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Original Article

Duration and dose of antiepileptic drugs and serum calcium levels in children

Arinta Atmasari[1], Masayu Rita Dewi[1], Aditiawati[1], Masagus Irsan Saleh[2]

Abstract

Background Many factors contribute to language development in chilBackground Antiepileptic drugs (AEDs) may affect calcium metabolism through several mechanisms. Much evidence has confirmed that carbamazepine and valproic acid, as the most widely used AEDs in epileptic children, leads to decreased serum calcium levels. This effect was suggested to be time and dose dependent. However, correlations between AEDs and calcium levels in Indonesian epileptic children have not been well studied.

Objective To investigate possible correlations between total calcium levels and durations of therapy as well as doses of carbamazepine and valproic acid.

Methods This analytical, cross-sectional study was performed from March to May 2015 in the Neuropediatric Outpatient Ward of Mohammad Hoesin Hospital, Palembang, South Sumatera. A total of 60 epileptic children taking carbamazepine and or valproic acid monotherapy were included and grouped accordingly. A single blood test was done for every participant to measure total serum calcium level. Correlation between daily dose or duration of AED with calcium level was assess using the Spearman-rho test.

Results The mean total serum calcium levels in the carbamazepine and valproic acid groups were 9.48 (SD 0.83) mg/dL and 9.58 (SD 0.63) mg/dL, respectively. There was a statistically significant moderate correlation between the duration of carbamazepine therapy and total calcium level (r = 0.36; P=0.001). The cut-off point for duration of therapy was 23 months. There were no significant correlations between total calcium level and mean daily carbamazepine dose, nor between total calcium level and duration and dose of valproic acid therapy.

Conclusion Longer duration of carbamazepine therapy is associated with low total serum calcium level, but carbamazepine dose is not. In addition, duration and dose of valproic acid are not associated with low total serum calcium level. **[Paediatr Indones. 2017;57:104-7. doi: http://dx.doi.org/10.14238/pi57.2.2017.104-7]**.

Keywords: *calcium level; therapeutic duration; drug dose; antiepileptic drugs*

Antiepileptic drugs (AEDs) are the primary choice of therapy for epileptic patients at any age and gender. Treatment is sometimes prolonged and may require large doses as well as drug combinations. Therefore, the adverse effects of AEDs should be considered during treatment. One such effect is on calcium metabolism.[1,2] Calcium plays an important role in various physiological functions in the body including the blood clotting process, sodium and potassium cell membrane potential maintainance, signal transduction between hormone receptors, neuromuscular excitability, integrity of cell membrane, enzymatic reactions, neurotransmission, and bone structure formation. Clinical symptoms of hypocalcemia range from mild to severe. In plasma with calcium concentration 50% below normal, peripheral nerve fibers become excited, spontaneously spreading impulses to the peripheral skeletal muscle and triggering tetanic muscle contractions or even seizures. Extreme hypocalcemia can cause cardiac dilatation, blood clotting disorders, and death.[3]

Antiepileptic drugs have been widely reported

From the Department of Child Health[1] and Health and Medicine Research Unit[2], Sriwijaya University Medical School/Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera, Indonesia.

Reprint requests to: Arinta Atmasari, Department of Child Health, Sriwijaya University Medical School, Jalan Jenderal Sudirman KM 3,5, Palembang, South Sumatera, Indonesia. Tel. +62-813-16071883; E-mail: arinta.dr@gmail.com.

to reduce serum calcium levels, which interferes with bone metabolism, decreasing bone density mainly through induction of the cytochrome P450 (CYP450) enzyme system in the liver. Decreased calcium levels elevate parathyroid hormone and increase bone turnover characterized by hyperphosphatemia. This mechanism mainly occurs in the group of enzyme-inducers, such as phenobarbital, phenytoin, and carbamazepine. However, recent research also showed that non-enzyme inducing AEDs, such as valproic acid, may also cause hypocalcemia through inhibitory effects of the AED metabolites on calcium ions.[1,2] These effects have been suggested to be time and dose dependent. Many studies reported that epileptic children treated with AEDs (carbamazepine or valproic acid) over a certain period of time experienced decreased total calcium levels.[4-6] Furthermore, dose reductions led to normalization of the calcium concentration.[7]

The effects of AED on total serum calcium levels in epileptic children in Indonesia have not been well studied. The objective of this study was to assess for possible correlations between durations of therapy and doses of AEDs (carbamazepine or valproic acid as the most widely used AEDs in epileptic children) and total serum calcium levels.

