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Review

Valproate decreases vitamin D levels in pediatric patients with epilepsy

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ABSTRACT

Purpose: To compare Vitamin D (Vit D) levels in children with epilepsy on valproate monotherapy with healthy controls.

Methods: A meta-analysis performed on articles identified from PubMed and Web of Science online databases evaluated using National Institute of Health National Heart, Lung, and Blood Institute Study Quality Assessment Tools. Subgroup analyses and publication bias assessments were also performed.

Results: Eleven publications were eligible based on inclusion/exclusion criteria for the meta-analysis. Results noted a decrease in the mean Vit D level in children with epilepsy on valproate monotherapy compared with healthy children with a Standard Mean Difference = -0.313 [-0.457, -0.169]. Cumulative meta-analysis showed progressive negative effect of valproate therapy on Vit D levels across time. Other antiepileptic medications caused a similar effect on Vit D status. There was no evidence of publication bias in the analyses. Type of study design and country of origin introduced heterogeneities into the meta-analyses.

Conclusion: This meta-analysis provides evidence that long-term therapy with valproate causes a decrease in Vit D levels in children. Therefore, in children with a seizure disorder on long-term valproate therapy, 25-OH-Vit D levels should be monitored and appropriate supplementation implemented if levels are deficient.

1. Introduction

Individuals with epilepsy being treated with chronic antiepileptic drug (AED) therapy represent approximately 1% of the general population [1,2]. Vitamin D (Vit D) deficiency is commonly reported in adult patients with epilepsy on AED therapy [3], particularly in patients on older AEDs that induce hepatic metabolism such as carbamazepine and phenobarbital [4]. Valproate and other newer AEDs (*e.g.* lamotrigine, oxcarbazepine) are generally considered to have minimal effects on hepatic metabolic enzymes, and thus, considered to have a lower potential to affect Vit D levels [5–7]. However, several studies have shown that valproate induces CYP3A4 and CYP24A1, which are involved in Vit D catabolism [8–11], making valproate a candidate AED to cause Vit D deficiency.

Vit D is essential for calcium and bone homeostasis, especially in children because childhood and adolescence are the most critical periods for bone development. The role of Vit D is not limited to bone health as it also has important roles in many extra-skeletal targets throughout the body, such as the muscles, immune system, and the cardiovascular system [12,13]. Thus, Vit D deficiency due to chronic AED therapy has additional risks beyond the decreased calcium absorption, secondary hyperparathyroidism, decreased bone density, and elevated serum alkaline phosphatase associated with bone homeostasis [14].

There are two main forms of Vit D, Vit D2, a plant and yeast sterol product, and Vit D3, the form synthesized by mammals. In humans, Vit D3 is synthesized through UVB-radiation-induced photosynthesis in the skin with less than 10% derived from dietary sources (mostly D3 and minimal amounts of D2) [15]. Total 25-hydroxyvitamin D (25-OH-Vit D) concentration in serum is the major index used to monitor the Vit D level, which includes both 25-OH-Vit D2 and 25-OH-Vit D3 [14,16]. Serum concentrations of 25-OH-Vit D less than 20 ng/mL are generally

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considered as the breakpoint for Vit D deficiency [12].

Currently, the risk of Vit D deficiency in children with seizure disorders treated chronically with AEDs is unclear and specific clinical guidelines on monitoring Vit D levels in children do not exist. Given that valproate, carbamazepine and phenobarbital are of proven efficacy and frequently administrated to children with epilepsy [17], understanding the long-term risk of Vit D deficiency imposed by chronic AED therapy in children is critical to avoiding deleterious effects on healthy development.

Numerous studies have reported on the effect of valproate therapy on Vit D levels, but due to the varying cut-offs for 25-OH Vit D blood concentration defining deficiency (< 10 ng/mL [18,19], < 12 ng/mL [20], < 20 ng/mL [21–23]), small sample size, and inconsistent methodology conflicting conclusions on the effect of long-term valproate therapy in children are reported. To bring clarity to this issue we conducted a pooled analysis of the available literature using the meta-analysis method.

