Klinik Çalışma - Araştırma / *Original Article*

Does Valproate Therapy Decrease the Bone Mineral Density in One-Year Follow-Up in Children?

Çocuklarda Bir Yıllık Valproat Tedavisi Kemik Mineral Dansitesini Azaltıyor Mu?

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Objectives: Epilepsy is a chronic disease that requires long-term antiepileptic therapy. The aim of this study was to evaluate the side effects of valproate, the most commonly used antiepileptic, on bone mineral metabolism.

Patients and Methods: The study comprised of 61 patients (38 girls, 28 boys; mean age 81.2±44.5 months; range 12 to 168 months) who received valproate because of epilepsy or prophylaxis of febrile seizures. All cases were evaluated in terms of bone mineral metabolism disturbances by assessing bone mineral density and biochemistry parameters, before and after 12 months of valproate therapy.

Results: At the end of one year of valproate therapy, there were no statistically significant differences in calcium, phosphorus and alkaline phosphatase levels that might show bone mineralization disturbance. Osteoporosis was recorded in two cases (3.3%).

Conclusion: The side effects of valproate on bone mineral metabolism are usually contradictory. In order to determine osteopenia signs; bone biochemistry, 25- OH vitamin D3, hormonal parameters and bone mineral density, which are not enough for evaluation alone, have to be evaluated together. Patients taking valproate therapy should have bone mineral density measurements yearly, because mineral changes in bone (defeats) could not be predicted with these biochemical parameters beforehand.

Key words: Epilepsy; valproate; bone mineral density.

Amaç: Epilepsi uzun sureli antiepileptik tedavi gerektiren kronik bir hastalıktır. Bu çalışmanın amacı, en sık kullanılan antiepileptik ilaç olan valproatın kemik mineral metabolizmasına olan yan etkilerini değerlendirmektir.

Hastalar ve Yöntemler: Bu çalışma epilepsi veya febril konvulziyon profilaksisi amacıyla valproat başlanan 61 hastada (38 kız, 28 erkek; ort. yaş 81.2±44.5 ay; dağılım 12-168 ay) yapıldı. Bütün olgularda valproat tedavisi öncesinde ve 12 ay sonrasında, kemik mineral metabolizmasındaki bozukluklar açısından kemik mineral dansitesi ve biyokimyasal parametrelere bakıldı.

Bulgular: Bir yıllık valporat tedavisi sonrasında kemik mineralizasyon bozukluğunu gösterebilecek kalsiyum, fosfor, alkalen fosfatazda istatistiksel olarak anlamlı farklılık tespit edilmemiştir. İki hastada (%3.3) osteoporoz tespit edilmiştir.

Sonuç: Valproatın kemik mineral metabolizması üzerine yan etkileri tartışmalıdır. Osteopeni belirtilerini değerlendirmek için, kemik biyokimyası, 25-hidroksi D vitamini, hormonal parametreler ve kemik mineral dansitesinin tek başlarına değerlendirilmesi yetersizdir, mutlaka bu parametreler birlikte değerlendirilmelidir. Biyokimyasal parametreler bozulmadan, kemik mineral dansitesi değişiklikleri olacağından, valproat tedavisi alan hastalarda yıllık kemik mineral dansitesi ölçümleri yapılmalıdır.

Anahtar sözcükler: Epilepsi; valproat; kemik mineral dansitesi.

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The prevalence of childhood epilepsy, one of the chronic diseases in this period of life, is estimated as 0.5-1%.[1-3] Eighty percent of epilepsy may be taken under control with proper drug therapy.[2-4] Recently, with the clinical use of electrophysiological methods, recognition of types and pathophysiologies of epilepsies, discovery of different neurotransmitters and invention of new drugs, the success rate of epileptic therapy increased.[3,5]

Valproate (VPA) is widely used in childhood epilepsy because of its broad spectrum and its safety. Besides, it has fewer side effects on cognitive functions and school performance as compared with the other antiepileptic drugs.[1,4,6] Recently, many side effects of VPA on bone mineral metabolism therapy have been reported.[1-9] These side effects may be due to its influence on the renal tubules such as forming a Fanconi-like disease and causing much more loss of phosphorus (P) and calcium (Ca).[7,8] However, exact mechanism of its effect on bone metabolism is still disputatious.[9]

Osteoporosis is a disease of bone that leads to an increased risk of fracture. In osteoporosis the bone mineral density (BMD) is reduced, bone microarchitecture is disrupted, and the amount and variety of non-collagenous proteins in bone is altered. Studies on bone mineral metabolism of the children taking VPA treatment are usually comparative with healthy children.[6,10,11] Bone mineral metabolism may be affected by age, weight, height, body mass index, gender, and genetics, so that measurements on the same case will decrease the personal changes before and after the treatment.[9,12,13] Therefore, our aim was to evaluate the bone mineral metabolism of the children who take VPA therapy with biochemical, hormonal, and BMD tests.

