



Brief Communication

Safety and tolerability of Vitamin D3 5000 IU/day in epilepsy

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ABSTRACT

Purpose: Preclinical and early clinical research indicates that Vitamin D3 may reduce seizures in both animal models and open-label clinical trials.

Methods: This is an initial report of an ongoing pilot study of oral Vitamin D3 5000 IU/day in subjects with drug-resistant epilepsy. After Institutional Review Board (IRB) approval and informed consent, subjects with less than one focal onset or generalized tonic-clonic seizure per month were enrolled. Subjects entered a 4-week baseline, followed by a 12-week treatment period. Serum 25, OH Vitamin D3, Blood Urea Nitrogen (BUN), creatinine, and calcium levels were monitored at baseline and at 6 and 12 weeks.

Results: High-dose Vitamin D3 5000 IU/day was well tolerated. Serum 25, OH Vitamin D3 levels increased significantly at six and twelve weeks. Vitamin D insufficiency, defined as a 25, OH Vitamin D3 level of <20 ng/ml normalized in all subjects with insufficient vitamin D levels. Median seizure frequency declined from 5.18 seizures per month to 3.64 seizures per month at 6 weeks and to 4.2 seizures per month at 12 weeks. The median percent change in seizure frequency was –26.9% at six weeks, and –10.7% at 12 weeks (not significant, Wilcoxon Signed Rank Test, $P > 0.34$).

Conclusions: High-dose oral Vitamin D3, 5000 IU/day was safe and well tolerated in subjects with epilepsy. Vitamin D levels increased significantly at 6 and 12 weeks but never exceeded potentially toxic levels, defined as >100 ng/ml. To reduce variability, we will now recruit subjects who only have three or more seizures per month.

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1. Introduction

Vitamin D3 is a fat-soluble vitamin that is important in calcium, phosphate metabolism, and bone metabolism and is a modulator of inflammation and cardiovascular health [1,2]. Low levels of vitamin D are associated with a higher risk for neurological disorders, especially multiple sclerosis, Parkinson's, and Alzheimer's disease [3–5]. People with epilepsy often have insufficient levels of vitamin D, defined as a 25, OH Vitamin D3 level of <20 ng/ml [1,6–8].

Preclinical and early human data indicate that Vitamin D3 plays a role in regulating or inhibiting seizures via membrane and genomic mechanisms [9]. In the membrane mechanism, Vitamin D3 binds to membrane-specific vitamin D receptors, reducing excitability by modulating calcium and chloride conductance across the cell membrane. In the genomic mechanism, Vitamin D3 reduces gene expression of two proconvulsant inflammatory cytokines: interleukin-1b (IL-1b) and tissue necrosis factor-alpha (TNF- α) [9]. Vitamin D plays a role in regulating or inhibiting seizures [9–13]. In 1984, Siegel et al. found that seizures triggered by electrical stimulation of rat hippocampi were reduced after

parenteral vitamin D infusion [10]. Kalueff et al. found that vitamin D increased the time to seizures and reduced the duration and severity of seizures in a pentylenetetrazol model of acute seizures [11,12]. In humans, Hollo et al. reported a 40% mean reduction in seizures in 13 subjects with epilepsy, with 38% experiencing a 50% reduction in seizures [13].

We report the initial results of a pilot open-label study of Vitamin D3 supplementation in drug-resistant epilepsy that failed at least two anti-epileptic drugs alone or in combination. The purpose of this study was to determine the safety and tolerability of a fixed dose of oral Vitamin D3 5000 IU/day in persons with epilepsy.

