Monitoring the Risk of Decreasing Bone Mineral Density in Children Receiving Valproate

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The Risk of the Bone Mineral Density Decreasing in Children Treated with Valproate

Valproate Alan Çocuklarda Kemik Mineral Yoğunluğunda Azalma Risk İzlemi

Bu çalışma 21.05.2013 tarihinde Sivas’da yapılan XV. Ulusal Çocuk Nöroloji Kongresinde sözlü bildiri olarak sunulmuştur.

Özet
Amaç: Antiepileptik ilaçların olumsuz yan etkileri kemik mineral yoğunluğunun azalma riskine karşı bakımdan önemlidir. Bu çalışmadan kemik mineral yoğunluğu azalma riski için bir ilaç takibi sunulmuştur.

Özlem: Antiepileptik ilaçların olumsuz yan etkileri kemik mineral yoğunluğunun azalma riskine karşı bakımdan önemlidir. Bu çalışmadan kemik mineral yoğunluğu azalma riski için bir ilaç takibi sunulmuştur.

Abstract
Aim: Unfavorable side effects of antiepileptic drugs may permanently affect the bone health of pediatric epileptic patients. This study aimed to examine the long-term effects of bone metabolism of valproic acid, which is used in the treatment of epilepsy in pediatric patients in the study.

Material and Method: This prospective study enrolled 25 subjects with epilepsy (14 male, 11 female), who were otherwise healthy, aged between 4-17 years of age, who had started to receive antiepileptic monotherapy for the first time during the one-year period (each patient was followed for one year) in Cumhuriyet University, Faculty of Medicine, Division of Pediatric Neurology. The patients were divided into pre-puberty and puberty groups. Levels of Ca, P, ALP, PTH, and BMD and Z-scores were analyzed at the baseline and at the end of the study.

Results: Mean Ca and P values were similar in both groups and there was no significant difference. ALP values decreased in both groups, with the puberty group showing a more marked decrease. PTH values showed a slight decrease in the pre-puberty group, in contrast to the puberty group in which they showed a slight increase. However, in both situations, no statistical significance was observed. In the pre-puberty group, vitamin D showed a slight decrease compared to baseline values. In the puberty group, vitamin D levels showed a marked decrease compared to baseline values. Weight and height percentages based on age showed a greater increase in the puberty group compared to the pre-puberty group. Bone mineral density was significantly increased in both groups. Mean Z-scores increased in the pre-puberty group whereas they markedly decreased in the puberty group.

Discussion: In the study performed given the height, weight, and bone mineral density targets that must be reached in pediatric patients treated for epilepsy, we think that height-weight for age, bone mineral density, and also Z-score measurements will yield more predictive results in the follow-up of pediatric patients. In addition, we consider that Z-score is likely to detect bone mineral density decrease earlier than relying only on BMD (g/cm2) measurements.

Keywords
Children, Valproate, Bone Mineral Density, Z-Score, Epilepsy

DOI: 10.4328/AEMED.94
Received: 26.05.2016
Accepted: 01.06.2016
Published Online: 01.09.2016

The Annals of Eurasian Medicine
Introduction
A group of medicines referred to as "antiepileptic drugs" (AEDs) are widely used worldwide for the treatment of epileptic diseases frequently encountered during childhood. In the case of prolonged use, antiepileptic drugs have unfavorable side effects on the central nervous system, hematopoietic system, skeletal system, liver, and endocrine system [1]. Hepatic microsomal enzyme induction of the antiepileptic drugs is known to have unfavorable effects on bone mineral metabolism, leading to increased D vitamin metabolites and decreased absorption of calcium in the intestine [2-4]. These unfavorable side effects may permanently affect the bone health of pediatric epileptic patients in the later stages of their life, ultimately leading to osteopenia [2, 3]. To evaluate the symptoms of osteopenia, it is inadequate to individually assess bone biochemistry vitamin 25(OH)D, hormonal parameters, and bone mineral density. These measurements absolutely should be considered together as part of the overall picture. Annual bone mineral density measurements should be performed in adult and pediatric patients treated with AEDs in order to detect alterations in bone mineral density that are not reflected in the biochemical marker results [5].

