THE EFFECTS OF SODIUM VALPROATE MONOTHERAPY ON THE BODY'S VITAMIN K STATUS IN CHILDREN

ÇOCUKLARDA SODYUM VALPROAT MONOTERAPİSİNİN VÜCUT K VİTAMİNİ DURUMUNA ETKİLERİ

VITAMIN K STATUS IN CHILDREN WITH EPILEPSY

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Öz

Amaç: Çalışmamızda, daha önce literatürde bulunmayan, sodyum valproat (VPA) kullanan çocuklarda vücut K vitamini durumunu ve bir yıllık VPA kullanımının K vitamini durumuna etkilerini incelemeyi amaçladık. Gereç ve Yöntem: Cumhuriyet Üniversitesi Tıp Fakültesi, Çocuk Nöroloji Bilim Dalında bir yıllık sürede, ileriye dönük olarak yapılan çalışmaya, 4-17 yaşlar arasında ilk kez antiepileptik ilaç (VPA) başlanan 25 olgu (14 erkek, 11 kız) ile benzer yaş gurubundan 25 (12 erkek, 13 kız) çocuk kontrol grubu olarak alındı. Tanner kriterlerine göre pre-puberte ve puberte olarak iki gruba ayrılan hastaların tedavi öncesi ve tedaviden bir yıl sonra osteokalsinin karboksile (cOC) ve unkarboksile (ucOC) fraksiyonları ELISA (enzime linked immun assay) yöntemi ile ölçüldü. Unkarboksile osteokalsinin karboksile osteokalsine oranı UCR (Uncarboksile Carboksile Rate) olarak, başlangıç ve sonuç UCR'leri arasındaki fark Delta-UCR olarak tanımlandı. Bulgular: Karboksile osteokalsin pre-puberte grubunda minimal bir artış göstermesine karşın puberte grubunda azaldığı görüldü. Unkarboksile osteokalsinin pre-puberte grubunda daha fazla olmak üzere her iki grupta da başlangıç değerlerine göre azaldığı görüldü. UCR değerleri pre-puberte grubunda azalma, puberte grubunda ise artma gösterdi. Puberte grubunda Delta UCR'nin negatif bir değer aldığı görüldü. Tartışma: Pre-puberte grubu hastalarımız için VPA kullanılmasının, kemik K vitamini durumunu negatif sonuçlar gösterecek kadar kötü etkilemediği görülmüştür. Çalışmamızın sonuçları, puberte grubu hastalarımızda vücut K vitamin durumunun bozulma eğiliminde olduğunu (UCR'de artış), ihtiyacı karşılamada zayıflama olduğunu (cOC'de azalma) ve kemik metabolizmasının olumsuz etkilendiğini (Delta UCR'nin negatif değeri) göstermektedir.

Anahtar Kelimeler

Valproik Asit; Vitamin K; Osteokalsin

Abstract

Aim: Our study aimed to investigate Vitamin K status in children using sodium valproate (VPA), a subject not formerly reported in the literature and the effects of VPA use for a period of one year on Vitamin K status. Material and Method: The study conducted prospectively at the Department of Neurology, Faculty of Medicine, Cumhuriyet University over a period of one year included 25 children (14 male, 11 female) aged between 4 to 17 who received VPA for the first time and 25 children (12 male, 13 female) in a similar age range as the control group. Patients were divided into two stages as pre-puberty and puberty according to Tanner's criteria, and the carboxylated (cOC) and undercarboxylated (ucOC) fractions of osteocalcin were measured using the ELISA (Enzyme Linked Immunoassay) method both pre-therapy and one year post-therapy. The ratio of undercarboxylated osteocalcin to carboxylated osteocalcin was described as UCR, and Delta-UCR the difference between start and end of UCRs. Result: Although carboxylated osteocalcin demonstrated a minimal increase following VPA treatment in the pre-puberty group, it was observed to decrease in the puberty group. We noted that, although higher in the pre-puberty group, undercarboxylated osteocalcin was observed to decrease compared with their start values in both groups. UCR values decreased in the pre-puberty group and increased in the puberty group. We noted a negative Delta-UCR value in the puberty group. Discussion: We noted that the use of VPA for our pre-puberty group of patients did not affect the body's Vitamin K status to the extent that it would have negative results. The results of our study demonstrate that the body's Vitamin K status tended to decline in our puberty group patients (increase in UCR), that there was a weakened capacity to meet the need (decrease in cOC), and that the bone metabolism was negatively affected (negative Delta-UCR value).

