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Comparison of Calcium Serum Concentration, Alkaline Phosphatase Serum and Bone Mineral Density Based on the Treatment Duration of Anti-epilepsy in Epilepsy Children

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ABSTRACT

Objective: This research aimed to determine the difference between levels of serum calcium, alkaline phosphatase and bone mineral density based on the treatment duration of anti-epilepsy drugs in epilepsy children.

Materials and methods: A cross sectional study was done in pediatric neurology outpatient department of Sanglah Hospital from May until July 2017. Forty-three samples were eligible in this study with the inclusion criteria being 1-11 years old epileptic patient, who were on first line of anti-epilepsy medicines (carbamazepine, phenobarbital, phenytoin, valproic acid) for 6 months or more regularly and agreed to join the research. Blood sample for calcium, ALP level and bone mineral density (BMD) were taken on each sample. Data was analysed by one way ANOVA for normal distribution variables and Kruskal-Wallis for abnormal distribution variables.

Results: Bivariate analysis of one way ANOVA has revealed a significant difference of calcium levels based on duration of treatment (P=0.028). Post Hoc test showed the differences of the mean of calcium levels based on duration of treatment 0.28 (P=0.008; IK 95% 0.078-0.481). There were no significant difference of bone density (P=0.463) and serum ALP (P=0.087) based on duration of treatment.

Conclusion: Long term antiepileptic treatment may reduce the serum calcium level significantly without inducing the severe hypocalcemia. Calcium and vitamin D supplementation should be considered for epileptic patient who are on long duration of treatment.

Keywords: Alkaline phosphatase, Anti-epilepsy, Bone mineral density, Calcium, Children

INTRODUCTION

Epileptic patients will need to take anti-epilepsy medication for long period and have serious risk of any side effects such as the disturbances of mineral and bone metabolism [1,2]. Epilepsy has strong correlation with fracture. Some of them are caused by seizure or fall. Side effects of anti-epilepsy medication (bone metabolism) have been reported since four decades ago and identified as risk factor of less bone density and calcium metabolism abnormality [3]. First line anti-epilepsy medicine that related to bone metabolism disturbance is the enzyme inducer such as carbamazepine, phenytoin and phenobarbital [4-6]. They induce microsomal enzyme of the liver and increase catabolism and inactivation of vitamin D. Other drug which is non-enzyme inducer or enzyme sparing drugs such as valproic acid may have direct effect on bone by recruiting osteoclast and altering renal function [4,6,7].

Antiepileptic medicines such as carbamazepine induce cytochrome P450 enzyme in liver to increase vitamin D conversion into inactive metabolite. Decrease in the active vitamin D, biologically, will decrease the absorption of calcium in the intestine which then causes hypocalcemia and subsequent increase of circulating parathyroid hormone in further. Secondary hyperparathyroidism can be measured by detecting decrease in serum calcium and phosphorus level along with increase in of serum total alkali phosphatase level [8].

Alkaline phosphatase is a marker of bone forming processed and osteoblast activity. This enzyme is a glycoprotein that is found on the surface of plasma membrane of osteoblast

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which can be used to predict disturbances of any bone mineralization diseases and disorders [9]. Data of any changes in calcium serum level, alkaline phosphatase level, and bone density in long-term AED treatment was still controversial. Data about the side effects of AED treatment calcium serum level, alkali phosphatase level and bone density in epilepsy children in Indonesia, especially Bali has never been reported. This research aimed to determine the difference between level of serum calcium, alkaline phosphatase and bone density based on the treatment duration of anti-epilepsy drugs in epileptic children.

