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Original Article

Analysis of carbamazepine side effects associated with bone metabolism, folate and vitamin B_{12} serum levels in Isfahan epileptic patients

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Abstract. According to previous publications, chronic uses of AEDs reduce bone health, increase homocysteine levels, alkaline phosphates and many other biochemical changes. The aim of this study was to investigate carbamazepine (CBZ) effects on bone density, serum levels of folate, vitamin B12 and other biochemical variables. Twenty-one adult epileptic patients who received CBZ for treatment of epileptic attacks were enrolled. Bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry method. Biochemical indices of bone metabolism, including serum calcium, phosphorus, alkaline phosphatase contents and also serum levels of folate, vitamin B12, homocysteine were measured. All clinical, laboratory and pharmacological data were recorded in d-Base and analyzed using SPSS (version 16) for windows. BMD Z-scores, and 25-dihydroxyvitamin D3 concentrations was not differ significantly, but it seems that, the female patients had diminished BMD at the femoral neck ($p \leq 0.05$). Folate or vitamin B12 levels tend toward lower values. This seems to be connected to a tendency toward higher mean corpuscular volume (MCV) with a mean of 84.9 fl (ranged from 59-120 fl). There was no correlation between $CBZC_0$ and homocysteine levels ($p \leq 0.63$). In compare to normal value the serum calcium content was lower with a mean of 7.8 mg/dl (ranged; 7.0-8.9 mg/dl; $p \leq 0.04$). With a mean of 213 U/L serums alkaline phosphatase was significantly higher ($p \leq 0.01$) than normal values. Due to the need for chronic prescription strategy in order to control convulsion attack, pharmacotherapy with AEDs may consequence to changes in serum contents of calcium, phosphorus, alkaline phosphatase in addition to decrease in BMD and increase in homocysteine levels. Further studies related to efficacy and side-effects of CBZ as the most prescribed AEDs in Iranian epileptic population seem to be valuable.

Keywords: Carbamazepine, homocysteine, bone metabolism, folate

Introduction

Epilepsy is one of the most common chronic neurological disorders, and its significances encompass future beyond the event of seizures. Antiepileptic drugs (AEDs) are widely used as a chronic treatment strategy to control seizure attack and carbamazepine (CBZ) is commonly used AEDs. There is evidence for the presence of bone disease in epileptic patients. The special effects of AEDs on bone metabolism and the endocrine system are not completely recognized [1-5]. According to previous publications, CBZ affect bone metabolism, vitamin B12 and folic acid levels by induction or inhibition of cyochrom-P450 linked to metabolic events [4-17]. Bone is a metabolically dynamic tissue which experiences constant formation, maintenance and resorption that termed as osteoblasts, osteocytes and osteoclasts. Under regular situations, bone osteoclasts and osteoblasts are strongly joined to each other, so that the amount of bone detached is continuously identical to the quantity of recently bone formed. This equilibrium is accomplished and controlled over the exploit of several systemic hormones and local mediators. [1] Adult epileptic patients are in abundant danger for bone damages. This could be associated to underling disease, imbalance and the effects of AEDs on bone strength. Biochemical abnormalities of bone uptake comprising hypocalcaemia, hypophosphatemia, vitamin D deficiency and augmented alkaline phosphatase have been described previously. Chronic treatment with particular drugs deliberates a higher risk of osteomalacia that is accredited to vitamin D deficit. Several studies have shown that enzyme-inducing AEDs are associated with reduced levels of 25- hydroxyvitamin D [7-17]. Bone mineral density (BMD) is a differentiation that could be made between osteopenia versus osteoporosis (T score; −1 to

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−2.5 vs < −2.5 SD) respectively. Therefore, normal value is a T-score of -1 0r higher. In 1994, the world health organization (WHO) established a classification of bone mineral density (BMD) according to the standard deviation (SD) differences between a patients' BMD and that of a young-adult reference population. This value is how commonly expressed as a "T-score". A T-score that is equal to or less than -2.5 is consistent with a diagnosis of osteoprosis; a T-score between -1.0 and – 2.5 is classified as low bone mass (osteopenia); and a T-score of -1.0 or higher is normal [1]. Many studies have demonstrated that low BMD is associated with an increased risk of fracture [1, 12-17]. Another side-effects related to CBZ-therapy in epileptic patients could be mentioned as its' effect on metabolic events related to homocysteine levels that could be results as demethylation of methionine. To be metabolized, it needs cofactors folate, vitamin B6 and vitamin B12 which are needed in homocysteine metabolic pathway either through re-methylation or trans-sulfuration. Impaired homocysteine metabolic pathways results to hyperhomocysteinemia (hHcy). hHcy is a risk factor for decreased mental function in epileptic patients. It seems that AEDs may change metabolic pathways of homocysteine, leading to an alteration of plasma homocysteine levels. Hyperhomocysteinemia has been reported for some AEDs in epileptic patients after chronic treatment including with CBZ and sodium valproate. According to previous publications subsequent to AEDs serum biochemical such as homocysteine, folate, and vitamin B12 could be changed in epileptic patients. Treatment with most of the frequently used AEDs is linked with decreased folate or vitamin B12 serum concentrations and could be a risk factor for hyperhomocysteinemia.