PATIENTS AND METHODS

This study was performed in Pediatric Neurology and Nuclear Medicine Clinics of Trakya University between September 2003 and February 2005. The study included 66 patients who received VPA therapy because of the diagnosis of epilepsy and complex febrile seizure with clinical and EEG findings.

The criteria of the inclusion in working group were;

1- Being in childhood (age between 1-18 years)

2- Taking antiepileptic therapy for the first time in life

3- Taking only VPA therapy (monotherapy)

4- No restriction in physical activation

5- Not having mental-motor retardation that will impede physical activation

6- No diet restriction and feeding difficulty

7- Not having any disease that makes growth and developmental retardation

8- Not taking any other drug that will affect bone mineral metabolism.

With these criteria, the study was carried out in 61 patients taking VPA therapy for the first time. It compromised of 26 boys (52.6%) and 35 girls (57.4%) with the mean age of 81.2±44.5 (range 12-168) months.

All of these cases were evaluated before and after 12 months treatment and all of their demographic data including name, surname, birth date, age, and gender were noted. After a morning fasting weight, height, body mass index were measured and physical examinations of the cases were performed.

Our cases were also investigated for bone mineral metabolism changes. For this purpose 3 ml. venous blood samples were drawn from left antecubital vein for analyzing calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) levels. Serum VPA levels and bone mineral density were measured before and after one-year treatment.

The study was appropriated for Helsinki Declaration and ethical permission for this study was obtained from the local ethical committee. All of the cases included in the study were informed about the study and their parents signed an approval.

After an initial scanning, VPA monotherapy was started with a dose of 15-40 mg/kg/day. All cases were followed up for 12 months for seizure

control, use of the drug regularly, side effects and anthropometric measurements. The cases who got polytherapy because of not controlling the seizures and who got out of control were excluded from the study.

Bone mineral density measurements were executed with dual energy X-ray absorptiometry (DEXA) (Norland XR-36 analyzer, Norland Medical System, USA). Bone mineral density was measured at the points of 2, 3, and 4 lumbar vertebrae at A-P position, the femoral neck and the greater trochanter. The normal reference values of bone mineral density were based on a study made on healthy Turkish children.[12] Cases were asked to lie on supine position and physiological lordosis was corrected by elevating knees while measuring the lumbar areas. Extremity measurements were taken from the ones used less. Femur neck measurements were performed while their legs were at the position of slightly internal rotation and abduction.

In order to increase the reliability of our study, all densitometry results were evaluated by the same nuclear medicine experts who did not know anything about the cases. The value of Z score being below -2 at the points of lumbar vertebrae and/or the femur neck and/or the greater trochanter was accepted as osteoporosis.[14]

Statistical analyses

In addition to the descriptive statistical methods, Student's t test (paired t test) was used to compare age, weight, height, BMI, BMD, biochemical parameters, before and after VPA therapy. Results were documented as mean ± standard deviation (min-max). All data processing was done with the Minitab Release 13. The level of significance in all statistical tests was set at $p<0.05$.

Table 1. The demographic values of working group

Age (months)*	81.2±44.5
Gender**	35 girls (57.4%)
	26 boys (42.6%)
Epilepsy history in family**	10 (15.2%)
Bone disease history in family**	1 (1.6%)
Obesity in family**	11 (17.2%)
Type of epilepsy	
Generalized epilepsy**	47 (77%)
Partial epilepsy**	8 (13.1%)
Complex febrile seizure**	6 (9.8%)

*Data are presented as mean ± SD; **Number of cases (% of all cases).

RESULTS

All of the patients got VPA therapies because 47 of them were diagnosed as generalized epilepsy, eight were partial (focal) epilepsy and six were complex febrile seizure. The demographic values of working group are shown in Table 1.

The mean VPA dose was 28.0±5.2 (15-40) mg/kg/day; and after one-year treatment the serum VPA level was measured as 75±17.3 (50-128) μg/ml. None of the patients taking VPA had hypocalcaemia and hypophosphatemia that were thought to be a sign of impairment in bone mineralization and also ALP levels before and after the treatment did not change significantly (Table 2).

At the beginning of the study the mean BMI level was 16.4±2.4 (12.4-23.4) /kg/m². After one-year treatment, the mean BMI level was 16.9±2.5 (12.7-24.5) kg/m². This increase in BMI was significant ($p<0.001$).

According to Z scores, osteoporosis was established in two of our cases at the point of femur neck and in one at the point of L2-L4 in

Table 2. The biochemical values of cases before and after one-year treatment with VPA

	Initial	Last	*p*
Ca (mg/dl)	9.5±0.5 (8.4-11.0)	9.7±0.9 (8.5-11.6)	NS
P (mg/dl)	4.9±0.6 (3.6-6.0)	5.0±0.6 (3.7-7.0)	NS
ALP (U/L)	202.4±76.5 (118.0-479.0)	203.8±79.8 (71.0-520.0)	NS

All data are presented as mean ± SD (min-max). NS; Not significant.