MATERIALS AND METHODS

This was a cross sectional study performed in pediatric neurology outpatient department of Sanglah Hospital from May until July 2017. Inclusion criteria included 1-11 years old epileptic patient, who were on first line anti-epilepsy medicines (carbamazepine, phenobarbital, phenytoin, valproic acid) for 6 months or more regularly and agree to join the research. Exclusion criteria were epileptic patient with severe neurological deficit, consume regular calcium and vitamin D supplementation during treatment and received other anti-epilepsy medication, already in puberty period (Tanner stage 3), under-nourished, had metabolic illness that might affect bone metabolism such as liver disorder, kidney, hematology, parathyroid, gastrointestinal, malignancy and consume medication that affect bone metabolism such as glucocorticoid, bisphosphonate, thiazide, anticoagulant and steroid. Data recorded include age, gender, body weight, height, number of anti-epilepsy medication, and duration. The blood samples were taken for calcium and ALP level and bone mineral density (BMD) in the same day. Serum calcium level measured by immuno-radiometric assay Roche/Hitachi cobas c 311/501 analyzer. The ALP level was measured by calorimetric method to determine ortho-phosphoric monoester phospho-hydrolase at the serum. The BMD was checked by trained radiographer with scan dual-energy X-ray (C.B.D. DEXA) GE Healthcare en CORE 2007. All of the measurements were done in Pathology clinic lab and radiology department of Sanglah Hospital Bali. All of the data gathered were analysed using SPSS 22.0 software. Normality data test using Shapiro-Wilk followed by one way ANOVA for normal distribution variables and Kruskal-Wallis for abnormal distribution variables. This research has been approved by Ethical Commission of FK UNUD/RSUP Sanglah Denpasar Bali.

RESULTS

There were 68 epileptic children who came to pediatric neurology outpatient department of Sanglah Hospital. Ten subjects had severe cerebral palsy, five subjects had congenital hypothyroidism, five subjects had just started treatment, three subjects had puberty (Tanner 3 stage), two subjects had refused to join the study. At the end, there were 43 subjects fulfilled the inclusion criteria. Twenty-seven (56.2%) subjects were male (mean, 6.7 years old). Out of 43 subjects, 14 subjects were on antiepileptic drugs for 6 months – 1 year duration of treatment, 13 subjects for 1-2 years, and 16 subjects for more than 2 years. Median of treatment duration was 20.1 months. Most of them (60.4%) took non-inducer AED (anti-epilepsy drug) and 17 patients (39.6%) took inducer AED. As many as 37 (86%) subjects only took one medication (monotherapy). Subject characteristic described in **(Table 1)**.

Table 1. Subject characteristics were based on the duration of anti-epilepsy drugs treatment.

Characteristics	The duration of anti-epileptic drugs treatment			TOTAL n=43
	6 months – <1 year n=14	1-2 years n=13	>2 years n=16	
Gender				
Male, n	11	9	7	27
Female, n	3	4	9	16
Age (year), mean (SD)	7.4 (3)	5.5 (3)	7.3 (3)	6.7 (3)
Body weight (kg), mean (SD)	24.9 (9)	19.3 (9)	23 (9)	22.4 (9)
Body height (cm), mean (SD)	118.2 (20.3)	104.5 (20.8)	117.3 (20.7)	113.3 (20.6)
AED				
AED *Inducer*, n	5	6	6	17
AED *Non-inducer*, n	9	7	10	26
AED				
Mono-therapy				

CBZ, n	6	4	4	14
PB, n	2	2	0	4
PHT, n	1	0	1	2
VPA, n	4	5	8	17
Poly-therapy				
VPA+CBZ, n	1	0	0	1
VPA+PB, n	0	2	1	3
VPA+DPH, n	0	2	0	2

Bivariate analysis of one way ANOVA revealed the significant differences of calcium level based on duration of treatment (p=0.009). Post Hoc test showed significant differences of the mean of calcium level based on duration of treatment between 6 months to 1 year of treatment with >2 years AED treatment (p=0.003; CI 95% 0.12-0.53). There was no significant difference of bone density (p=0.463) and serum ALP (p=0.087) based on duration of treatment **(Table 2)**.