Methods

This cross sectional study was conducted in the Neuropediatric Outpatient Department of Mohammad Hoesin Hospital, Palembang, South Sumatera, from February to April 2015. We recruited subjects by consecutive sampling. Inclusion criteria were all epileptic patients aged between 6 months to <15 years, who had undergone valproic acid or carbamazepine treatment for at least 1 month, and whose parents provided informed consent. Exclusion criteria were children with pre-existing chronic kidney disease, liver failure, malnutrition, or hypoalbuminemia, as well as those who took other AEDs, calcium or vitamin D supplementation, or steroid or diuretic therapy.

Duration of therapy was defined to be the length of AED usage on a regular basis, expressed in months. Dose of therapy was defined to be the average maintenance AED dose in the past month, expressed in mg/kg/day. Total calcium level was defined to be blood calcium level obtained through venous blood test, including calcium ions, protein-bound calcium, and organic or complex–bound calcium. Low total calcium levels (hypocalcemia) was defined as a total calcium level below the reference value, according to age.[8]

We collected data on duration and dose of AEDs by history taking and retrieving data from the medical charts. Non fasting blood tests was done to measure total serum calcium level. Total calcium levels were measured by *COBASS INTEGRA®*.

Spearman's correlation test was used to analyze the correlation between the duration as well as the dose of valproic acid or carbamazepine and total calcium level. Significance was set at $P<0.05$ with 95% confidence intervals (CI).

Results

From February to April 2015, 30 epileptic children taking carbamazepine and 30 others taking valproic acid met the inclusion criteria. There were more males in the carbamazepine group and more females in the valproic acid group. The median ages in the carbamazepine and valproic acid groups were 52.5 and 57.5 months old, respectively. The median durations of therapy were 13 months in the carbamazepine group and 12 months in the valproic acid group. The median maintenance doses were 15 mg/kg/day in the carbamazepine group and 20 mg/kg/day in the valproic acid group. The mean total serum calcium levels were 9.48 mg/dL in the carbamazepine group and 9.58 mg/dL in valproic acid group. The characteristics of subjects are presented in **Table 1**.

Hypocalcemia was found in 13 patients (22% of all subjects), 9 patients (30%) in the carbamazepine group and 4 patients (13%) in the valproic acid group. The distribution of subjects' total calcium levels in both groups are shown in **Table 2**.

There was a statistically significant moderate correlation between the duration of carbamazepine therapy and low total serum calcium level, with a weak correlation coefficient ($r=0.36$; $P=0.001$). There was no correlation between daily carbamazepine dose with total calcium level ($r=0.03$; $P=0.878$).

For children taking valproic acid, there seems to be a weak correlation between valproic acid and total serum calcium although this was not statistically

Table 1. Characteristics of subjects (n=60)

Characteristics	Therapy group	
	Carbamazepine (n=30)	Valproic acid (n=30)
Gender, n		
Male	16	12
Female	14	18
Median age (range), months	53 (9-174)	58 (12-192)
Median duration of therapy (range), months	13 (2-72)	12 (2-108)
Median dose (range), mg/kg body weight/day	15 (5-30)	20 (10-40)
Mean total calcium level (SD), g/dL	9.48 (0.83)	9.58 (0.63)

Table 2. Distribution of hypocalcemia in the carbamazepine and valproic acid groups

Antiepileptic drugs	Calcium level		Total
	Low	Normal	
Carbamazepine, n	9	21	30
Valproic acid, n	4	26	30
Total	13	47	60

significant (r=0.35; P=0.057). No significant correlation between average daily dose of valproic acid and total serum calcium levels (r=0.11; P=0.56) was found.

Discussion

Our study demonstrated moderate correlations between total serum calcium level and carbamazepine duration of therapy. Valproic acid therapeutic duration also seemed to moderately correlate with total calcium level although this was not statistically significant. No correlations were found between daily dose of AED and total calcium level.