Earlier studies described that CBZ provoke the production of an extensive variety of monooxygenase and conjugating enzymes. These agents are well recognized to decrease the level and activity of many lipid- and non-lipid-soluble drugs. As a result enzyme-inducing AEDs such as CBZ may deliver to the progress of a number of comorbidities, including osteoporosis, sexual dysfunction, vascular disease and cognitive function [17-24]. It is still not completely clear whether that long term treatment with CBZ, could be an important risk factor for metabolisms of bone and homocysteine [21]. As prescriptions of CBZ in Iranian epileptic patients increasing [2-5], therefore study of biochemical changes and bone turnover was of interest that investigated.

Materials and Methods

A cross-sectional study in patients under treatment with CBZ monotheray visited Isfahan Epileptic Clinics was carried out between the years 2012 to 2013. Only patients who received CBZ with no history or laboratory results expressive of liver or bone disease were nominated. Patients with CBZ monotherapy for a period of at least six months were entered in this study. The study was conducted at Isfahan Neurosciences Research Centre (INRC) and Isfahan Urology and Kidney Transplantation Centre and was approved by the Institute Research Ethics Committee (IREC; Grant No; 291158). For each subject BMD referred to be measured by dual X-ray absorptiometry called DXA technology. DXA measured bone mineral content (BMC in grams) and bone area (BA, in square centimeters), then calculated "area" BMD in g/cm2 by divided BMC by BA. T-score, the value used for diagnosis osteoporosis, is the mean BMD of a young-adult reference population from the patients' BMD divide by the standard deviation (SD) of young-adult population. Z-score, used to compare the patients' BMD to a population of peers, calculates by subtracting the mean BMD of an age, ethnicity and sex-matched reference population from the patients' BMD and divide by the SD of the reference population. Fasting morning blood was obtained for measurements of albumin, total calcium and CBZ. Sample for homocysteine, was collected in EDTA vial and was measured using Enzyme Immunoassay (EIA). Serum calcium concentrations were measured by standard autoanalzyer technique (normal, 8.2–10.6 mg/dl). Serum 1, 25-dihydroxyvitamin D (3) (normal range, 20–74 pg/ml) was measured by radioimmunoassay. Serum alkaline phosphatase (normal range, 4-40 u/l) was measured by competitive enzyme immunoassay. Trough level of CBZ (normal range, 7–14 mg/L) was measured by enzyme immunoassay for each patient. Levels of calcium, phosphate, alkaline phosphatase, demographic, clinical, hematological-biochemical and pharmacological data were recorded in d-Base.

Statistical analysis

Statistical analyses were done using the SPSS for windows, version 16 (SPSS Inc., Chicago, IL). Descriptive statistics such as means, median and range was calculated for variable of interest and correlation between variables was defined by Multiple Logistic Regression analysis (Step-Wise). A p value of ≤0.05 was considered as significant.

Results

Twenty-one patients (comprised of 10 females and 11 males) with a mean age of 27 years as ranged from 18 to 50 years were studied. The range for serum total alkaline phosphatase in patients received AEDs polytherapy was 87-559 IU/1, for those with CBZ monotherapy, the value ranged from 87 to 553 with a mean of 213 IU/1, seems to be significantly higher than normal values (60-360 IU/1, $p \leq 0.01$). With a mean homocysteine level of 9.6±1.7 (normal values; 5-15 µmol/ L), there was no correlation between CBZC0 and homocysteine levels (Pearson's correlation $r= 0.083$, $p \leq 0.63$). Folate (normal range; 2.7-17 ng/ml) or vitamin B12 (normal range; 200-800 pg/ml) levels tended toward the lower side of the reference ranges with a mean value of 3.4 ng/ml and 250 with disparities among individuals. This seems to be connected to a tendency toward higher mean corpuscular volume (MCV). As the mean normal value related to MCV ranged from 79 to 96 fl, in the small number of studied patients in here was with a mean of 84.9 fl that ranged from 59-120 fl. The mean level of serum calcium content was 7.8 mg/dl (ranged; 7.0-8.9 mg/dl) seems to be significantly $(p \leq 0.04)$ lower when compared to normal values, ranged from 8.2 to