Keywords

Bone Metabolism, Sodium Valproate; Vitamin K; Osteocalcin

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Introduction

Treatment of common childhood epileptic disorder is primarily medical and lasts at least two years in patients with seizure control. Sodium valproate (VPA) is the most widely used drug for the treatment of epilepsy because it is the most preferred in both focal and generalized seizures. VPA negatively effects bone metabolism; the drug has disrupted the formation and resorption stability of bone turnover by stimulating osteoclast activity and thus is believed to cause bone loss [1]. However, it could not be developed as a fully explanatory model.

The main factors that play a role in bone mineral metabolism are the genetic and environmental factors, diet, vitamins and hormones, drug use, sport, and activity [2]. It is known that vitamin K plays an important role by carboxylation in making the active osteocalcin, which is an essential protein for bone mineral density in healthy children. Additionally, studies of the effects on bone mineral metabolism of vitamin K status in the body have been remarkable in recent years [3-5]. As a result of research done on this subject, it has been proposed to advocate vitamin K for healthy adolescent children and post-menopausal women [3, 4, 6].

Vitamin K status, effects of drugs on the body condition of vitamin K, and implications of bone metabolism in children with epilepsy using antiepileptic drugs have not been observed previously. Our study aimed to investigate Vitamin K status in children using sodium valproate (VPA), a subject not formerly reported in the literature and the effects of VPA use for a period of one year on vitamin K status.

Material And Method

This study was prospectively performed in Cumhuriyet University, Faculty of Medicine, and Division of Pediatric Neurology during a one-year period. It included 25 children (14 males, 11 females) aged between 4 to 17 who received antiepileptic drugs (VPA) for the first time and continued the therapy with the single drug, and 25 children (12 males, 13 females) in a similar age range as the control group. 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.

Informed consent was obtained from the families of both the control group and the patient group with epilepsy.

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 at 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 [7]. Caution was paid to ensure the regular use of the antiepileptic drugs selected by the diagnoses of the subjects (Sodium Valproate: 20 mg/kg/day) via per oral route, as tablets or suspension, continuously for one year.

To evaluate the growth and development of the subjects in the study period taking the puberty period into consideration, “height and weight for age” and “percentage of height and weight for age” were individually calculated for girls and boys at baseline and at end of the study utilizing the scales prepared for Turkish children [8]. Members of the patient group were assigned into two different age groups including pre-puberty (4-7 years of age) and puberty group (8-17 years of age) according to Tanner’s criteria, and the distribution of these two groups of data were examined for statistical differences.

Blood samples of the patients were taken intravenously in the morning hours. Serum samples obtained from centrifuged blood samples were stored at -70° C for work of carboxylated and uncarboxilated osteocalcin values. The baseline and end time of the study sample were studied together.

Carboxylated (cOC) and undercarboxylated osteocalcin (ucOC) fractioned osteocalcin were measured by ELISA method (enzyme linked immunoassay) using a commercial kit (Takara Bio Inc., Japan). The ratio of undercarboxylated osteocalcin (ucOC) and carboxylated osteocalcin (cOC) were UCR described as a marker of vitamin K status in the body (UCR = ucOC/cOC).

High levels of UCR were used as an indicator of reduced and insufficient vitamin K in the body [9, 10]. The difference of calculated UCR at the beginning and end of a year in the study period was defined as Δ UCR (Δ-UCR = UCR1 (start) - UCR 2 (final)). Over time, the increase of Δ-UCR indicates the improvement of vitamin K status in the bone and the decrease in deterioration.

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 software. The descriptive statistics criteria (median, min-max) was used in the study. Also, Chi-square test was used for the gender distribution of the research and control group and Wilcoxon test to compare values before and after treatment of the patient group. Mann Whitney-U test was used in the comparison of the investigation and control groups. $P<0.05$ values were considered as significant.

Ethics Board Approval

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

Results

Of 25 subjects enrolled into the study (14 males, 11 females), mean age was 10.0 ± 4.4 years (4-17 years) and mean age of control group (12 males, 13 females) was 10 ± 4.1 years (3-17 years). There was no statistically significant difference between gender groups ($p >0.050$) [Table 1]. Pre-puberty group were 11 cases (4 females, 7 males) and puberty group 14 (7 females, 7 males) [Table 2].