Table 2. Comparison of calcium serum concentration, alkaline phosphatase serum and bone density based on the treatment duration of anti-epilepsy drugs in epilepsy.

Characteristics	**The duration of anti-epileptic drugs treatment**			***p value***
	6 months – <1 year n=14	**1-2 years n=13**	**>2 years n=16**	
Calcium (mg/dL), mean (SD)	9.5 (0.3)	9.4 (0.2)	9.2 (0.3)	0.009[a]
ALP (U/L), median (min-max)	169.5 (128-339)	222 (141-441)	236.5 (144-395)	0.087[b]
Bone Mineral Density (g/cm^2), mean (SD)	0.81 (0.09)	0.77 (0.08)	0.76 (0.09)	0.463[a]

a: one way Anova; b: Kruskal Wallis

DISCUSSION

Bone and mineral metabolism disturbances caused by side effect of AED threatened millions of epileptic patient especially in children who have growth spurt [10]. Antiepileptic medicines such as carbamazepine induce cytochrome P450 enzyme in liver to increase vitamin D conversion into inactive metabolite. This may decrease calcium absorption in intestine that leads to hypocalcemia and high level of parathyroid hormone. Secondary hyperparathyroidism can be detected by low serum calcium and phosphorus and high level of alkaline phosphatase [8].

This study revealed significant differences of serum calcium level based on duration of treatment. Children who took more than 2 years of AED, significantly had lower calcium level (0.28 mg/dl) than those who took 6 months to 1 year treatment. The mean serum of calcium level (8.8-10.8 mg/dl) showed descending trend as treatment progressed, however it was still in normal range in children who were 1-12 years old. These results are statistically significant but not in clinical. This research is correlated with previous studies that reported hypocalcemia in epileptic patient with long duration of treatment with incidence of 3-30% [11-13].

This study revealed decreased level of calcium after 2 years of treatment without induced hypocalcemia. Human body has compensation mechanism to keep calcium homeostasis in serum, by calcium in food or bone resorption [13]. Several previous studies found bone metabolism disturbance after long duration of treatment especially after non-inducer AED usage [14,15]. A meta-analysis study by Zhang et al showed long term effect of anti-epilepsy medication to lumbal, trochanter, femoral neck and overall bone density [16]. It is suspected in enzyme inducer (activation of cytochrome P450) cause lower level of vitamin D [8]. In non-inducer AED such as valproic acid, there is an activation of pregnane X receptor which promotes gene expression of vitamin D [17]. Anti-epilepsy drugs also reduce calcium absorption and vitamin D activation in intestine [7]. The subjects of this study mostly used non enzyme inducer monotherapy with 20 months' median duration of treatment [18].

Serum alkaline phosphatase can be used as biochemical marker of bone mineralization. A meta-analysis study showed that children who consumed AED had increased level of ALP, but only those who consumed carbamazepine and newer class of AED. ALP might show liver metabolism more than bone metabolism [16]. Voudris et al. [19] suggested isoenzyme of ALP measurement because higher sensitivity and specificity. This study did not find any significant differences of serum ALP and duration of treatment. This study has several limitations. We did not calculate the number of calcium intake, vitamin D level, parathyroid hormone level, sunlight exposure, that also affect bone metabolism. We also did not measure the liver function test that might affect serum ALP. This was a cross sectional study which was unable to prove the causal relationship and natural history of illness.

CONCLUSION

Long term antiepileptic treatment may reduce the serum calcium level significantly without inducing the severe hypocalcemia. Calcium and vitamin D supplementation should be considered for epileptic patient on long duration of treatment. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DISCLOSURE

Neither of the authors has any conflict of interest to disclose.

