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The effects of oxcarbazepine treatment on vitamin B12 and folate levels, thyroid functions, sex hormones, and bone mineral density in epileptic patients

Research Article

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Abstract: The aim of this study was to evaluate vitamin B12 and folate levels, thyroid functions, sex hormones and bone mineral density in idiopathic epileptic patients taking oxcarbazepine as monotherapy. Newly diagnosed pediatric patients with idiopathic partial epilepsy taking oxcarbazepine (OXC) as monotherapy were enrolled in this study. The pre-treatment and 6 months post-treatment values of vitamin B12, folate, thyroid functions, sex hormones, and bone mineral density (BMD) were obtained from all patients. A total of 32 patients (22 (68.8%) males and 10 (31.2%) females) were included in this study. The mean age was 7.4 ± 3.2 years (range: 2-14 years). There were no significant differences between the pre-treatment and 6 months post-treatment values of vitamin B12, folate, thyroid functions, sex hormones, and BMD. However, the 6 month post-treatment sex hormone binding globulin (SHBG) values (159.92 ± 48.14 nmol/L) were significantly higher than the pre-treatment values (137.88 ± 43.12 nmol/L) (p=0.009). We found that OCX treatment in children did not have an effect on serum folate and vitamin B12 levels, thyroid functions, sex hormones and BMD but caused increased SHBG. Over time, the increase in serum SHBG levels may lead to diminished bioactivity of sex steroids, and thus to reduced fertility. The further studies are needed to demonstrate the clinical importance of increased SHBG levels.

Keywords: *Epilepsy • Oxcarbazepine • Vitamin B12 • Hormones • Bone mineral density*

1. Introduction

There are a large number of studies regarding the effects of traditional antiepileptic drugs on serum vitamin B12 and folate levels, thyroid functions, sex hormones and bone mineralization. Folic acid and vitamin B12 are required for the conversion of homocysteine to methionine. Serum folic acid and vitamin B12 levels may be influenced by antiepileptic drug usage [1-6]. Some antiepileptic drugs have been reported to decrease serum thyroxine levels; however the patients have remained clinically euthyroid [7-9]. In females, hyperandrogenism, menstrual disorders, polycystic ovary and hyperinsulinism, and in males, impaired sperm quality and motility, delayed sexual development and small testes have been reported [10,11]. They may therefore cause important changes in adolescents during pubertal development and on fertility. Additionally, it has been known for over 30 years that some antiepileptic drugs have predisposed patients to bone fractures by decreasing bone mineral density (BMD) [12-16].

Oxcarbazepine (OXC) is widely used for the treatment of partial and secondary generalized seizures in adults and children. It is the 10-keto analog of carbamazepine (CBZ) and is metabolized through different pathways compared to CBZ in the liver. There are only a few studies that have focused on the effects of OXC on vitamins, hormones and bone mineralization. The aim of this study was to evaluate vitamin B12 and folate levels, thyroid functions, sex hormones and BMD in idiopathic partial epileptic patients taking OXC.

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Table 1. Comparison of pre-treatment and 6 months post-treatment folate and vitamin B12 levels.

	Pre-treatment+	Post-treatment+	p value*
Vitamin B12 (pg/mL)(N: 197-866)	540.63±285.65	597.85±333.69	0.318
Folate (ng/mL)(N: 3.1-17.5)	9.47±3.76	9.09±2.92	0.547

+Data were shown as mean ± standard deviation.
** Statistical analysis was performed by related samples t-test. The level of statistical significance was set at p<0.05.*

2. Material and Methods

Newly diagnosed pediatric patients with idiopathic partial epilepsy (aged 2-14 years) were enrolled in this study. We excluded from the study: patients who were on antiepileptic drugs or any other drugs that could affect bone metabolism (*e.g.*, non-steroidal anti-inflammatory drugs, calcium, vitamin D, multivitamin preparations); who were non-ambulatory; who had any neurologic deficit and underlying renal, hepatic, endocrine, cardiac, neurometabolic or any other chronic diseases, and whose treatment were discontinued before 6 months. . Their diagnostic tests including cranial magnetic resonance imaging, tandem-mass spectrophotometry, urinary and blood amino acid and organic acid screening were all normal.

