use of noncommercial preparations of vitamin D is that, except for dose, there were no differences between the daily, weekly, or monthly dose of vitamin D

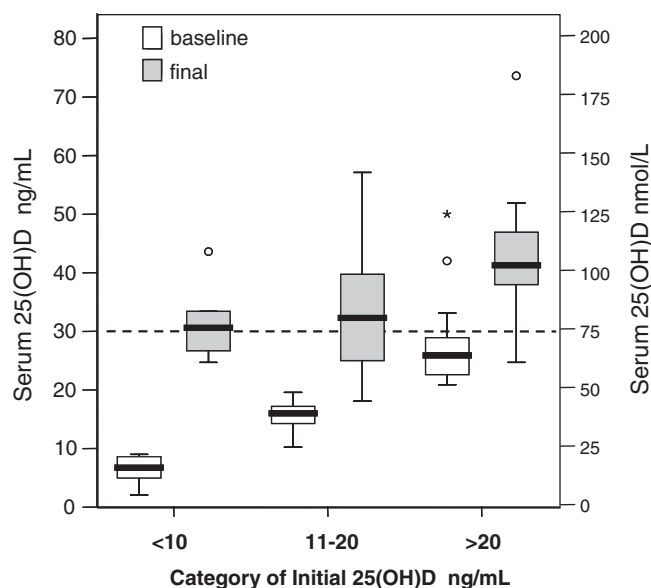


FIG. 2. Pooled results for all 48 patients, stratified according to the serum 25(OH)D concentration on d 0 (*open box plots*). The *shaded box plots* show quartile values after 2 months (8 wk) of receiving the equivalent of 1500 IU/d vitamin D3. The *dotted line* indicates the 30 ng/ml (75 nmol/liter) goal desired for serum 25(OH)D in patients with osteoporosis. The *open circles* and *asterisk* are individual values determined by SPSS software as outliers.

in terms of patient product composition or behavior that might have altered bioavailability of the vitamin D. Each dose was administered as a single milliliter of ethanol added to a drink, eliminating perceptible differences for the patients concerning the physical nature of the vitamin D administered among the groups, and minimizing variations of the proportion of dose consumed.

The results obtained with vitamin D in ethanol are applicable to other formulations of vitamin D. We recently demonstrated that bioavailability, based on serum 25(OH)D response, of high-dose vitamin D that was fortified into cheddar cheese, or into low-fat cheddar, when consumed weekly, is identical in a direct comparison with bioavailability using vitamin D in ethanolic solution, as in the present protocol (20).

One potential limitation of the present study is that it was not blinded. Although blinding could have been achieved, *e.g.* by administering placebo ethanol for 27 of 28 d to the monthly dose group, this would have introduced complexity and a source of error to the study. Moreover, blinding was not necessary because all patients received the active agent, and because the outcome of the experiment, serum 25(OH)D, could not have been modified through a placebo effect. Another limitation was the relatively short 8-wk protocol used. A protocol of longer duration would have produced higher mean 25(OH)D concentrations, but this could not have affected the conclusions comparing dosing intervals. Like the comparisons at earlier time points in this study, relative 25(OH)D contrasts among groups beyond 2 months have remained unchanged (16). Another limitation is that we did not record functional or clinical outcomes, but those were beyond the scope of what we had intended to accomplish with this work.

Although statistical power remains a question for any study showing no statistical difference, we do not consider the potential true differences in 25(OH)D among dose regimens, if any, to be clinically significant. At the outset, our trial was powered for a probability of 80% to detect a difference of 1 SD. We observed a 4-nmol/liter difference in mean final 25(OH)D between daily and weekly dose strategies. If this difference was real, and assuming the 8.5 nmol/liter SD observed, then a trial of 144 patients would be required to demonstrate the difference (21). Like the higher final serum 25(OH)D observed with monthly dosing, a difference among groups requiring such a large study is not likely to be clinically significant. After 8 wk, the intervention produced statistical increases within the reference ranges of serum 1,25(OH)₂D and calcium. Overall, there was a significant decline in serum PTH concentration, indicating that for the patients as a whole, serum 25(OH)D had not been adequate at the beginning of the trial, not surprisingly. The increase in 25(OH)D suppressed PTH, and it resulted in a modest increase in 1,25(OH)₂D and in serum calcium. If 25(OH)D concentrations were to increase further, it is not likely that 1,25(OH)₂D and calcium concentrations would continue to increase further because there is tight homeostatic regulation by 1,25(OH)₂D to maintain a constant concentration of ionized calcium (22, 23). The increases in 1,25(OH)₂D and calcium in this study indicate that 25(OH)D was inadequate initially; however, once 25(OH)D concentrations exceed 30 ng/ml, serum

1,25(OH)₂D does not continue to increase (22, 24), and calcium absorption reaches a plateau (25).