When compared to the results obtained at baseline and after one year, the height and weight of patients increased significantly in the pre-puberty group ($p = 0.003$). Height and weight gain were significantly higher in the puberty group ($p = 0.001$). These increases were for length; there was no significant difference for “the percentage of height for age” of both groups ($p> 0.050$). The increases of “weight percentages by age” were meaningless as statistics in the pre-pubertal group while in the puberty group they were significant ($p = 0.006$) [Table 2].

There was no statistically significant difference among age groups in terms of values of carboxyl-carboxylated osteocalcin, Δ-UCR, and UCR in the pre-puberty and puberty in comparison ($p >0.050$) [Table 2].

Carboxylated osteocalcin levels were decreased more in the puberty group than in pre-puberty group (p>0.050). It is seen that carboxylated osteocalcin values were reduced minimally in the pre-pubertal group, while there were minimal increases in the puberty group (p <0.050). UCR values did not change in the pre-pubertal group while showing an increase in pubertal groups (p> 0.050).

The values of Δ-UCR (0.11) having positive in the pre-pubertal group were observed to take a negative value in pubertal age groups (p> 0.050) [Table 2].

Table1. The comparison of the demographic characteristics and biochemical results of the patient and control groups

	* Patient Group (n=25) (Median) (min-max)	*Control Group (n=25) (Median) (min-max)	***P Value
Female (n)	11	13	****0.774
Age (year)	11.00 (4-17)	10.00 (3-17)	0.969
Weight (kg)	28.80 (12.00-68.50)	33.00 (12.00-75.00)	0.522
Height (cm)	140.00 (91.00-169.00)	139.00 (91.00-179.00)	0.861
**Percentage of weight for age (%)	89.90 (64.17-122.30)	94.00 (82.10-102.60)	0.053
**Percentage of height for age (%)	97.50 (81.40-107.30)	99.00 (88.90-102.10)	0.385
Carboxylated OC (cOC) ng/mL	15.40 (3.36-22.79)	6.15 (2.89-14.80)	0.076
Uncarboxylated OC (ucOC) ng/mL	8.71 (7.88-8.74)	8.2 (0.31-8.74)	0.163
UCR (ucOC/cOC)	0.56 (0.38-2.54)	0.83 (0.08-2.63)	0.118

* The initial (baseline) values of the patient group
** It indicates that should be percentage of weight and height for their age, according to the scales prepared for Turkish children (8).
*** Mann-Whitney U test
**** Chi-square test

Discussion

The growth of children is not the same at all ages due to features of pre-puberty and puberty. Monitoring the BMI of children is not thorough enough. In our study, we compared the height and weight goals according to chronological ages of the children instead of BMI. The results obtained from by the scale arranged for Turkish children has provided that the physiological increase from growth of pre-pubertal and pubertal children compared with the reference values for a prospective study.

There was no significant difference between the initial and final results of "the percentage of height for age" despite the significantly increased height of pre-puberty and puberty patients (p >0.050). The percentage of height for age, which upon initial measurement had no difference with the control group, showed no significant changes but a slight decrease after using VPA for a year (p>0.050). Our patients have provided the percentages of the height needed according to their age. These results suggested to us that the height growth of patients is not significantly affected by VPA treatment [Table 2].

It has been reported that the weight gain begins, especially in the first 3-6 months of treatment in 44-71% of patients with epilepsy, and is most common to occur when treated with VPA, carbamazepine, or gabapentin [9]. Some anti-epileptic drugs such as Topamax and Levetiracetam are known to cause weight loss [10, 11]. In some adult patients, it is suggested that VPA increases serum leptin levels, lipid accumulation caused by inhibiting to beta oxidation of mitochondrial fatty acids, the result of reducing palmitate connected to albumin to increase long chain fatty acids. It is leads to warning lipogenesis by increasing insulin and made increased appetite by lowering blood sugar [12, 13]. It has been reported that children who received VPA treatment have a 40% risk of weight gain at the onset of puberty [14].

While the values of the weight percentages by age had no difference at the beginning of the study, the values obtained at the end of the study were found significantly higher, particularly in the puberty group, (p = .006). It show that VPA used for one year caused significant weight gain in our patients, similar to other studies discussed above [12- 14] [Table 2].