Blood samples were obtained between 8.00 and 8:30 a.m. after an overnight fasting, and samples were stored frozen at -80°C until analyzed. OXC was administered twice daily (30 mg/kg/day) to all patients. Pre-treatment and 6 months post-treatment complete blood count, serum glucose, urea, creatine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), calcium, phosphate, alkaline phosphatase (ALP), folate, vitamin B12, thyroid and sex hormone levels, and BMD were obtained for all patients. The levels of serum folate and vitamin B12 were measured in the autoanalyser Immulite 2000, by using suitable kits, (DPC Diagnostic Products Corporation, Los Angeles, USA) and pursuant to its user guide kit by immune-assay method. Free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) levels were measured with the immunochemiluminescent measurement technique on the ADVIA Centaur (Bayer Corporation, Tarrytown, NY) device. Sex hormone binding globulin (SHBG) levels were measured with the immunochemiluminescent technique on the IMMULITE 1000 (DPC-Diagnostic Products Corporation, Los Angeles, CA, USA) device. Free testosterone (fT) levels were measured with a radioimmunassay kit (Diagnostic System Laboratories, TX, USA). BMD values were measured by dual energy x-ray absorbtiometry (DXA) at L2-L4 levels of the lumbar vertebrae using a DXA Norland (Fort Atkinson, WI. USA) XR-36 densitometer.

Approval for the study was obtained from our hospital ethics committee and informed consent was taken from the parents.

Descriptive statistics were shown as mean standard deviation. Log transformed was done for parameters and then statistical analysis was performed by related samples t-test. $P<0.05$ was considered statistically significant.

3. Results

A total of 32 patients (22 (68.8%) males and 10 (31.2%) females) were included in this study. The mean age was 7.4 ± 3.2 years (range: 2-14 years). Pre-treatment and 6-months post-treatment complete blood count, serum glucose, urea, creatinine, AST, ALT, serum calcium, phosphate and ALP values were within normal limits. There were no significant differences between pre-treatment and 6-months post-treatment values for serum folate, vitamin B12, thyroid and sex hormones (FSH, LH, E2) and BMD (Tables 1, 2, 3, respectively). However, 6-months post-treatment SHBG values were significantly higher than the pre-treatment values (Table 2).

4. Discussion

Antiepileptic drugs have many side effects on some vitamins, thyroid functions, sex hormones and bone mineralization. Some antiepileptic drugs have been shown to cause hyperhomocysteinemia by decreasing serum folate levels [1,4-6]. Karabiber *et al.* found significantly lower serum folate levels and higher homocysteine levels in CBZ group compared to the control group [1]. Apeland et al. have observed a decrease in folic acid levels and an increase in homocysteine levels in 42 adult patients taking CBZ as monotherapy [5]. Vitamin B12 levels have been shown to change according to the antiepileptic medication used [1,17,18]. It has been reported that CBZ treatment has decreased vitamin B12 levels and increased homocysteine levels [19-21]. It can therefore be said that patients using CBZ are under the risk for atherosclerotic vascular disease due to the increase in the plasma homocysteine levels [2].

Table 2. Comparison of pre-treatment and 6 months post-treatment thyroid and sex hormone levels.

	Pre-treatment+	Post-treatment+	p value*
fT3 (pg/dL)(210-440)	368±71	380±54	0.311
fT4 (ng/dL)(0.8-2.2)	1.27±0.46	1.24±0.48	0.374
TSH (μIU/mL)(0.7-6.4)	2.1±1.17	2.31±1.31	0.348
FSH (mIU/mL)(0.26-3)	2.11±2.34	1.88±1.57	0.414
LH (mIU/mL)(0.02-0.3)	0.22±0.39	0.36±0.78	0.213
Estradiol (pg/mL)(11-38)	5.65±1.42	6.14±2.92	0.413
SHBG (nmol/L)(29-141)	137.88±43.12	159.92±48.14	0.009
fTestosterone (pg/mL)(0.1-0.2)	0.72±0.88	0.97±1.01	0.111

+ Data were shown as mean ± standard deviation.
** Statistical analysis was performed by related samples t-test. The level of statistical significance was set at p<0.05.*

Table 3. Comparison of pre-treatment and 6 months post-treatment BMD values.