2. Materials and methods

2.1. Literature searching strategy

PubMed and Web of Science (WOS) were searched thoroughly from January 1980 to July 2018. Combined terms “valproate vitamin D”, “valproic acid vitamin D”, “VPA vitamin D”, “valproate vit D”, “valproic acid vit D”, “VPA vit D” were used to search PubMed. For WOS the combined terms used were “valproate vitamin D”, “valproic acid vitamin D” and “VPA vitamin D”. Non-English publications were excluded from this analysis. Retrieved articles were processed in succession and duplicate publications were excluded. All remaining literature was reviewed by title and abstract to eliminate reviews, letters to the editor, comments, case reports, animal studies, molecular and cellular studies, and previous meta-analyses. Relevant clinical and epidemiologic studies were combined into a pool. Articles in the pool underwent context screening in accordance with defined inclusion/exclusion criteria. All qualified studies were individually reviewed to search for additional relevant studies within the articles’ references.

2.2. Criteria of study selection and exclusion

Eligible studies were original research-based articles that: 1) measured Vit D level in blood and included the mean and standard deviation (SD), or standard error of the mean (SEM), or this data was obtainable from the authors, 2) included only children whose epilepsy was treated with valproate therapy, 3) had a control group of healthy children or patients on other medication treatment that did not include an AED. Studies were excluded from the analysis if they were: 1) conducted in adult patients, 2) not related to either valproate or Vit D, 3) not a “case-control” study design, or 4) lacked Vit D data.

2.3. Data extraction and study quality evaluation

We collected information from each selected article, *e.g.,* first author, year of publication, countries of patients, study design, Vit D levels in patients and control groups and details associated with valproate therapy. The methodological quality of each study was rated using the NIH quality assessment tool for observational cohort and cross-sectional studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). All assessments were completed by two people working separately. If any inconsistent result for a particular article occurred, it was resolved by discussions among the entire group conducting this analysis.

2.4. Statistical analysis

The statistical analyses were conducted using the software STATA SE 11.0 (Stata Corporation, College Station, TX, USA). The “Metan” [24] command was used to combine the continuous data of Vit D concentrations (mean ± SD). The SEM values in studies were converted into SD values based on the formula $SD = SEM \times \sqrt{n}$. Due to the measurement of Vit D using different methods and the use of different units (ng/mL, μg/L or nmol/L), the pooled results are expressed in terms of the standardized mean difference (SMD) and their 95% confidence interval (CI). Cochran’s Q-statistic was used to estimate within and between study variations. If a significant Q-statistic ($I^2 > 50\%$, $p < 0.1$) occurred indicating heterogeneities across studies, then the random effects model was used for the meta-analysis [25]. Otherwise the fixed effects model was the default. A Cumulative meta-analytic method [26] was applied to identify how estimates of the negative effect on Vit D levels evolve over time. Subgroup analyses were conducted by stratifying according to variables such as countries of subjects to determine potential sources of heterogeneities. Publication bias was assessed by Begg’s and Egger’s tests with no publication bias defined by both p values > 0.05 [27].

3. Results

3.1. Identification of eligible studies

Our search strategy produced 332 and 160 publications from PubMed and WOS respectively. Non-English publications and duplicates were excluded and yielded 90 and 121 papers in PubMed and WOS. During title and abstract screening, 64 PubMed derived and 97 WOS extracted publications were recognized as either animal/cellular research, reviews, letters to the editor, or not related to Vit D testing in children. Consequentially, 26 original articles retrieved from PubMed and 24 obtained from WOS were integrated into a pool to undergo further evaluation. Two more articles [28,29] were added by manual screening. After 18 duplicates were removed from the pool, full context evaluation was considered among the remaining 34 publications (refer to Table S1). The context of these 34 articles was evaluated thoroughly to distinguish the studies were in accordance with the inclusion and exclusion criteria. Finally, 11 eligible articles were selected after removal of unqualified literature for various reasons (procedure as shown in Fig S1). We summarized the reasons that individual articles were included or excluded in Table S1. Despite efforts to contact the authors, unavailability of raw data from primary articles was the most common cause of exclusion from enrollment.