Pediatric patients, as developing organisms, must be evaluated differently than adult patients. Osteopenia is most likely to be detected in the growth stages of life, during which bone mineral density physiologically increases naturally. Body-mass index follow-up alone is unlikely to demonstrate the height and weight targets required to be reached in children. In our study of pediatric patients treated for epilepsy, given the differences in pubertal status that must be considered together as part of the overall picture. Annual bone mineral density measurements should be performed in adult and pediatric patients treated with AEDs in order to detect alterations in bone mineral density that are not reflected in the biochemical marker results [5].

Material and Method
This study was prospectively performed in Cumhuriyet University, Faculty of Medicine, Division of Pediatric Neurology. The study enrolled 25 subjects (14 male, 11 female) between 4-17 years of age, who were diagnosed with first-onset idiopathic generalized epilepsy. Patients were excluded from the study if they were receiving any other drug affecting bone metabolism, if they had a nutritional problem or difficulty, limitations in physical activity, mental retardation that might limit physical activity, muscle and skeletal system diseases, or diseases that cause growth and development disorders. Age, body measurements (weight, height, and weight-height for age), medical history, neurological examinations, and types of seizures were recorded for all subjects at baseline and the end of the one-year follow-up period. Patients were diagnosed according to ILAE 1989 classification based on evaluation of the types of seizures, medical history, examination results, and laboratory and EEG findings [6]. Precautions were taken to ensure that the prescribed antiepileptic drugs were continuously taken by the patients for one year (Sodium Valproate: 20 mg/kg/day, via per oral route, as tablets or suspension). To evaluate the growth and development of the subjects in the study period, taking the puberty status into consideration, "height and weight for age" and "percentage of height and weight for age" were individually calculated for girls and boys at the baseline and at the end of the study utilizing the scales prepared for Turkish children [7]. Patients were assigned either to the pre-puberte (4-7 years of age) and puberte (8-17 years of age) group, and the distribution between these two groups was studied for statistical difference.

All subjects were evaluated not only for routine biochemistry and hemogram but also for alkaline phosphatase (ALP), calcium (Ca), phosphor (P), parathormone (PTH), vitamin D (25(OH)D), and vitamin D3. Bone mineral density (DEXA application) was included in the study and Z-scores were calculated. Blood samples of the patients were taken via venous route in the morning hours in the non-fasting state. Blood samples taken for PTH, Ca, P, ALP, and routine tests were analyzed on the same day.

PTH and vitamin D were analyzed in the serum samples obtained from the patients at the initiation of the therapy and at the end of one year with an ECLIA (electrochemiluminescence immunoassay) device (Cobas e 601 Roche, Germany) using a commercially available kit (Cobas, Germany) which utilizes the chemiluminescence immunologic evaluation method. PTH serum normal values were accepted as 9-65 pg/mL for children between 2-18 years of age [8].

Serum samples were analyzed for calcium (Ca) using calcium indirect ion selective electrode (ISE) and for phosphorus (P) by the Beckman Coulter LX-20 auto analyzer which utilizes colorimetric assay methods. The normal range for calcium is 8.8-10.8 mg/dL in childhood. Normal limits for phosphorus are in the range of 2.7-5.6 mg/dL.

ALP (alkaline phosphatase) was analyzed as U/L by Beckman Coulter LX-20 auto analyzer which utilized the enzymatic kinetic rate method. The resulting outcomes were evaluated by the normal ranges of the patients for their age and gender [8]. A DEXA (Dual Energy X-Ray Absorptiometry) Hologic QDR-4500 (Hologic Inc., Waltham, USA) device was used to measure patients’ bone density. Measurements were performed from the lumbar vertebrae of the patients (L1-L4) at the initiation and at the end of the AED treatment. Patients’ bone mineral density (g/cm2) and Z-scores at the initiation of AED treatment and at the end of one year were obtained from these measurements.

Statistical Analysis
Statistical analyses were performed using SPSS 16.0 software. The results were expressed as mean and standard deviation (± SD). Significance test was used between pre- and post-treatment values of the investigation groups. Mann Whitney-U test was used in the comparison of the two groups. The correlation between the biochemical variables (PTH, vitamin D, Ca, P, ALP) detected using DEXA was analyzed by Pearson correlation coefficient. P<0.05 values were considered as significant.

