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SHORT COMMUNICATION

Bone turnover markers in epileptic patients under chronic valproate therapy

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Background: The effects of chronic valproic acid administration on bone health have been a matter of concern and controversy. In this study, the bone status following valproate intake was assessed by using several bone-related biochemical markers. **Materials and Methods:** In this case-control study, 62 epileptic patients and 40 age- and gender-matched controls were enrolled. The patients had been under chronic valproate therapy (758 ± 29 mg/day) for at least the past 6 months, without any vitamin D/or calcium supplementation. Serum markers of bone turnover (carboxy-terminal telopeptide of type I collagen (CTX) and bone-specific alkaline phosphatase [BALP]), calcium, phosphorus, total alkaline phosphatase, and parathyroid hormone levels were measured in both groups. **Results:** The markers of bone turnover as well as other measured bone biochemical parameters did not statistically differ between the two groups. **Conclusion:** Valproate therapy at the mentioned doses does not seem to change bone turnover in adult epileptic patients.

Key words: Bone turnover markers, epilepsy, valproate sodium

INTRODUCTION

A large body of evidences indicate that both epilepsy and antiepileptic therapy can have detrimental effects on bone metabolism.[1] Sodium valproate (VPA) is a widely used broad-spectrum antiepileptic and mood stabilizer. Although this drug is fairly well tolerated with relatively few side effects, its adverse endocrine and metabolic effects have always been a matter of concern and controversy. Many side effects of VPA on bone mineral metabolism therapy have been reported. Reduction in bone density,[2-5] increase in bone turnover markers,[6-8] hypo- or hypercalcemia,[9-11] and elevated parathyroid hormone (PTH) levels[3] have been observed in some studies, but not confirmed by others.[3,12-15] Plasma levels of vitamin D were also both reported to be reduced[16] or normal[3,9,10] in these patients.

Despite considerable investigations, the skeletal complications of chronic valproate intake have remained controversial and even some of the physicians prescribe calcium/vitamin D as a routine practice during valproate therapy. The necessity and consequences of such supplementation are not fully clear yet. The current study was designed to assess the bone health status in a group of valproate-treated patients, by using a panel of bone-related biochemical markers.

MATERIALS AND METHODS

This case-control study was performed in outpatient clinic, Department of Neurology, Alzahra University Hospital, from December 2008 to July 2009. The cases comprised 62 (48 female, 14 male) epileptic patients. Control group consisted of 40 (32 female, 8 male) apparently healthy, age- and gender-matched individuals attending a local laboratory for checkup. Diagnosis of epilepsy was based on clinical and EEG findings. The inclusion criteria for the patients' group were taking VPA monotherapy for at least the past 6 months (without calcium/vitamin D supplementation), not having any obvious disease or pregnancy, and not taking any other drug. Fasting blood sample was collected for measurements of calcium, phosphorus, total alkaline phosphatase (ALP), intact PTH, and the bone turnover markers, carboxy-terminal telopeptide of type I collagen (CTX) and bone-specific alkaline phosphatase (BALP). Calcium, phosphorus, and total ALP were measured by spectrophotometeric methods, and PTH, BALP, and CTX were measured by commercial immunoassay kits from Biosource (Grand Island, USA), Quidel (San Diego, USA) and Nordic Bioscience (Herlev, Denmark), respectively.

Statistical analysis

Multivariate analysis of variance (MANOVA) was used to compare between-group data (IBM SPSS statistic editor, version 19).

RESULTS

All the results are expressed as mean (±SEM). The age of the study population was 25.6 (±0.55)

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Table 1: Bone-related biochemicals in epileptic patients under at least 6 months sodium valproate treatment and healthy controls

	Patients Means (±SD)		Controls Means (±SD)	
	Male *n*=14 (23%)	Female *n*=48 (77%)	Male *n*=8 (20%)	Female *n*=32 (80%)
Age (years)	24.9 (±1.2)	25.8 (±0.6)	22.5 (±0.2)	23.5 (±0.8)
Calcium (mg/dl)	9.2 (±0.2)	9.3 (±0.1)	9.0 (±0.2)	9.1 (±0.1)
Phosphorus (mg/dl)	3.5 (±0.3)	3.9 (±0.1)	3.6 (±0.1)	3.8 (±0.1)
Total alkaline phosphatase (IU/L)	184.2 (±16.9)	167.5 (±16.0)	170.6 (±25.6)	166.6 (±13.3)
PTH (U/L)	32.5 (±2.1)	28.9 (±1.9)	32.2 (±3.2)	27.4 (±1.3)
CTX (ng/ml)	0.56 (±0.07)	0.77 (±0.10)	0.64 (±0.07)	0.65 (±0.14)
BALP (U/L)	29.2 (±4.3)	35.3 (±3.7)	27.4 (±2.6)	29.1 (±1.9)

PTH=Parathyroid hormone; CTX=Carboxy-terminal telopeptide of type I collagen; BALP=Bone-specific alkaline phosphatase

and 23.3 (±0.75) years in patient and control groups, respectively. In the patient group, 56 had primary generalized epilepsy and the other 6 were diagnosed with localization-related epilepsy. Valproate dosage was 758 ± 29 mg/day and the duration of antiepileptic therapy was 8.5 ± 1.1 years. Mean results of the routine biochemical tests, calcium, phosphorus, and total ALP were normal with no statistically significant differences between patients and controls. Serum CTX and BALP levels did not differ significantly between the groups (Wilks $\lambda = 0.963$; ≈F6, 90=0.581; $P = 0.745$) [Table 1].

DISCUSSION

In the present study, there were no statistically significant differences between the two groups in terms of bone-related biochemical markers.

These findings are compatible with part of the previous publications[12] and disagree with some others.[6,8,15,16] Studies regarding the bone turnover markers' status during valproic therapy have yielded conflicting and even contrary results. For example, Verrotti *et al*. have reported that both markers of bone formation, such as BALP and resorption including carboxy-terminal propeptide of type I procollagen, have been significantly increased with this drug.[6] Elevation of the BALP during valproic therapy was also shown by Krishnamoorthy *et al*.[7] Nevertheless, these have not been constant findings. Pack *et al*. did not observe any increase in bone ALP and urine N-telopeptide by valproic.[12]

The real causes of these discrepancies among different studies are not clear, but a long list of different factors could be suspected. Age, duration of treatment, type of concurrent drugs used, lifestyle, and socioeconomic and geographic conditions are some of the factors that can influence VAL's adverse bone effects.

As the serum levels of bone turnover markers are highly sensitive to anti-osteoporosis chemotherapy, the patient group consisted of those who had not used any vitamin D/calcium supplementation during their past 6-month period of valproate therapy. In addition, the age range was limited to post-pubertal and pre-menopausal periods.

Cross-sectional nature and lack of bone mass density evaluation are the two major limitations of this study. Lack of increase in bone turnover markers, on the other hand, does not completely rule out the possible development of bone loss in the future.

In conclusion, these findings indicate that bone mineral metabolism may not be affected by VAL. Whether this drug can cause bone loss in the long term or in special subpopulations of epileptic patients remains to be elucidated. More studies are still needed to clarify real requirement for vitamin D/calcium supplementation during VPA treatment.

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