May Long Term Oxcarbazepine Treatment Be Lead to Secondary Hyperparathyroidism?

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Background and Purpose The adverse effects of newer antiepileptic drugs are not well-known. This study assessed the impact of oxcarbazepine (OXC) treatment on bone turnover.

Methods Forty-four children with idiopathic focal (and/or secondarily generalized) epilepsy who had been treated with OXC for more than 1 year were compared with 33 healthy, age- and sex-matched children. Serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone, osteocalcin, calcitonin, and 25-hydroxyvitamin D, and bone mineral density were measured to evaluate and compare bone mineralization between the two groups.

Results The serum levels of calcium, osteocalcin, 25-hydroxyvitamin D, and bone mineral density did not differ significantly between the study and control groups. However, serum levels of parathyroid hormone, alkaline phosphatase, phosphorus, and calcitonin differed significantly between the two groups.

Conclusions These findings suggest that OXC treatment leads to secondary hyperparathyroidism with high-turnover bone disease and/or impaired intestinal calcium absorption.

Key Words oxcarbazepine, bone mineralization, children.

Introduction

Long-term use of antiepileptic drugs (AEDs) renders a patient more vulnerable to their side effects,1,2 and the patient must then struggle with these side effects in addition to the primary disease. Although several studies have shown that commonly used AEDs may lead to osteopenia/osteoporosis, osteomalacia, and bone fractures,3,4 there is little information available on the effect of oxcarbazepine (OXC) on bone metabolism.5,6 Mintzer et al.7 demonstrated that OXC monotherapy significantly reduced the level of 25-hydroxyvitamin D (25-OHD), and changed other bone biomarkers in a pattern suggestive of secondary hyperparathyroidism. Although OXC is only a limited enzyme inducer, they stated that OXC may have some dose-dependent cytochrome P-450 (CYP-450) induction properties, or may have an effect on osteoblast proliferation.

It might be possible to avoid the side effects of OXC if the underlying mechanisms were known. Several markers, such as serum levels of 25-OHD and calcium, and bone mineral density (BMD), have been used to identify these side effects. The present study assessed the effects of OXC monotherapy on bone mineralization in terms of the serum levels of parathyroid hormone (PTH), alkaline phosphatase (ALP), calcium, phosphorus, 25-OHD, osteocalcin, and calcitonin, and the BMD.
Table 1. Demographic and laboratory findings of the patients

|                     | Study group (mean±standard deviations) | Control group (mean±standard deviations) | p     |
|---------------------|----------------------------------------|------------------------------------------|-------|
| Age (year)          | 9.65±3.04                              | 10.24±2.86                               | NS*   |
| Sex [M/F]           | 22/22                                  | 17/16                                    | NS**  |
| Ca (mg/dL)          | 10.13±0.41                             | 9.95±0.39                                | 0.059*|
| P (mg/dL)           | 4.99±0.50                              | 4.62±0.62                                | 0.003*|
| ALP (U/L)           | 326±92                                 | 274±84                                   | 0.011*|
| PTH (pg/mL)         | 42.95±10.49                            | 35.70±9.79                               | 0.003*|
| Calcitonin (pg/mL)  | 2.16±0.54                              | 2.70±1.42                                | 0.046*|
| Osteocalcin (ng/mL) | 23.68±8.66                             | 21.85±2.67                               | 0.193*|
| 25 Hydroxy Vit D3 (ug/L) | 20.23±4.77               | 21.04±3.70                               | 0.421*|
| Z score             | -0.15±1.14                             | -0.35±0.92                               | 0.374*|
| BMD (g/cm²)         | 0.64±0.25                              | 0.78±0.22                                | 0.419*|

* t-test, **Chi-square test.
ALP: alkaline phosphatase, BMD: bone mineral density, Ca: calcium, M/F: male/female, NS: not significant, P: phosphorus, PTH: parathyroid hormone.

Methods

This study involved two groups: group 1 comprised 44 children aged between 5 and 15 years with idiopathic focal (and/or secondarily generalized) epilepsy who had been treated with OXC as a first-line AED for at least 1 year, while group 2 was the control group that comprised 33 healthy, age- and sex-matched children. Patients with height and weight measurements below the 3rd percentile, using any drug that may affect bone metabolism, receiving any other AED, and with chronic illnesses other than epilepsy were excluded from the study. Serum levels of PTH, ALP, calcium, phosphorus, 25-OHD, osteocalcin, and calcitonin, and the BMD value were evaluated in both groups and statistically compared.

Blood samples were obtained at between 8:00 and 8:30 a.m. after an overnight fast. The serum fraction was obtained by centrifugation (at 20000×g for 10 min at 4°C) after storing the whole blood at room temperature for 1 hour. Serum was stored at -80°C until analysis. Serum levels of calcium, phosphorus, and ALP were measured spectrophotometrically with an autoanalyzer using commercial kits (AU-2700, Olympus, Hamburg, Germany). The serum level of 25-OHD was determined using a high-performance liquid chromatography system with a fluorescence detector. Serum levels of PTH, osteocalcin, and calcitonin were determined with a chemoluminescence technique using an autoanalyzer with commercial kits (Roche E 170, Roche Diagnostics, Mannheim, Germany).

BMD was assessed using dual-energy X-ray absorptiometry (QDR4500 Elite Hologic, Bedford, MA, USA) in the lumbar spine at levels L2-L4. Approval for this study was obtained from the Medicine Ethics Committee of Gulhane Military Medical Academy Faculty. Informed consent to participate was obtained from the parents of all patients.