Ethics Board Approval
The study was approved by the local ethics board with the decree dated 30.09.2009, numbered B.30.CUM.O.1H.00.00/06 and 2009-09/05.

Results
Of the 25 subjects enrolled in the study (14 male, 11 female),
the mean age was 10.0±4.4 years (4-17 years). When biochemical markers are analyzed according to the pre-puberty and puberty groups, mean Ca and P values were similar and there was no significant difference (p>0.05).

ALP values showed a decrease in both groups, being more noticeable in the puberty group (p<0.05). In contrast to the slight decrease of PTH levels in the pre-puberty group, PTH levels showed a slight increase in the puberty group. However, none of these results showed a statistical significance (p>0.05).

In the pre-puberty patients, vitamin D showed a slight decrease compared to baseline (p>0.05). In the puberty patients, vitamin D showed a marked decrease compared to baseline (p<0.05) (Table 1).

In the distribution by age, “weight and height percentages by age” showed a greater increase in the puberty group compared to the pre-puberty group (p>0.05). Bone mineral density was seen to be significantly increased in both groups (p<0.05). Mean Z-scores were increased in the pre-puberty group and decreased in the puberty group. This increase observed between baseline and final values in the pre-puberty group was statistically significant (p<0.05) (Table 2).

When biochemical markers were examined, it was seen that the results of some patients were out of normal ranges. Values out of normal range were defined as below 11 ng/ml for vitamin D, above 65 pg/ml for PTH, below the age-matched threshold for ALP, below 2.7 mg/dl for P in one patient, and above 5.6 mg/dl in one patient. As Z-scores below -2.0 were considered as "low bone density for the chronologic age," the values equal to or below this value were considered to be abnormal. In the puberty group, Z-scores were below -2.0 (abnormal low value) in one patient in the values at the beginning of the year and in the values of four patients at the end of the year. None of our patients had a Ca value out of the normal range (Table 3).

**Discussion**

Epilepsy is one of the important chronic diseases of the childhood period. With a prevalence of 0.5-1%, it affects approximately 50 million people worldwide, 55-60% of whom are children [9, 10].

Medical treatment for this chronic disease lasts for at least two years in patients with controlled seizures and even longer in those with uncontrolled seizures. As valproate (VPA) is the drug of choice for the treatment of both focal and generalized seizures, it is the most commonly used drug in the treatment of epilepsy.

Standard follow-up charts to monitor the side effects observed during the use of AED have not yet been defined for either adult or pediatric patients. It is crucially important to prevent and to treat long-term side effects of AEDs in children, who are growing organisms. Low bone density related to the use of AED largely remains undiagnosed, unscreened, and untreated [11].

Significant bone metabolism disorders that may develop as an effect of AEDs include osteoporosis and rickets. The underlying pathophysiology has not been fully explained and is probably multifactorial. The effects that the drug shows on bone metabolism have been suggested to be hypocalcemia, hypophosphatemia, decreased vitamin D, increased parathormone (PTH), and increased alkalen phosphatase (ALP) [2, 3, 5, 12-21]. In addition to these mechanisms, as a hepatic enzyme inhibitor, VPA has been suggested as decreasing bone mineral density by stimulating osteoclastic activity [21].

Ca and P levels are the main elements of bone metabolism. The studies that have reported Ca and P abnormalities related to the use of AED are conflicting and their comparison is difficult due to different study designs and age groups [13, 18, 22-30]. In our study, it was detected that Ca was minimally elevated, P remained unchanged, and PTH and ALP levels decreased in the pre-puberty group. However, these values did not show any statistical difference. In the puberty group, Ca and P showed a minimal decrease (P>0.05).