KEY **POINTS**

- Epileptic patients will need to take anti-epilepsy medication for long period and have serious risk of any side effects such as the disturbances of mineral and bone metabolism.
- First line anti-epilepsy medicine that related to bone metabolism disturbance is the enzyme inducer such as carbamazepine, phenytoin and phenobarbital.
- Those induce microsomal enzyme of the liver and increase catabolism and inactivation of vitamin D, others may have direct effect on bone by recruiting osteoclast and altering renal function.
- Long term antiepileptic treatment may reduce the serum calcium level significantly without induced the severe hypocalcemia.
- Calcium and vitamin D supplementation is considered for epileptic patient with long duration of treatment.

REFERENCES

1. Baek JH, Seo YH, Kim GH (2014) Vitamin D levels in children and adolescents with antiepileptic drug treatment. Yonsei Med J 55: 417-421.
2. Shakirullah NA, Aslam K, Muhammad N (2014) The prevalence, incidence and etiology of epilepsy. IJCEN 2: 29-39.
3. Sheth RD, Harden CL (2007) Screening for bone health in epilepsy. Epilepsia 48: 39-41.
4. Farhat G, Yamout B, Mikati MA (2002) Effects of antiepileptic drugs on bone density in ambulatory patients. Neurology 58: 1348-1353.
5. Nicholas JM, Ridsdale L, Richardson MP (2002) Fracture risk with use of liver enzyme inducing antiepileptic drugs in people with active epilepsy: Cohort study using the general practice research database. Seizure 22: 37-43.
6. Omid Y, Hasan ST, Amir SM (2015) Bone mineral density in ambulatory children with epilepsy. Indian J Pediatr 82: 225-229.
7. Lee RH, Lyles KW, Colon C (2010) A review of the effect of anticonvulsant medication on bone mineral density and fracture risk. Am J Geriatr Pharmacother 8: 34-46.
8. Khrisnamoorthy G, Karande S, Ahire N (2009) Bone metabolism alteration on antiepileptic drug therapy. Indian J Pediatr 76: 377-383.
9. Mintzer S, Boppana P, Toguri J (2006) Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. Epilepsia 47: 510-518.
10. Hasaneen B, Elsayed RM, Salem N (2017) Bone mineral status in children with epilepsy: Biochemical and radiologic markers. J Pediatr Neurosci 12: 138-143.
11. Pack AM (2003) The association between antiepileptic drugs and bone disease. Epilepsy Curr 3: 91-99.
12. Richens A, Rowe DF (1970) Disturbance of calcium metabolism by anticonvulsant drugs. Br Med J 4: 73-76.
13. Smith MV, Crofoot K, Rodriguez-Proteau R (2007) Effects of phenytoin and carbamazepine on calcium transport in Caco-2 cells. Toxicol In Vitro 21: 855-862.
14. Oner N, Kaya M, Karasalihoglu S (2004) Bone mineral metabolism changes in epileptic children receiving valproic acid. J Pediatr Child Health 40: 470-473.
15. Petty SJ, Paton LM, O'Brien TJ (2005) Effect of antiepileptic medication on bone mineral measures. Neurology 65: 1358-1365.
16. Zhang Y, Zheng Y, Zhu JM (2015) Effects of antiepileptic drugs on bone mineral density and bone metabolism in children: A meta-analysis. J Zhejiang Univ-Sci B 16: 611-621.

17. Cerveny L, Svecova L, Anzenbacherova E (2007) Valproic acid induces CYP3A4 and MDR1 gene expression by activation of constitutive androstane receptor and pregnane X receptor pathways. Drug Metab Dispos 35: 1032-1041.

18. Feldkamp J, Becker A, Witte OW (2000) Long-term anticonvulsant therapy leads to low bone mineral density-evidence for direct drug effects of phenytoin and carbamazepine on human osteoblast-like cells. Exp Clin Endocrinol Diabetes 108: 37-43.

19. Voudris K, Moustaki M, Zeis PM (2002) Alkaline phosphatase and its isoenzyme activity for the evaluation of bone metabolism in children receiving anticonvulsant monotherapy. Seizure 11: 377-380.