Should vitamin D supplementation routinely be prescribed to children receiving antiepileptic medication?

SCENARIO

You are the paediatric registrar at an epilepsy clinic. A mother of a 9-year-old patient with childhood absence epilepsy asks if he should be taking vitamin D. He is currently prescribed sodium valproate. You wonder if you should prescribe vitamin D supplementation alongside his antiepileptic medication.

STRUCTURED CLINICAL QUESTION

In children with a clinical diagnosis of epilepsy on antiepileptic drugs (AED) (population), is there evidence to suggest that they should receive supplemental vitamin D (intervention) to improve their bone health (outcome)?

SEARCH

We searched OVID MEDLINE in June 2020 with the keywords (Child OR Paediatrics OR Pediatrics) AND (Vitamin D OR Vitamin D Deficiency OR Cholecalciferol OR Calcitriol) AND (Anti-Epileptic Drug OR Anti-Epileptic Medication OR Anti-Convulsant Drug).

The search was limited to articles in English from the year 2000. Sixty-five articles were identified.

Twenty articles were included after initial scrutiny and four were selected for full-text review. One further study was identified on review of article references. These were graded according to the Oxford level of evidence (table 1).[1]

COMMENTARY

Vitamin D deficiency is common worldwide. Vitamin D is protective for musculoskeletal health. Children treated with AED are known to have problems with bone metabolism and bone mineral density (BMD) loss. Enzyme-inducing AEDs (phenytoin, carbamazepine, primidone and phenytoin) increase vitamin D metabolism due to induction of cytochrome P450. Newer, non-enzyme-inducing antiepileptic drugs (NEIAEDs) can affect bone metabolism in a variety of ways, including stimulation of osteoclast activity, direct action on bone cells, parathyroid hormone resistance, inhibition of calcitonin secretion and reduced calcium absorption.[2 3]

It is recommended that all children aged 1–4 years receive 400 international units (IU) of vitamin D daily. This should also be considered for older children and adults in at-risk groups. Children receiving enzyme-inducing antiepileptic drugs (EIAEDs) are at increased risk of vitamin D deficiency and should be given advice regarding dietary intake and supplementation.[4] This was highlighted in a cross-sectional study by Kija *et al*, who demonstrated statistically significant reduced 25-hydroxyvitamin D (25(OH)D) levels in children on EIAED compared with healthy controls.[5] This cross-sectional study compared vitamin D levels in children with epilepsy (at least one EIAED for >3 months) compared with healthy controls. Vitamin D deficiency was more evident in children receiving EIAED but not statistically significant. This was a small study, and although EIAED demonstrated lower vitamin D level, this has not been translated into increased risk of vitamin D deficiency or effect on bone health.

Increased risk of vitamin D deficiency with EIAED has also been demonstrated in a randomised controlled trial by Viraraghavan *et al*.[6] They compared the effect of AED with high-dose vitamin D supplementation versus AED alone by analysing 25(OH)D levels at baseline and at 6 months. All children in this study were receiving 'older' AED (phenytoin, valproate, phenobarbitone and carbamazepine). This study was limited to children recently prescribed AEDs. The intervention group received a monthly oral dose of vitamin D of 60 000 IU. Both groups were comparable at baseline, but at 6 months, the

Table 1 Summary of included studies

Citation	Study group comparison	Study group intervention	Study type	Outcome	Key result	Comments
Kija *et al*[5]	EIAED versus NEIAED Exclusion criteria: chronic conditions or medications affecting vitamin D metabolism	75 CWE: median age 9 years (1–17 years) 75 healthy controls: median age 3 years (1–12 years)	Cross-sectional study (3)	Comparison of 25(OH)D level between the two groups	CWE on EIAED had lower mean 25(OH)D compared with control (p=0.08) Vitamin D deficiency occurred in 16.2% CWE group vs 8.8% control group (p=0.29)	Lower 25(OH)D level but did not equate to increased risk of 25(OH)D deficiency
Viraraghavan *et al*[6]	EIAED only Exclusion: vitamin D supplements or chronic conditions affecting vitamin D metabolism	64 CWE intervention group (AED and monthly high-dose vitamin D), n=35 Control group (AED only), n=29	Prospective RCT (1b)	25 (OH)D level following 6 months of high-dose treatment versus control	Mean 25(OH)D higher in intervention group compared with control group (p=0.005) Decrease in 25(OH)D levels at 6 months in control group (p=0.01)	VPA included- not defined as EIAED Short follow-up time, 6 months
Durá-Travé *et al*[7]	NEIAED only Exclusion: chronic conditions affecting vitamin D/bone health metabolism	90 CWE receiving either VPA (n=59) or LEV (n=31) compared with healthy control(n=244)	Cross-sectional study (3)	25(OH)D level alongside other biochemical markers of bone health	25 (OH)D level higher in the control group (p=0.037) Multiple logistic regression analysis showed that VPA monotherapy (OR 1.9, 95% CI 1.1 to 3.8) and LEV monotherapy (OR 3.3, 95% CI 1.5 to 7.5) were associated with an increased risk of vitamin D deficiency	Direct cause of low 25(OH)D not established
Mikati *et al*[8]	EIAED versus NEIAED Exclusion: chronic conditions affecting vitamin D metabolism	78 CWE comparison of low-dose (n=40) vs high dose(n=38) vitamin D on 25(OH)D and BMD	Prospective RCT (1b)	25(OH)D level BMD via DEXA lumbar spine and total body at 1 year	BMD increased from baseline (p<0.001) No difference between low and high doses on BMD Mean 25(OH)D did not differ between EAIED and NIAED.	Unable to compare the effect of placebo versus low-dose vitamin D on BMD as this was not felt to be ethical in childhood study
Shellhaas *et al*[9]	EIAED versus NEIAED Exclusion: underlying renal, metabolic bone or endocrine disorder	78 CWE	Cross-sectional study (3)	25(OH)D level identification of risk factors for 25(OH)D deficiency	75% of cohort 25(OH)D insufficient Univariate analysis: no difference in mean 25(OH)D between EIAED and NEIAED Girls (OR 4.07, 95% CI 1.18 to 13.97) and increased BMI (OR 4.07, 95% CI 1.047 to 1.392) risk factors for low 25(OH)D	No control comparison