Table 3. The mean values of bone mineral density initially and after one-year treatment at the points of L2-L4 vertebrae, the femur neck and the greater trochanter and Z scores

	Initial	Last	*p*
L2-4 BMD (gr/cm^2)	0.56±0.20 (0.22-1.55)	0.57±0.16 (0.27-1.19)	NS
Femur neck BMD (gr/cm^2)	0.59±0.15 (0.20-1.04)	0.63±0.15 (0.28-1.06)	<0.001
Trochanter BMD (gr/cm^2)	0.53±0.13 (0.26-0.86)	0.54±0.13 (0.29-0.85)	NS
L2-4 Z-score (SS)	–0.14±0.69 (–1.8-2.1)	–0.13±0.68 (–2.05-2.03)	NS
Femur neck Z-score (SS)	–0.39±1.22 (–3.9-5.2)	–0.33±0.65 (–2.77-1.10)	NS

All data are presented as mean ± SD (min-max). NS; Not significant.

those who took VPA. However, in the statistical analysis we determined that VPA did not reduce BMD and did not increase the fracture risk after one-year treatment significantly. The median BMD initial values at the points of L2-L4 vertebra, the femur neck and the greater trochanter and Z scores are shown in Table 3.

DISCUSSION

The side effects of VPA on bone mineral metabolism were shown with biochemical, hormonal and DEXA methods so far, but no common pathogenesis or conclusion could be reached after these studies.[6,8-10] There are few cross-sectional studies which compare bone densitometries of healthy children and children who take long-term antiepileptic therapy and the results are incompatible.[6,9,10,15] Our study's superiority is lowering the errors by measuring BMD before and after one-year antiepileptic therapy. Because, BMD measurements using DEXA are difficult to apply in childhood. Furthermore, the measurements are highly affected by age, gender, race, nourishment. Two measurements lower these side effects.

In the literature there are many studies reporting that antiepileptics have no side effects on BMD.[6,9,10,16] Akın et al.[6] reported that children taking carbamazepine or VPA for about one year did not have a decrease in BMD measured by DEXA. Erbayat et al.[9] also reported 36 cases taking VPA and carbamazepine more than one year and their BMD did not differ from the healthy ones. Moreover, in the other studies reported from Turkey, Altunbaşak et al.[16] did not determine a decrease in BMD who had taken long-term VPA therapy. On the contrary, Kafalı et al.,[17] reported 13 cases taking VPA therapy for 1.8±0.7 years who had a decrease in BMD and this decrease was evident in girls. Sheth et al.,[10] reported cases using VPA for 3.1±1.7 years who had a decrease in BMD. Wettengl et al.[18] also reported 39 cases who had a decrease in BMD determined with DEXA taking carbamazepine or VPA. Similarly, Öner et al.[19] in a study created in our region reported a correlation between long-term and high-dose therapy and found a decrease in the BMD values of patients who used VPA more than six months.

The changes in different studies may be due to DEXA methods being new and that standard values have not been constituted for children yet. Moreover, BMD values changed due to age, height, weight during childhood. For these reasons, in order to approve the side effects of drugs on bone mineralization in a growing organism, it will be helpful to show the effects of the drug on BMD increase in one year. We determined osteoporosis according to "Z" scores at the points L2-L4 in just one patient, femur neck in two patients, in the direction of DEXA values accepted in World Osteoporosis Congress.[20] These findings were interpreted as using VPA did not decrease BMD in one year and did not increase fracture risk.

The first publications about the relation between antiepileptic drug levels, therapy time and bone mineralization reported that whenever drug level and drug using time increased, the side effects on bone mineralization have increased. However, later on, some studies

claimed that the BMD changes were independent from the drug levels and using times. Öner et al.,[19] in spite of all these opinions, reported that patients taking high-dose and long-term VPA therapy had this side effect evidently. In our study, because of making measurements at the end of one year in all patients, we could not determine any relation between BMD and drug using time, but no obvious decrease in BMD was proved during drug use. Studies with long-term and different dose of drug usage are required to prove this claim.

In conclusion, the side effects of VPA on bone mineral metabolism are usually contradictory. According to stages, in order to determine osteopenia signs; Ca, P, ALP, calcitonin, PTH, 25- OH vitamin D3 and hormonal parameters, which are not enough for evaluation alone, have to be evaluated together. However, the role of these parameters in the evaluation of bone mineral metabolism is restricted. Likewise, there are several studies reporting a decrease in bone mineralization in epileptic patients while these hormonal and biochemical parameters are normal.[21] Patients taking VPA therapy should have bone mineral density measurements yearly, because mineral changes in bone (defeats) could not be predicted with these biochemical parameters beforehand.

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