3.2. Classification, characteristics and risk of bias in selected publications

More than half of the reviewed 11 articles were of good or fair quality according to NIH quality assessment criteria (details are shown in Table S2). Major studies (6 out of 11) were conducted in Mid-eastern countries such as Turkey [14,22,30–32] and Iran [19]. Cross-sectional study design was the most common method applied among the 11 studies. Only one article [22] did not provide the gender information of its subjects. Most of the studies included both male and female subjects, but they did not report Vit D status in each gender group treated with valproate monotherapy. These studies all included a control group consisting of subjects not on valproate medication treatment. Two studies [21,33] did not include healthy children as control group. Another study [19] recruited untreated patients with epilepsy to be controls. The duration of valproate treatment was more than six months in all the studies including years of valproate therapy in some reports. Most of the eligible studies had more than two “case-control” comparisons, *e.g.*, valproate treatment *vs.* healthy controls, carbamazepine treatment *vs.* valproate treatment groups. All the studies measured 25-OH-Vit D levels, except for two [21,32] which reported 25-OH-Vit D3 and non-specified Vit D, respectively. The detailed characteristics of individual study are shown in Table 1.

Table 1
Characteristics of the 11 eligible studies selected to perform meta-analysis.

First Author	Publication date	Country of patients	Study type	M/F (n) in VPA group	Age (years, mean ± SD) of VPA group	VPA Duration (mean ± SD)	VPA dosage (mean ± SD)
Gabriele Rieger-Wettengl	2001	Germany	CS	9/10	12.5 ± 3.7	≥ 1 year	NA
Sefer Kumandas	2006	Turkey	CS	17/16	8.8 ± 2.0	33.72 ± 15 months	NA
Arzu Babayigit	2006	Turkey	Retro-CS	15/16	11.18 ± 4.07	3.32 ± 1.09 years	15-40 mg/kg/day
Markus Rauchenzauner	2010	Austria	CS cohort	38/ 47	12.42 ± 3.33	> 6 months	869 ± 380 mg / day
Ayse Aksoy	2011	Turkey	CS	28/25	8.42 ± 2.03	3.23 ± 1.09 years	19.23 ± 4.42 mg/kg/day
Mehmet Ibrahim Turan	2014	Turkey	CS	NA	8.2 ± 3.8	≥6 months	NA
Jung-Hyun Baek	2014	Korea	Retro-	90/53	11.21 ± 4.49	4.92 ± 3.68 years	NA
Omid Yaghini	2015	Iran	Retro-	68/52	7.4 ± 2.4	≥ 6 months	NA
Hepsen Mine Serin	2015	Turkey	CS	32/27	8.6 ± 4.6	≥ 2 years	NA
Teodoro Durá-Travé	2018	Spain	CS	18/41	School age (n = 30) and Adolescent (n = 29)	2.5 ± 1.4 years	20.7 ± 4.7 mg/kg/day
Mini Sreedharan	2018	India	CS	13/25	8.2 ± 2.9	≥ 6 months	NA