Table 2. The distribution of initial (baseline) and final values of the study in the pre-puberty and puberty age group

	Pre puberty			Puberty* (n=25)		
* (n=25)	BMV (n=11) (min-max)	FMV (n=11) (min-max)	**P value	BMV (n=14) (min-max)	FMV (n=14) (min-max)	**P value
Height (cm)	111.00 (91.00-118.00)	114.00 (95.00-123.00)	0.003	155.00 (139.00-169.00)	158.00 (145.00-173.00)	0.001
PHA (%)	99.10 (81.40-107.30)	97.00 (81.80-100.00)	0.139	97.45 (93.30-103.50)	97.20 (92.90-103.40)	0.172
Weight (kg)	17.50 (12.00-22.00)	20.00 (15.50-26.20)	0.003	42.60 (828.00-68.50)	49.75 (32.00-70.20)	0.001
PWA (%)	92.80 (64.17-109.80)	93.70 (74.50-113.30)	0.374	85.50 (64.90-122.30)	88.15 (66.60-123.10)	0.006
cOC ng/mL	15.63 (8.42-22.79)	14.43 (7.16-22.81)	0.790	14.86 (3.36-22.76)	11.54 (5.10-22.80)	0.433
ucOC ng/mL	8.71 (7.88-8.73)	8.69 (6.23-8.740)	0.124	8.71 (7.88-8.74)	8.72 (5.85-8.73)	0.562
UCR	0.53 (0.38-1.03)	0.53 (0.20-1.21)	0.139	0.58 (0.38-2.34)	0.72 (0.25-1.70)	0.875
Δ-UCR	0.11 (-0.18-0.36)			-0.04 (-1.32-1.28)		***0.403

* BMV: Baseline Median Values, FMV: Final Median Values,
PHA: Percentage of Height for Age, PWA: Percentage of Weight for Age,
cOC: Carboxylated Osteocalcin, ucOC: Uncarboxylated Osteocalcin,
UCR: ucOC/cOC, Δ-UCR: The difference between UCR1 and UCR2
** Wilcoxon test
*** Mann-Whitney U test

Osteocalcin is a bone matrix protein which is synthesized from mature osteoblasts (Gla proteins). Osteocalcin's primary feature is its calcium binding property that is induced by three vitamin K dependent gamma- carboxyglutamic acid remnants. Osteocalcin's functions as a protein are not definitively known despite its role in the mineralization process [15]. Vitamin K is the cofactor of the five known Gla proteins in the human body. In order for these proteins to function well, the human body requires a sufficient amount of vitamin K supplement [16].

Urine and serum measurements of vitamin K do not provide adequate informa-

tion regarding the tissue levels. The ideal measurement is to directly test the gamma-carboxylation states of the Gla proteins in tissue. cOC, a small Gla protein that is synthesized in bones, and ucOC, that is found in the blood circulation, enables the analysis of the bodies' vitamin K levels. These are the primary indicators of vitamin K levels in bones [17, 18]. Dietary vitamin K is sufficient to the carboxylation of osteocalcin. Metabolic activity and the increase of osteocalcin production during the bone development and the skeleton growth increase the deprivation of vitamin K in bones. In case of inadequate dietary supplement, a subclinical vitamin K deficiency can occur due to the increased need. This increases bone turnover and therefore leads to osteoporosis by hindering children's bone densities from reaching a healthy level. In healthy adults, depending on the amount received, approximately 10-30% of osteocalcin becomes under-carboxylate (ucOC). Research conducted on adults, although unclear in the explanation of pathophysiological mechanism, has indicated that increased levels of ucOC have negative correlation with hip bone mineral density (BMD) and positive correlation with risks of bone fractures [6, 16, 18, 19]. There is very limited research on vitamin K levels and bone metabolisms of children [2-5, 20, 21, 22]. We haven't found any research on vitamin K levels of children who use anti epileptic drug (AED) and its effects on their bone mechanisms.

In the comparison between the pre-treatment levels of the patients and the control group, the cOC, ucOC, and UCR levels were statistically insignificant.

When we examined our patients in groups of pre-puberty and puberty, we observed slight decrease in the pre-puberty cOC and ucOC levels. UCR levels did not change and Delta-UCR had positive levels. It can be inferred from these results that, although statistically insignificant, the vitamin K levels in the bones weren't sufficient to meet the body's need (decrease in cOC), yet the overall vitamin K levels in the body hadn't been worsened (decrease in ucOC, stability in UCR, positive values of Delta-UCR). These results may indicate that, although we lack definitive information on how the VPA affects vitamin K levels in the bones in pre-puberty patients, at least it does not have adverse effects that can be observed in laboratory tests.