Bone mineral density	Pre-treatment+	Post-treatment+	p value*
Total L1-L4 (g/cm^2) (n=32)	0.494±0.102	0.537±0.127	0.255
Z score (n=32)	0.99±0.70	0.90±1.08	0.821

+ Data were shown as mean ± standard deviation.
** Statistical analysis was performed by related samples t-test. The level of statistical significance was set at p<0.05.*

Six months of OXC-therapy did not change the levels of serum folate and vitamin B12.

Many studies have reported that some antiepileptic drugs have influenced thyroid hormone levels [7-9,22]. Cramer and Jones reported that fT4 levels were low in patients taking CBZ [23]. Eiris-Punal *et al.* have reported low T4 and high TSH levels in patients taking CBZ and that subclinical hypothyroidism could develop in these patients [24]. Caksen *et al.* reported that, although statistically not significant, long-term CBZ treatment caused a decrease in serum total and free T4 levels and that T4 levels returned to normal once the treatment was discontinued [25]. It has been reported that thyroid hormone changes during CBZ treatment were associated with the increase in thyroid hormone metabolism and the activation of hepatic P-450 enzyme system [7]. It has also been reported that OXC in high doses caused the activation of hepatic P-450 enzyme system. In our study, we did not find any significant differences between the pre-treatment and 6-months post-treatment fT3, fT4 and TSH levels.

It has been reported that some antiepileptic drugs affected pubertal development or fertility of adolescents by changing sex hormone levels [10,11]. It is not known whether such effects are due to the epilepsy itself or the antiepileptic drugs [26]. CBZ treatment has been reported to cause hyposexuality, impotence and menstrual disorders in adults by influencing the levels of sex steroids and SHBG. Isojarvi *et al.* showed that CBZ treatment increased the SHBG levels [9,27]. The increase in SHBG levels results in decreased serum levels of bioactive E2 and testosterone [9,28]. SHBG is synthesized in the liver and is an effective stimulant of the liver microsomal enzyme system like CBZ. CBZ probably increases the blood SHBG level directly by increasing its synthesis in the liver. Some authors suggest that increased sex hormone metabolism increases the SHBG levels [29]. It has been reported that OXC can affect sex hormone metabolism, especially at high doses [10,28]. We did not find statistically significant differences between the pre-treatment and 6-months post-treatment FSH, LH, E2 and fT levels. However, post-treatment SHBG values were higher than the pre-treatment values. It may be associated with liver enzymes inducing caused by OXC.

It has been reported that antiepileptic drugs might predispose to bone fractures in patients by decreasing the BMD [12-15]. Osteomalacia or osteoporosis developing in patients using antiepileptic drugs can present, with radiological, biochemical and pathological findings. However, it may rarely cause clinical findings. Akin *et al.* have reported that BMD was not affected in epileptic patients receiving CBZ treatment [16]. Vestergaard et al. have found a significant relation between antiepileptics affecting the liver such as CBZ and OXC and increased fracture risk [30]. These antiepileptic drugs influence the cytochrome P 450 system in the liver and increase the vitamin D catabolism. The decreased intestinal calcium absorption as a result of the induction of the cytochrome P 450 enzyme system can lead to inactive vitamin D production, secondary hyperparathyroidism, increased urinary calcium and phosphate excretion and increased bone turnover, resulting in BMD reduction [12,13]. We did not find a significant difference between the pre-treatment and 6-months post-treatment BMD values.

In conclusion, we found that OCX treatment in children did not have any effect on serum folate and vitamin B12 levels, thyroid functions, sex hormones and BMD values within the first 6 months. However, we found that OCX treatment increased SHBG levels. Over time, the increase in serum SHBG concentrations may lead to diminished bioactivity of sex steroids, and thus to reduce fertility. Therefore, further studies are needed to demonstrate the clinical importance of increased SHBG levels.

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