First Author	BMI (kg/m^2)	Assay for VitD	Vit D in VPA-treated group(N; Mean(SD) ng/mL)	Vit D in healthy control group(N; Mean(SD) ng/mL)	Vit D in CAR-treated group(N; Mean(SD) ng/mL)	Vit D in other medication treated group(N; Mean (SD) ng/mL)	Other medication	Note	Ref
Gabriele Rieger-Wettengl	NA	RI	19;25(14)	NA	20;18(7)	NA	NA		[33]
Sefer Kumandas	NA	HPLC	33;15.1(3.5)	22;16.6(4.7)	33;9.8(3.2)	NA	NA		[30]
Arzu Babayigit	17.49 ± 2.85	NA	31;17.87(7.27)	30;22.3(7.12)	23;20.47(11.6)	14;24.07(14)	Oxcarbazepine		[14]
Markus Rauchenzauner	0.4 ± 1.3	CEI	85;43.2(25.6)	41;49.9(33.8)	NA	40;52.6(31.5)	Oxcarbazepine, Sulthiame, or Lamotrigine	BMI (SD score)	[18]
Ayse Aksoy	17.44 ± 2.92	RI	53;37.68(30.73)#	50;38.82(27.33)#	23;26.12(24.19)#	NA	NA	# nmol/L	[31]
Mehmet Ibrahim Turan	NA	ECL	51;22.6(77.8)	44;23.1(78.3)	45;16.8(44.9)	48;20.1(88.7)	phenobarbital		[22]
Jung-Hyun Baek	NA	NA	49;36.83(11.66)	NA	NA	30;30.41(9.53)	Oxcarbazepine		[21]
Omid Yaghini	NA	IRA	30;14.51(1.82)	NA*	NA	60;10.88(1.14)	Phenobarbital, Carbamazepine, and Primidone	*Epileptic patients withouttreatment as control	[19]
Hepsen Mine Serin	NA	NA	28;19.5(8.1)	20;21.9(7)	11;20.19(7.02)	20;22.8(11.08)	Levetiracetam		[32]
Teodoro Durá-Travé	0.02 ± 0.59	CL	59;23.37(9.11)	244;26.97(7.09)	NA	31;22.64(9.08)	Levetiracetam	BMI (Z-score)	[23]
Mini Sreedharan	15.1 ± 2.8	ELISA	28;23.4(11.7)	109;31.2(17.5)	28;26.3(21.9)	NA	NA		[20]

Note: CAR, carbamazepine; CEI, Competitive enzyme immunoassay; CL, Chemiluminescence; CS, cross-sectional; ECL, Electrochemiluminescence; IRA, Immunoradiometric assay; M/F, Male/Female; Retro-, retrospective; RI, Radioimmunoassay; NA, not available; SD, standard deviation;

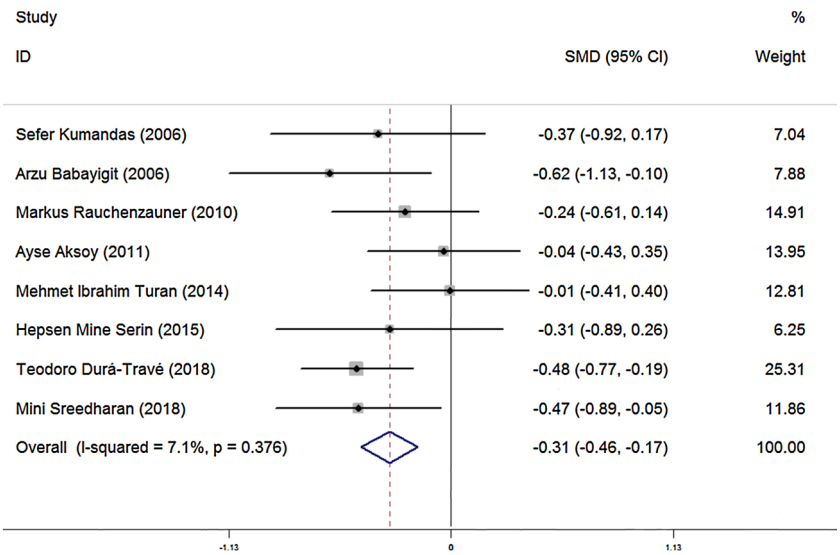

Fig. 1. Forest plot regarding valproate decreased Vit D level in epileptic children compared with healthy children.