Statistical methods

All data analysis was performed using the SPSS 11.5 package program (SPSS, Chicago, IL, USA). Continuous and categorical variables are expressed as mean±SD values and percentages and frequencies, respectively. Comparisons between groups were performed by t-test. The sex distributions for group 1 (study group) and group 2 (control group) were compared by Chi-square test. The level of statistical significance was set at p<0.05.

Results

The study group (group 1; n=44) comprised 22 males (50%) and 22 females (50%) aged between 5 and 15 years (9.65±3.04 years). The control group (group 2; n=33) comprised 17 males (51%) and 16 females (49%), all healthy, aged between 5 and 15 years (10.24±2.86 years). The mean duration of OXC therapy in group 1 was 16 months (12-23 months). The serum levels of PTH, ALP, phosphorus, and calcitonin differed significantly between the study and control groups (p<0.003, 0.011, 0.005, and 0.046, respectively). However, for the serum levels of calcium, osteocalcin, and 25-OHD, and the BMD did not differ significantly between the two groups. The biochemical and bone-turnover parameters are presented in Table 1.

Discussion

Several studies have shown that the affect of AEDs on bone metabolism may lead to osteopenia/osteoporosis, osteomalacia, and bone fractures. Hypocalcemia in patients with refractory epilepsy may lead to osteopenia and osteoporosis that could eventually increase the number of bone fractures, which makes the follow-up of epileptic patients more difficult. The present study detected increased serum levels of PTH, ALP,
and phosphorous, decreased serum levels of calcitonin, and normal levels of calcium in patients with idiopathic focal (and/ or secondarily generalized) epilepsy who had been receiving OXC monotherapy as a first-line AED for more than 1 year.

Long-term AED treatment is known to affect bone metabolism.7 Although the incidence of bone disease due to AEDs was reported in the literature to be 19-56%, only 8% of those patients had radiologically confirmed rickets.11 The prevalence of osteomalacia in patients receiving long-term AEDs was reported to be 10-30%, while those of hypocalcemia increased serum levels of ALP were 10-30% and 40%, respectively.12

Many theories have been proposed to explain the effects of AED use in relation to the pathogenesis of bone disease, although the exact mechanism remains to be established.7 An increase in serum PTH levels associated with AED therapy has been reported.7,13-15 Mintzer et al.7 suggested that by inducing the CYP-450-mediated catabolism of 25-OHD to less biologically active metabolites, AEDs lead to a decrease in vitamin-D-mediated bone mineralization and intestinal calcium absorption. This in turn causes a compensatory increase in PTH, which stimulates the production of 1α-hydroxylase, the enzyme responsible for the conversion of 25-OHD to 1,25-dihydroxyvitamin D (1,25-OHD), which explains the maintenance of 1,25-OHD levels seen in AED-treated patients.7 The chronic elevation of PTH required to maintain 1,25-OHD levels, which is referred to as secondary hyperparathyroidism, causes an increase in bone turnover, which leads to long-term loss of bone mass. Similarly, Bouillon et al.15 reported increased PTH levels, low serum 25-OHD levels, and relative hypocalemia in patients receiving anticonvulsant treatment. In the present study we found increased serum levels of PTH, ALP, and phosphorous, decreased calcitonin levels, and normal serum 25-OHD and calcium levels, which may also be referred to as secondary hyperparathyroidism. In secondary hyperparathyroidism, serum calcium levels are often maintained within the normal range and ALP levels are elevated, which is thought to be related to compensatory stimulation of osteoblastic activity in bone.10

ALP measurement is an adjunct test for assessing high bone turnover.17 High ALP levels are generally related to liver or bone disease, which can be differentiated by a concurrent increase in liver function tests or bone biochemical parameters. The normal liver function tests in the present study suggested to us that high ALP levels are more suggestive of bone disease than liver disease. Verrotti et al.18 reported increased bone-turnover markers independent of vitamin D deficiency in patients receiving AEDs. Another study found normal serum levels of vitamin D metabolites, and bone biopsies revealing increased osteoid formation but normal calcification, accelerated mineralization rate, and decreased mineralization lag time (indicative of increased bone turnover) in patients receiving long-term AED therapy.14 Therefore, OXC might have effects on osteoblastic activity, osteoid formation, and calcification, although osteoblasts may synthesize sufficient osteoid while mineralization may be deficient.

Another suggested mechanism is the ineffective absorption of fat-soluble vitamin D and/or impaired intestinal calcium absorption. In a study of rats that examined the effects of AEDs on intestinal calcium transport, rats treated with phenytoin had markedly decreased calcium absorption.19 OXC may thus have interfered with intestinal calcium absorption in the patients in the present study. The other proposed mechanism is calcitonin deficiency. Calcitonin is a hormone that is produced by the thyroid gland and inhibits osteoclast-mediated bone resorption. In an in vitro study by Vernillo et al.,20 calcitonin secretion was reduced in osteoblastic rat osteosarcoma cells exposed to phenytoin in the culture media, compared with control cells. Thus, calcitonin deficiency may accelerate bone turnover, resulting in increased bone resorption.3 In the present study we found a decrease in calcitonin levels that may have been associated with OXC treatment.

In conclusion, OXC treatment may cause increased serum levels of PTH, ALP, and phosphorous, and decreased levels of calcitonin, which may be due to the induction of CYP-450-mediated catabolism of 25-OHD to less biologically active metabolites, or to high-turnover bone disease or impaired intestinal calcium absorption. In turn, this may cause a compensatory increase in PTH and an increase in bone-turnover markers. It should be kept in mind that OXC treatment may lead to secondary hyperparathyroidism and that such patients should be routinely followed-up with regular PTH, ALP, phosphorous, and calcitonin blood biochemistry testing.

Conflicts of Interest
The authors have no financial conflicts of interest.

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