ALP values also showed a statistically significant decrease in the puberty group (p<0.05) (Table 1). Although the studies of Verotti, Voudis, Kafali, and Erbayat [31, 23-25] highlighted the ALP elevation in patient groups, our study demonstrated
that ALP values were not affected in the pre-puberty group and decreased in the puberty group during one-year of therapy. In some of these studies, bone ALP isoenzymes were analyzed [24]. The majority of the circulating ALP activity is related to bone and liver isoenzymes and it has a bone origin in 80% of the pediatric cases [16, 32]. Although bone ALP isoenzyme has a high specificity for osteoblastic function, the evaluation of total ALP is generally sufficient for patients without hepatic pathology [26]. In our study, because we thought that the total ALP levels would adequately reflect bone status, bone isoenzyme was not studied. Decreased ALP observed in our patients in the puberty group may be explained by the fact that, normally, ALP levels peak in the age group of 10-13 years, after which they gradually decrease. Accordingly, physiological decrease of ALP levels was observed over time in our patients. Similar to our study, the study performed by Elliot et al. revealed that the use of AED led to a decrease in ALP levels over time [27]. Our results are consistent with those obtained in the studies performed by Akın, Aksoy, Giray, Ecevit, Kumandaş, Rauchenzauner, Tekgül, and Sönmez [2, 13, 22, 28-30, 33, 34].

In patients treated with VPA monotherapy, many studies have found the levels of vitamin D to be within the normal range [17, 35-41]. In contrast, a cross-sectional study conducted on 71 adult and pediatric patients who received AED for at least six months found low mean levels of vitamin D and inadequate levels of vitamin D in more than half of the patients [42]. Tekgül et al. and Nicolaïdou et al. [28, 43] reported a trend for decreased levels of vitamin D, which were measured before the intake of AED and three years after the intake of VPA. In the majority of the studies, serum levels of PTH were reported to be within the normal range [17, 30, 31, 35, 36, 39-41]. Contrary to these studies, very few studies reported decreased serum levels of PTH [13, 38, 43].

In our study, as a result of one-year of VPA monotherapy, mean 25(OH)D levels showed a significant decrease but the levels of PTH remained unchanged compared to baseline. In the age-based distribution, the decrease in the levels of 25(OH)D was greater in the puberty group than in the pre-puberty group and a slight increase was observed in the levels of PTH. It was detected that, in the puberty group, this was accompanied by slight decreases of Ca and P compared to baseline, although it remained within the normal range. Although no threshold was defined for the vitamin D deficiency in the children, the levels of 25(OH)D below 11 ng/ml (27.5 nmol/L) are considered as vitamin D deficiency [44]. The most physiological status of the serum levels of 25(OH)D for the organism is values that cannot lead to an elevation of PTH and the absorption of sufficient amount of Ca [45].

Although the results of our study showed adequate serum Ca levels within the normal range, it was observed that, especially in the puberty group, the levels of 25(OH)D decreased and the levels of PTH increased compared to baseline. These results suggested that PTH elevation might be a response through a compensatory mechanism secondary to decreased 25(OH)D levels that occurred due to drug use in the patients. It also suggests that the patients of the puberty group who were within the rapid growth age range were more influenced by the side effects of AED.

Fragility or robustness of the bone is proportional to the regularity and the amount of mineral substance (Ca, P) of the bone structure. DEXA (Dual Energy X-ray Absorptiometry) is currently the accepted gold-standard method. The predictive value of BMD measured using DEXA for a future fracture is very high; each decrease of a standard deviation in the BMD of the lumbar vertebrae leads to a 2.3-fold increase in the fracture risk [46]. In some studies performed on children and adults using VPA, BMD values for the femoral neck and lumbar vertebrae did not show a significant difference [5, 28, 30, 31, 36, 38, 39]. However, many authors highlight the significant decrease of BMD in epileptic patients who received a long-term VPA therapy [13, 18, 27, 35, 47-49]. These studies were generally conducted by comparing the measurements of BMD obtained from several sites such as the femoral neck, radius, and lumbar vertebrae with the measurements obtained in the control group. Similar results were also found in adults [27, 41]. In the study performed by Farhat et al. [50], total body BMD was found to be lower in adults compared to young adults and vertebral BMD was detected to be lower than total body BMD in the children. Sheth et al. [47] investigated axial (2nd, 3rd, and 4th vertebrae) and appendicular (distal radius) BMD measurements in children who received VPA for at least 18 months. They demonstrated the decreases of BMD by 14% and 10% in the axial and appendicular sites, respectively. In another study, children treated with VPA for more than six months showed a decrease by 31.9% in the BMD measured from the femoral neck compared to untreated children [33]. As a result of these studies, it was concluded that long-term VPA therapy could lead to osteopenia in male and female children [17, 49, 51, 52]. VPA shows a dose-response relation. However, most recent studies show that VPA monotherapy had less effect on bone markers and BMD compared to phenytoin and CBZ therapies [27, 53].