10.6 mg/dl. In compare to normal value related to serum phosphorus levels (2.5-4.5 mg/dl) the mean value in population studied was 2.3 mg/dl as ranged from 2.3 to 4.0 mg/dl in population studied. BMD Z-scores and 25-

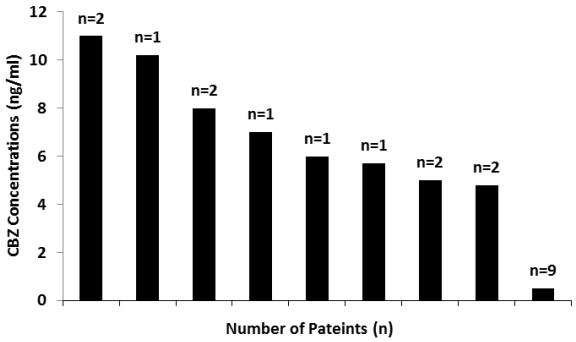

Figure 1 Variability of CBZ concentrations among twenty one epileptic patients.

dihydroxyvitamin D3 concentrations did not differ significantly. The mean 25-dihydroxyvitamin D3 seems to lie in lower parts of recommended normal values or 20-60 pg/ml. The mean value in population studied was 27.99 pg/ml with a range of 20 to 40.2 ng/ml. BMD was 0.809±0.017 g/cm2 (hip) and Z-score was −0.4±0.2. In the small number of females it seems that BMD at the femoral neck decreased. In the 8 out of 21 patients the minimum concentration for CBZ ranged from 4.8 to 8 mg/ml. As shown in figure 1, CBZ C0 was associated with marked irregularity and large discrepancy with a mean value of 6.8 ng/ml ranged from 0. 5 to 11 ng/ml (normal range; 4-12 ng/ml).

Discussion

For management of epileptic patients, considering of many factors behind a good approach to control convulsion attack seems to be necessary. Within this population morbidity and mortality related to hip fractures and cardiovascular disease have been reported to be widespread. Therefore, attention to metabolism related to bone and homocysteine could be categorized as one of the most important issue. As a result, in this study we aimed to investigate the effect of CBZ as a higher prescribed or best seller AEDs on metabolism of bone and biochemical markers such as homocysteine, folate, vitamin B12 and alkaline phosphatase levels. In spite of the side-effects of some AEDs including carbamazepine as an enzyme inducer and valproate sodium as an enzyme inhibitor of Cytochrome P450, there are limited data in our epileptic patients regarding the monitoring and treatment of bone health and bone disease in this population. Many studies recommend that patients with epilepsy under treatment with AEDs have an increased risk of fracture, low BMD, and variations in bone metabolism and showed an association between uses of anticonvulsant medications, reduced bone mineral density, and increased fracture risk. [12-15] Fall during convulsion attack, instability, immobility and a hereditary tendency to low BMD could be mentioned as several issues that expected to contribute related to the increased risk. [15] Fracture risks in patients with CBZ have been reported by many authors as 1.88% (95% CI;1.33–2.65), 1.31% (95%CI; 1.14–1.51). [7] In agreement with previous studies, serum alkaline phosphatase (ALP) levels were higher in patients. [12-17] Previous evidence suggests that CBZ affects bone metabolism by changing or reducing vitamin D concentrations. [17-24] In patients with epilepsy vitamin D receptor polymorphism is linked to low BMD, that could be arbitrated throughout vitamin D-parathormone mechanism [16]. According to many previous publications B6, B12 and folate are necessary for the metabolism of homocysteine to methionine [17-23]. An increase in serum levels of homocysteine could be a cause for hyperhomocysteinemia,[25] however due to inter and intra individual variability further studies on epileptic patients are needed to confirm this correlation with CBZ-montherapy. There is data indicating that homocysteine might be a risk factor for stroke and dementia. It has been shown that some enzyme inducer AEDs through cytochrome P450 might cause disparities in cholesterol, lipoprotein and homocysteine. Raised serum levels of homocysteine are a tough and self-directed prognosticator for augmented danger of atherosclerosis development in a dose-dependent consensus. This situation could lead to an increased level of the latent threat production for heart disease and endothelial dysfunction, asymmetric dimethylarginine or the regulator of nitric oxide. Asymmetric dimethylarginine is a product of methylation of L-arginine and endogenous nitric oxide synthase inhibitor. Nitric oxide plays a role in the seizure attack [21].

Finally, due to small size of patients in this study, further clinical investigations are desirable to monitor the prescription of CBZ in terms of therapeutic drug monitoring (TDM) among Iranian Epileptic population and its' association to bone, other biochemical variables and cardiovascular disease.

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Conflict of Interest

The authors declare no conflicts of interest.

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