In the puberty group, statistically insignificant changes were observed in tests. cOC levels decreased, ucOC levels slightly increased, and UCR levels increased in accordance with that. It was also observed that delta-UCR levels were negative [Table 2]. These results indicate that in cases of the patients who experience puberty phase in which the bone growth is observed to be fast, the vitamin K levels in the body tend to worsen (increase in UCR) and insufficient for the body (decrease in cOC). Thus, the bone metabolism is adversely affected (the negative values of Delta-UCR).

Theuwissen et al. have found that 42 healthy volunteer children had high ucOC levels (3.4-96.9 ng ml) in their vitamin K status study [22]. Van Summeren et al. have found that the cOC, ucOC, and UCR rates in children (app. 31.3 ng/ml, 15.4 ng/ml, and 2.3 ng/ml) are noticeably high. They have discovered a distinctive correlation between bone indicators and these rates, and thus, they have established the suboptimal vitamin K levels in healthy children [3]. The ucOC levels in this study are higher than both the initial levels of the patient group and the levels of the control group in our research (app. 8.6 and 6.8 ng/ml). However, neither in Turkey nor in another country do these indicators have any reference values that are specific to age. The apparent difference in the ucOC levels between ours and that of Van Summeren et al., which share the same research methods, is difficult to comprehend due to the scarcity of research relevant to the topic, the absence of reference values, and the socioeconomic, geographical, and structural differences among societies. However, our cOC rates are similar (14.4 ng/ml). Similar to Van Summeren's research, vitamin K levels in the bodies have been observed to be suboptimal in the healthy children in our control groups and in epilepsy- diagnosed patients who are yet to receive medical treatment.

Kalkwarf et al. have found noticeable variations in ucOC percentages and established a significant correlation between a sufficient state of vitamin K (indicated through ucOC percentage) and decreased bone turnover [23]. In Kalkwarf's research, with a different method from our study, ucOC's proportion to the serum total osteocalcin was measured and considered as the ucOC percentage. Similar to many research studies in the field, we have directly measured serum cOC and ucOC levels with a commercial kit, using ELISA method and comparing them in terms of ng/ml [3, 4, 6, 21]. In our research, increased bone turnover and poor levels of vitamin K has been observed in puberty phase children who received VPA.

O' Connor et al., in their research conducted on 223 healthy girls between the ages of 3 to 16, have compared the percentages of bone indicators, BMD, and ucOC and have found a negative correlation between the BMD values obtained from lumbar vertebrae and ucOC. They have stated that a sufficient vitamin K level is related to increased BMD and such a level reduces bone turnover [5]. Our research exhibits similarities with O'Connor's in terms of research results.

In their research which was conducted through similar methods as ours, Van Summeren et al. has found that UCR levels that are generally thought to be indicators of vitamin K deficiency in the bones, are observed to be high in healthy pre-pubertal children. They have also stated that UCR is correlated in advanced puberty with the exhibited puberty stage, and that UCR levels change in parallel with high growth speed [4]. The relation between UCR and pubertal development has been indicated in previous research as well [3]. Similar to Van Summeren's, in our research, despite the well state of vitamin K levels in pre-pubertal patients, we have observed insufficient levels of vitamin K indicated through increased UCR, decreased cOC, and negative values of Delta-UCR [4]. This situation can be explained through the increased UCR levels induced by an imbalance between the amount of vitamin K metabolically required during growth and the amount received daily, as well as through the imbalance in the originally suboptimal vitamin K state of the body caused by the use of VPA for a year.

As a result of our research, we have concluded that vitamin K levels in pubertal patients are adversely affected and VPA use can contribute to the situation. In general, it has been observed that the use of VPA has greater effect on vitamin K levels in pubertal patients compared to the patients in the pre-puberty group. Use of VPA in children, especially those in the puberty phase when growth occurs faster, can cause decrease in bone development, decrease in body vitamin K levels, hindrance from reaching maximum bone mass, and increased risk of osteopo-

rosis in adulthood. Therefore, vitamin K supplementation may be considered for children who receive VPA treatment. However, this research should be supported by further research with broader participation and a longer study period.

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Competing interests

The authors declare that they have no competing interests.

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