Side effects of VPA on the bone cannot be explained by vitamin D metabolism because it is not an indicator of the CYP-450 system. Instead, it is thought to impair the generation and destruction balance in the bone turnover by stimulating osteoclastic activity, thereby causing bone loss [53]. In the study performed by Coppola et al. [4] there were 63 controls and a group of 96 patients between 3 and 25 years old, consisting of children, adolescents, and young adults using AED mono- or polytherapy for at least two years. The investigators found lower BMD and Z-score values in the patients compared to the control group and a significant correlation between abnormal BMD and low physical activity, long-term AED intake, and severe mental retardation. Based on our results, baseline and final BMDs measured at the beginning and end of a 1-year interval did not show a decrease. In fact, there was a statistically significant increase in both the pre-puberty and puberty age groups. This suggests that there is an increase resulting from physiological growth of the children within one year. As a support for this finding, height percentage and weight percentage for the age of each patient did not show any significant change (Table 2). According to this, it may be stated that the level of growth in terms of weight and height was not affected in our AED user patients. Although AED used during the study process led to a decrease in the levels of 25(OH)D in our patients, it was seen that
AED did not prevent the increase of BMD. This is consistent with the results obtained from the studies performed by Tsukahara, Tekgül, El-Hajj Fuleihan, Andress, Vestergaard, Chou, Akin, Kafali, Erbayat, and Aksoy [17, 18, 28, 30, 31, 34, 35, 48, 52, 54-56]. In the studies conducted by Kumanandas and Kim [13, 38], the fact that the use of CBZ and VPA led to a decrease in the levels of 25(OH)D and the decrease observed in BMD were consistent with the results of our study.

In our study, the increase of BMD despite the use of AED could not be compared with a control group for ethical reasons. Therefore, we cannot tell based from BMD measurements alone whether the increase of BMD was affected by the intake of AED in the patients, whether the patients reached the BMD values consistent with their advancing age, and whether they have retardation and, if any, its extent.

Therefore, Z-scores results were obtained and compared with standard values of BMD measured in the same age group. Z-scores were calculated according to the standards for white race (Caucasian) in theDEXA device (there were no standard BMD values obtained for Turkish children). Z-scores equal to or below -2.0 were considered as “bone density low for the chronological age” and Z-scores equal to or above were considered as normal [46, 57].

In our study, in the pre-puberty group, Z-scores showed a physiologically evaluable, significant increase that might be correlated with BMD. At the same time, in the pre-puberty group, none of the patients was found to have a value below -2.0 (Tables 2 and 3). One-year AED therapy did not have an effect on Z-scores or on BMD values in the pre-puberty group. However, in the puberty group, Z-scores were not consistent with the increase of BMD and did not show any statistically significant increase. Furthermore, while the Z-score of one patient was below -2.0 in the baseline measurements of the puberty group, Z-scores of four patients obtained at the end of 1-year VPA therapy were found to be below -2.0 and evaluated as low bone density for the chronological age. The lack of increased Z-scores, or even Z-scores decreased below threshold in some patients, despite the significant increase of BMD measurements obtained in the puberty group, suggested that the patients did not reach adequate bone density because of the side effects of valproate on the bone metabolism.

Based on the literature, the majority of the studies that have investigated the effects of AEDs on bone density did not investi-gate Z-scores for the BMD (g/cm2) results obtained. This also investigated the effects of AEDs on bone density in children who use AEDs. Its evaluation along with Z-scores could be more beneficial in the early detection of the bone metabolism condition of these children.

Çalışma Cumhuriyet Üniversitesi Bilimsel Araştırma Projeleri (CUBAP) tarafından finanse edildi. Cumhuriyet Üniversitesi Tıp Fakültesi Hastanesinde gerçekleştirilmiştir.

Competing interests

The authors declare that they have no competing interests.

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How to cite this article: Ayvaz A, İçagasoğlu FD, Hashkek Z, Erceltek E. Monitoring the Risk of Decreasing Bone Mineral Density in Children Receiving Valproate. J Ann Eu Med 2016;4(3): 77-82.

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