AED, antiepileptic drug; BMD, bone mineral density; CWE, children with epilepsy; DEXA, dual-energy X-ray absorptiometry; EIAED, enzyme-inducing antiepileptic drug; LEV, levetiracetam; NEIAED, non-enzyme-inducing antiepileptic drug; 25(OH)D, 25-hydroxyvitamin D; RCT, randomised controlled trial; VPA, Sodium valproate.

control group revealed a statistically significant reduction in 25(OH) D levels from baseline. Of note, sodium valproate was included in this study and is not defined as an EIAED. The study was limited by its small sample size, loss to follow-up and short follow-up time (6 months).

Durá-Travé *et al* investigated the use of NEIAEDs on vitamin D levels.[7] A cross-sectional study compared children on NEIAED (59 sodium valproate and 31 levetiracetam) with a control group (254 healthy children). The primary outcome was biochemical markers of bone health, including 25(OH)D levels. Those within the AED group had undergone monotherapy with either agent for at least 12 months and were not receiving vitamin D-containing supplements. The mean 25(OH) D levels were significantly higher in the control group compared with those on NEIAED monotherapy. This study was of small size; biochemical markers were not performed prior to NEIAED initiation; and direct cause of low vitamin D levels was not established.

The aforementioned studies analysed either EIAED or NEIAED independently; however, Mikati *et al* and Shellhass *et al* were able to compare the two groups. Mikati *et al* was the only study to examine vitamin D dosage in patients on long-term AED therapy (>6 months). Children were randomly allocated to either low-dose (400 IU) or treatment-dose (2000 IU) vitamin D.[8] BMD was measured using dual-energy X-ray absorptiometry (DEXA)and compared with matched healthy controls. The proportion of children on either EIAED or NEIAED was appropriately matched. The mean 25(OH)D level did not differ significantly between the two groups following treatment. BMD increased significantly in both groups following 1 year of treatment.

In a cross-sectional study, Shellhaas *et al* studied the prevalence and risk factors for vitamin D deficiency in children with epilepsy.[9] Comparison was made between old (EIAED) and new AED. This study identified that 75% of this cohort had insufficient 25(OH) D levels. Statistical analysis revealed increased odds of female sex and increased BMI correlating with low 25(OH)D levels. Univariate analysis of patients on old versus new AED showed no difference in their vitamin D levels. This was a relatively small study with no healthy control comparison. Although the risk of low vitamin D was evaluated, this was not further applied to the effect on bone health.

There appears to be strong evidence to suggest that EIAEDs are associated with lower vitamin D levels and emerging data to support this as applicable to NEIAED. Difficulty with interpretation lies with no universal definition of a 25(OH)D level equating to vitamin D deficiency. Moreover, what protective level confers the most benefit for musculoskeletal health? Current paediatric practice would suggest that a 25(OH)D level less than 25 nmol/L to be consistent with vitamin D deficiency . These children should receive treatment dose vitamin D for 8–12 weeks (dosing available via British National Formulary for Children). Routine testing is not recommended for children receiving AEDs unless symptoms and signs of rickets, vitamin D deficiency or associated biochemical or X-ray abnormalities. No adverse effects were identified in any of the aforementioned studies from the use of vitamin D.

Low-dose vitamin D therapy (400 IU) is recommended for the healthy population, given that they are low-cost, low-risk and offer many benefits to the individual. Given that there is evidence that epilepsy and treatment with antiepileptic medication can adversely affect vitamin D levels and bone health, it is deemed to be a reasonable recommendation that children receiving antiepileptic medication should be prescribed 400 IU vitamin D prophylactically and primary prevention advice given with regard to sun exposure and dietary sources of Vitamin D.

Clinical bottom line

- Antiepileptic drugs (AEDs) are known to cause vitamin D deficiency in children with epilepsy (grade C).
- Prophylactic low-dose vitamin D (400 IU) may help to prevent vitamin D deficiency and low bone mineral density in children prescribed with AEDs (grade C).

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