2. Methods

Research committee approval was obtained from the Olive View-UCLA Medical Center Education and Research Institute for a pilot safety and feasibility study of oral vitamin D supplementation (5000 IU/day) in subjects with focal onset epilepsy (IRB # 840982-10). An investigational new drug application (IND) was submitted and approved by the US Food and Drug Administration for the study (IND # 129693). Adult subjects 18–65 years old with one or more focal onset seizure or generalized tonic-clonic seizures were recruited for the study. Subjects must have been exposed to at least two or more antiepileptic drugs alone or

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in combination at effective doses without becoming seizure-free. Patients who expressed interest in the study first underwent a phone screen, and if they met inclusion/exclusion criteria, were invited for an initial visit. At the initial visit, inclusion and exclusion criteria were reviewed, and a history and physical examination was performed. If subjects met inclusion criteria, they were provided with informed consent for enrollment in the study. Subjects and their caregivers were educated in the maintenance of a seizure calendar, and no changes in antiepileptic drug doses were allowed during the study. Subjects then entered a 4-week baseline period, followed by a 12-week treatment period. During the treatment portion of the study, patients were administered one Vitamin D3 5000 IU capsules daily (Nature Made®). Blood tests for vitamin D level and blood chemistries (calcium, blood urea nitrogen, and creatinine) were performed at study entry and at each treatment visit. Blood levels were also obtained at the beginning and end of the study for the major antiepileptic drugs (i.e., carbamazepine, phenytoin, lamotrigine, phenobarbital, or valproic acid) to determine the effect of vitamin D on major epilepsy drugs and their levels. Vitamin D insufficiency was defined as a serum 25, OH Vitamin D3 level of <20 ng/ml [1,8].

2.1. Statistical methods

The changes in seizure rate per day and vitamin D levels were evaluated at each visit relative to baseline nonparametrically using the Wilcoxon Signed Rank Test with Bonferroni adjustments for multiple testing as appropriate. Daily seizure rates were converted to seizures per month (defined as 28 days/month). Systolic blood pressure (SBP) was compared across visits under the repeated measures mixed effects model since this measure is known to follow the normal distribution. Given the small sample size, median values were used for seizure frequency and vitamin D levels. Missing values were inputted using last observation carried forward (LOCF).

3. Results

Eleven subjects were enrolled, and nine subjects completed the treatment period. Two subjects dropped out for reasons unrelated to the study. The average age was 35.5 years, average duration of epilepsy was 19 years, and the median baseline seizure frequency was 11.9 seizures per month. Oral Vitamin D3 5000 IU/day was well tolerated. No study-related adverse events were reported. At baseline, 5/9 (56%) had insufficient blood levels, defined as 25, OH Vitamin D3 <20 ng/ml [1,8]. Vitamin D3 normalized in all five subjects with insufficiency by 6 weeks. Median Vitamin D3 levels increased from a baseline level of 18.3 ng/ml (range: 7–39.4 ng/ml) to 43.4 ng/ml (range: 31–80 ng/ml) at 6 weeks and 53.0 ng/ml (range: 47–87 ng/ml) at 12 weeks (Fig. 1). The change in 25, OH Vitamin D3 levels were significant, $P = 0.0078$ at 6 weeks and 0.0039 at 12 weeks (Wilcoxon Signed Rank Test). There was no significant change in calcium, blood urea nitrogen, or creatinine levels, which remained within the normal range in all subjects. Systolic blood pressure did not change significantly throughout the study (repeated measures, mixed model, $P = 0.775$).

At baseline, the median seizure frequency was 5.18 seizures per month, range: 0.84–72.8. At six weeks of vitamin D supplementation, median seizure frequency was 3.64 seizures per month, range: 0.0–74.5. At twelve weeks, median seizure frequency was 4.2 seizures per month, range: 0–44.8. The median percent reduction in seizure frequency was 26.9% at six weeks and 10.7% at 12 weeks, (Wilcoxon Signed Rank Test, $P > 0.34$).