3.3. Difference of Vit D levels among valproate- or carbamazepine-treated children with epilepsy and healthy controls

We first pooled comparison of Vit D level in valproate treated patients *versus* healthy controls. A negative SMD of Vit D level was noted between valproate treated group and healthy controls (SMD = -0.313, [-0.457, -0.169]), see Fig. 1.), indicating a significant difference across these two groups in terms of a negative effect of valproate treatment on Vit D level. No evidence of heterogeneity was present across the related studies (I^2 = 7.1%, p = 0.376).

Cumulative analytic technology was utilized to address the effect of time on the difference in Vit D status. As shown in Fig S2, cumulative estimates were progressively more robust as evidenced by the narrowing 95% confident intervals by ascending year of publication.

We also combined data from carbamazepine treated children compared to healthy children, and a negative pooled (SMD = -0.484 [-0.919, -0.049]) on Vit D level was observed in the carbamazepine treated group compared with healthy participants. However, significant heterogeneity was present across studies (I^2 = 76%, p = 0.001). In total, both valproate and carbamazepine were associated with a decreased Vit D level in children with epilepsy when compared with healthy children. Interestingly, carbamazepine and valproate had a similar effect on the Vit D level as shown by directly comparing Vit D concentration in valproate-treated to carbamazepine-treated children (SMD = -0.309 [-0.155, -0.773]) with significant heterogeneity among studies (I^2 = 80.8%, p = 0.000).

Furthermore, there was no difference in Vit D level in valproate-treated children with epilepsy from the level in other anti-epileptic medication groups (SMD = 0.277, 95%CIs [-0.407, 0.961]), however, heterogeneity was suggested (I^2 = 93.0%, p = 0.000). Two articles [21,32] reported 25-OH-Vit D3 and non-specified Vit D status instead of 25-OH-Vit D data. We performed pooled analysis de novo by excluding these two references. The results showed that using 25-OH-Vit D data alone did not change our conclusions, producing only minor insignificant changes in the estimations of the pooled SMDs and their 95% CIs.

3.4. Potential sources of heterogeneity

The study design and country of origin of children was used as stratifying variables in conducting subgroup analyses to reveal potential heterogeneities. The results showed heterogeneities in both subgroups regarding comparison of Vit D levels in children who underwent valproate *vs.* carbamazepine monotherapy, valproate *vs.* other medication therapy, as well as that in children who received carbamazepine monotherapy *vs.* healthy children. All the results of subgroup analyses are shown in Table 2.

3.5. Publication bias

No potential publication bias was shown when comparing Vit D level in children treated by valproate monotherapy *vs.* healthy controls based on evidence from the Begg's and Egger's tests (Begg's statistic p = 0.902, Egger's statistic p = 0.963). Similar results were observed in the analyses of Vit D status in children with epilepsy treated by carbamazepine therapy *vs.* healthy children (Begg's statistic p = 0.260, Egger's statistic *p* = 0.311); valproate monotherapy *vs.* children with epilepsy treated by carbamazepine (Begg's statistic p = 0.764, Egger's statistic p = 0.739; valproate *vs.* other medication treatments in subjects with epilepsy (Begg's statistic p = 0.548, Egger's statistic p = 0.516)

Table 2
Potential source of heterogeneities.

Variables	I-squared	p value
Vitamin D in patients treated with carbamazepine vs. healthy controls		
Turkey	80.20%	0.000
India	–	–
Cross-sectional	0	0.85
Cross-sectional retrospective	–	–
Overall	76.00%	0.001
Vitamin D in patients treated with valproate vs. carbamazepine		
Germany	–	–
Turkey	85.30%	0.000
India	–	–
Cross-sectional	30.70%	0.205
Cross-sectional retrospective	–	–
Overall	80.80%	0.000
Vitamin D in patients treated with valproate vs. other medications		
Cross-sectional	31.70%	0.222
Cross-sectional cohort	–	–
Retrospective	96.40%	0.000
Turkey	39.20%	0.193
Austria	–	–
Korea	–	–
Iran	–	–
Spain	–	–
Overall	93.00%	0.000

Note: "-" means due to the limited study, I-squared and p value cannot be calculated.