In the carbamazepine group, the mean total calcium level was within normal limits, and 9 subjects (30%) had total calcium levels below normal. Of the 9 subjects, the lowest calcium level was 8.1 mg/dL in 2 subjects but they had no symptoms of hypocalcemia. The best explanation of this effect was that carbamazepine activated the orphan nuclear receptor, pregnane X receptor (PXR), which shares 60% homology in their DNA-binding domains to the vitamin D receptor (VDR), and is expressed in the intestine, kidney, and liver. The PXR has been shown to mediate induction of CYP2 and CYP3, the cytochrome P450 enzymes involved in drug metabolism. Emerging evidence shows that these PXR activators can increase the expression of the CYP24, a VDR target gene, in cultured cells and in vivo in mice. CYP 24 is an enzyme that directs the side chain oxidation and cleavage of 25(OH)2 D3 and 1ß, 25 (OH)2D3 to carboxylic acid end products (calcitroic acid), resulting in lower cellular concentration of active vitamin D. This induces a state of vitamin D deficiency and results in hypocalcemia, secondary hyperparathyroidism, and increased bone turnover, predisposing to low bone density and bone loss. However, this does not explain hypocalcemia with valproic acid reported in some studies, as valproic acid is an inhibitor of cytochrome P450 enzymes and is not among the known activators of PXR.[9] In the valproic acid group, mean calcium levels were generally within normal limits, only 4 subjects (13%) had low calcium levels according to age, and no hypocalcemia symptoms were observed in these patients either. Other reports suggested that valproic acid might cause hypocalcemia through its inhibitory effects on calcium ions by its metabolites.[1,2,7]

Correlation analysis revealed a positive and significant correlation between duration of carbamazepine therapy and low calcium level, though the strength of correlation was weak. Median durations of therapy in carbamazepine group was found to be at 23 months. This median duration was much longer than that of a previous study (2009) that showed a significant decrease in calcium level after 60 days of therapy on a maintenance dose, and a further decrease after 90 days.[6] An Indian study conducted in 114 epileptic children treated with AEDs (carbamazepine, phenobarbital, phenytoin, valproic acid, and combinations) who initially had higher levels of calcium and vitamin D, also reported the decline of calcium and vitamin D levels after 6 months of AED therapy on maintenance doses. These contrasting results may be due to differences in methodology and/or study populations.

We found no significant correlation between carbamazepine dose and total calcium levels, in contrast to another study reporting a significant decline of vitamin D and calcium levels after 6 months carbamazepine therapy at maintenance doses.[10]

Also, no significant correlation was found between duration of valproic acid therapy and total calcium level, nor between dose of valproic acid and total calcium level.

In our subjects, hypocalcemia induced by AED was considered to be mild, with the largest decrease not exceeding 11% below normal calcium levels. As such, we would expect to not observe hypocalcemic symptoms. We also noted that hypocalcemia was more common in the carbamazepine group compared to the valproic acid group. Beyond the effect of elucidating the different mechanisms of hypocalcemia between drugs, this observation might provide the impetus for future research comparing AEDs' effects on calcium levels so that pediatricians can choose the appropriate AED to minimize the risk of hypocalcemia and prepare supplementation if necessary.

Some limitations of this study were that we examined total calcium levels rather than ionized calcium to represent the calcium levels because our facilities lacked the capability to examine ionized calcium levels. Another limitation is that the sample size is limited and that is why perhaps we did not pick up statistically significant correlation in the valproic acid group. Calcium ions actively play an important role in metabolism and are considered to represent 50% of total calcium.[11] The measurement of total calcium was considered sufficient to represent the state of calcium ions, especially in medical centers with limited facilities. However, the ionized calcium levels would have given better results in terms of the effects of valproic acid metabolites. Also, we did not examine the base profile levels of vitamin D and parathyroid hormone, which are known to have important roles in calcium metabolism.10 Decreased levels of calcium could possibly be due to the low levels of vitamin D or parathyroid hormone, or influenced by various factors such as sun exposure and hypoparathyroidism. Another limitation was the possibility that consumption of high calcium foods a few hours before the blood test affected total calcium levels.

In conclusion, moderate positive correlation is found between duration of carbamazepine therapy and total serum calcium. No correlation is found between daily dose of AED and total calcium level. Further study is recommended to compare AED side effects on calcium metabolism in a clinical trial.

Conflict of interest

None declared.

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