4. Discussion

In this pilot trial, Vitamin D3 supplementation at 5000 IU/day was safe and well tolerated. Vitamin D3 levels increased significantly during the study, from a median level of 18.3 ng/ml at baseline to 53.0 ng/ml at

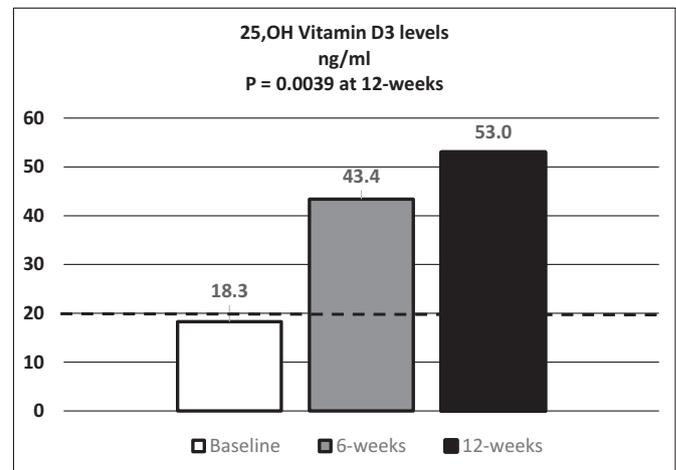


Fig. 1. Serum Vitamin D3 levels (25,OH Vitamin D3) at baseline, and 6 and 12 weeks after vitamin D 5000 IU/day. Insufficiency is defined as levels <20 ng/ml.

12 weeks (Wilcoxon Signed Rank, $P = 0.0039$). With a dose of Vitamin D3 5000/day, no subject experienced levels in the potentially toxic range (serum 25, OH Vitamin D3 level >100 ng/ml). Vitamin D supplementation was not associated with abnormally elevated levels of calcium, blood urea nitrogen, or creatinine. Vitamin D3 5000 IU/day was not associated with significant reductions in seizures, which may in part be due to the small sample size and variation in monthly seizure frequencies between patients. Moving forward, we will enroll subjects with only three or more seizures a month, which should reduce variability.

Preclinical and early clinical data indicate that Vitamin D3 may play a role in inhibiting seizures [9–13]. In 1984, Siegel et al. found that seizures triggered by electrical stimulation of rat hippocampi were reduced after parenteral vitamin D infusion. Fifty to 100 μ g of 1, 25 vitamin D stereotactically injected into rat hippocampus resulted in increases in seizure [10]. In a pentylenetetrazol model of acute seizures, Kalueff et al. found that Vitamin D3 increased the time to seizures and reduced duration and severity of seizures [11,12]. The duration of tonic-clonic seizures was reduced from 32 s in control mice to 10 s in Vitamin D3-treated mice. Also, mortality from pentylenetetrazol (PTZ) was reduced in mice treated with Vitamin D3 (2/11 in treated mice versus 6/11 in controls). Similar findings occurred in vitamin D receptor knock-out mice [11].

In humans, Hollo et al. studied 13 subjects with drug-resistant epilepsy [13]. Subjects were given a bolus of 40,000 to 200,000 IU of oral Vitamin D3 and then received maintenance therapy of 2000 to 2600 IU/day [13]. No patients developed toxic levels of vitamin D [13]. During the treatment period, subjects experienced a median reduction in seizures of 40%, and 5/13 (38.5%) experienced a $\geq 50\%$ reduction in seizures [13]. The effects on seizure frequency in the study by Hollo et al. are more robust than in our initial report, indicating that further study of vitamin D is needed.

5. Summary

In this pilot phase I study, Vitamin D3 supplementation of 5000 IU/day was safe and well tolerated in subjects with drug-resistant epilepsy. Oral Vitamin D3 reversed Vitamin D3 insufficiency in all subjects with levels <20 ng/ml by 6 weeks. This study provides evidence of the safety and tolerability of a fixed dose of Vitamin D3 of 5000 IU/day. Further study of Vitamin D3 in a larger cohort with at least three seizures per month is ongoing, and continued study of the role of vitamin D in epilepsy is indicated.

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Conflict of interest

The authors have no conflicts to report. Vitamin D3 capsules were provided without cost by Nature Made, a division of Pharmavite Inc, Valencia, CA.

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