4. Discussion

We collected data from 11 eligible studies with a total sample size of 640, resulting in the most comprehensive meta-analysis to the best of our knowledge estimating Vit D status in children with epilepsy related to valproate monotherapy. Several publications [6,28,29,34–43] were excluded from the meta-analysis due to the unavailability of retrievable raw data on Vit D status. Some of them [35,37] concluded that valproate monotherapy had a negative effect on Vit D level while others concluded valproate had no effect the Vit D levels. Since the meta-analysis combined weighted estimates from each study, it is not possible to estimate the effect inclusion of these studies would have on our meta-analysis.

Our results demonstrated a consistent decrease in the Vit D level in children with epilepsy treated with valproate. Similar findings were found in children treated with carbamazepine. The difference in the decline in the Vit D level between the valproate treatment group and the carbamazepine group was not significant. Our findings on the Vit D decrease in carbamazepine monotherapy was in agreement with a previously published meta-analysis [44]. When comparing results on Vit D level in children on valproate therapy, the previous meta-analysis [44] did not collect all reasonable relevant primary articles but reported that valproate treated patients had similar Vit D level as their control group. Due to the inclusion of only three primary articles, their analysis is deemed less robust than our meta-analysis.

Multiple factors, like diet, daily activities and sunlight exposure can affect Vit D status. These factors were not available as variables to perform combined analysis because of insufficient information from individual studies. Other factors, such as duration of valproate treatment, also influenced Vit D status. For example, 25-OH Vit D3 levels were significantly lower among children who were on AEDs therapy for longer than 2 years [21] and longer duration of therapy was associated with a greater negative impact on vit D levels [45]. We were able to collect length of valproate treatment and all were long-term treatment in the eligible studies. However, most of the data were noted as “more than” a certain months or years, making classification of subjects by duration of therapy unavailable for analysis.

According to the United States Endocrine Society criteria for classification of Vit D status, Vit D deficiency is defined by a 25-OH Vit D level less than 20 ng/ml (< 50 nmol/L) [23]. In the current meta-analysis, Vit D deficiency was not assessed among half (5 in 11) of the primary articles. In the remaining 6 articles, inconsistent criteria were used to determine Vit D deficiency in children, including 25-OH-Vit D < 10 ng/mL [18,19], < 12 ng/mL [20] and < 20 ng/mL [21–23]. Therefore, we did not perform meta-analysis on whether the valproate therapy contribute to deficiency of Vit D in children with epilepsy.

Study design and country of origin may be a source introducing heterogeneities to the meta-analysis of Vit D levels in children on valproate or carbamazepine therapy as our results show. Potential explanations such as seasonally related sun exposure, genetic variation, differing diets, and variations in study methodology could cause heterogeneity [46]. In particular, our clinical observation (data not shown) and data from a separate research group [23] noted that gender of participants was a contributable factor to decreased Vit D in patients with epilepsy treated with valproate. Further study is warranted to determine other important factors that contribute to low vitamin D levels in children on valproate therapy.

5. Conclusions

This meta-analysis found a decrease of Vit D level in children with epilepsy receiving valproate monotherapy compared with healthy children. The decrease in Vit D level in valproate treated pediatric patients was similar to that found in children on carbamazepine therapy. In view of the impact of Vit D deficiency on childhood development, routine monitoring of Vit D levels and supplementation to prevent Vit D deficiency is warranted in children on chronic valproate therapy.

Author contributions

F. Chen and T. Wang designed this paper. J.Y. Sun, H.L. Guo, Y.H. Hu, X.Y. Wen, F. SuDepartment of Clinical Pharmacy and X.P. Lu discussed this topic and provided comments. Z.J. Xu, X. Jing and G.Z. Li read through all references and summarized the data. T. Wang and F. Chen wrote the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.06.009.

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