The accepted long-term dose to maintain an average 25(OH)D serum concentration of 30 ng/ml (75 nmol/liter) is 800 IU/d (9). According to a recent metaanalysis of five randomized controlled trials of hip fracture risk and seven randomized controlled trials of nonvertebral fracture risk, vitamin D intakes of 700–800 IU/d reduced the risk of hip fracture by 26% (relative risk, 0.74) and any nonvertebral fracture by 23% (relative risk, 0.77) compared with calcium or placebo. No significant benefit was observed for vitamin D intake of 400 IU/d or less, and no significant benefit was observed in clinical trials in which mean serum 25(OH)D failed to exceed 28 ng/ml (70 nmol/liter) (2). Likewise, both cross-sectional 25(OH)D data (26) and meta-analyses of placebo-controlled clinical trials indicate that vitamin D lowers mortality rates (27).

Our study highlights the usefulness of measuring serum 25(OH)D to help determine the dose of vitamin D3 needed to achieve the goal of a serum 25(OH)D of at least 30 ng/ml (75 nmol/liter) within 8 wk. The use of 1500 IU/d was intended to serve as a loading dose. If the initial serum 25(OH)D is less than 20 ng/ml, then patients probably need to be started on a daily equivalent dose of vitamin D3 that is more than 1500 IU because half of them will not have attained that goal. If the initial serum 25(OH)D is over 19 ng/ml, then 1500 IU for 8 wk offers reasonable assurance that the 25(OH)D will exceed 29 ng/ml within 8 wk, so for such patients, a maintenance dose of 800 IU vitamin D3/d ought to suffice. Unless a patient frequently eats oily fish, it is very difficult to acquire that much vitamin D3 on a daily basis from typical dietary sources. Unprotected excessive exposure to medium-wave UV radiation of sunlight (UVB) causes sunburn and increases the risk of skin cancer. Therefore, vitamin D supplementation seems to be the safest practical way to improve serum 25(OH)D concentrations.

We conclude that if the cumulative vitamin D dose and the vehicle of administration are the same, then similar serum 25(OH)D concentrations will be attained. Although the initial dose of 45,000 IU vitamin D3 produced an initial transient increase in serum 1,25(OH)₂D, this did not cause hypercalcemia, and the transient increase did not recur on the subsequent dose. Therefore, the doses studied here are safe, and the related dosing interval can be selected freely, based upon the individually tailored regimen that the clinician and patient consider most likely to maximize long-term adherence with vitamin D supplementation. Furthermore, if a daily or weekly dose is missed and later remembered, then it can be taken as soon as it is remembered, or it can be added to the next dose.

Acknowledgments

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S.I.-S. has received grant support from Aventis (2004), Eli-Lilly (1996, 2000, 2004, 2005-present), Beaufour Ipsen Group (2001), Merck Sharp & Dome (1997, 2000, 2002), Novartis (2003), NPS (2003), Medison Pharma (2001), Sunlight Ultrasound Technologies

(1999), Neopharm Pharmaceutical (1998), Smith Kline Beecham (1997), and Transpharma (2007-present).

Disclosure Summary: B.R., T.S., and I.L.B. have nothing to declare. S.I.-S has received consulting and lecture fees from Aventis, Chemical and Technical Supplies, Eli-Lilly, Merck Sharp & Dome, Meditec, Transpharma, and NPS Allelix Corp. E.S. has received lecture fees from Aventis, Novonordisk, and Merck Sharp & Dome. R.V. has received lecture fees from Council for Responsible Nutrition, Merck, Lilly, Dairy Farmers of Canada, and consulting fees from Cytochroma, Ddrops, Fabutan, Alliance of Dietary/Food Supplement Associations, and Whitehall-Robbins. None of these provided product or financial support for this work.

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