ELSEVIER

Evaluation of Bone Turnover in Epileptic Children Using Oxcarbazepine

Ali Cansu, MD*, Ediz Yesilkaya, MD†, Ayşe Serdaroğlu, MD*, Tuğba Lüleci Hırfanoğlu, MD*, Orhun Çamurdan, MD†, Özlem Gülbahar, MD‡, Kıvılcım Gücüyener, MD*, and Peyami Cinaz, MD†

This study evaluated the effects of oxcarbazepine monotherapy on bone turnover in prepubertal and pubertal children. Thirty-four newly diagnosed pediatric patients with normal bone mineral density, serum biochemical markers of bone formation, and hormonal markers participated. Levels of 25-hydroxyvitamin D were significantly decreased after therapy compared with baseline values. Levels of γ-glutamyl transferase, phosphorus, alkaline phosphatase, osteocalcin, parathyroid hormone, and calcitonin had increased. However, only changes in osteocalcin and γ-glutamyl transferase levels were statistically significant compared with baseline values. Drug-induced osteopenia was evident in 3 patients with *z* scores of bone-mineral density less than −2.0, whereas these patients had *z* scores of less than −1.5 before treatment. Although 18 months of oxcarbazepine treatment exerted slightly adverse effects on bone metabolism, the effect seems insignificant in children with normal bone-mineral density. Although alterations in bone metabolism do not always suffice to explain the decrease in bone-mineral metabolism, we think that patients with osteopenia before the initiation of oxcarbazepine therapy should be followed carefully, especially in long-term treatment. **© 2008 Published by Elsevier Inc.**

Cansu A, Yesilkaya E, Serdaroğlu A, Hırfanoğlu TL, Çamurdan O, Gülbahar O, Gücüyener K, Cinaz C. Evaluation of bone turnover in epileptic children using oxcarbazepine. Pediatr Neurol 2008;39:266-271.

Introduction

A number of recent reports indicate that many antiepileptic drugs used in children (e.g., phenytoin, valproic acid, phenobarbital, and carbamazepine) cause a deterioration of bone mineralization [1-5]. The most frequently suggested mechanism behind such decreased bone-mineral density because of antiepileptic drug use involves the hepatic induction of the P-450 enzyme system, leading to increased catabolism of 25-hydroxyvitamin D, and causing relative hypocalcemia, increased levels of parathyroid hormone, and subsequent low bone-mineral density [3,4,6,7]. Direct effects of these drugs on bone cells were proposed as another mechanism of bone-mineralization defects in these patients [8,9]. The exact mechanisms are as yet unclear [4,5,10].

It was suggested that newer antiepileptic drugs may be less likely to exert adverse effects on bone, but very few reports are in favor of this suggestion [4,8]. Oxcarbazepine, a keto-derivative of carbamazepine, is a new antiepileptic drug whose structure closely resembles that of carbamazepine [11]. Its advantages over carbamazepine include better tolerability [12,13], a lower risk of allergic cutaneous reactions, a lower propensity for drug-drug interactions, and fewer metabolic and endocrine effects [13-16]. These advantages are attributable to the different biotransformation of oxcarbazepine. In contrast to carbamazepine, oxcarbazepine has a different metabolic pathway in the liver. It is mainly metabolized by reduction rather than oxidation, and does not appear to induce the oxidative P450-enzyme system to the same extent as carbamazepine [17,18]. Thus, oxcarbazepine was suggested as a safe antiepileptic drug since it has less induction effect on liver

From the *Department of Pediatric Neurology, †Department of Pediatric Endocrinology, and ‡Department of Biochemistry, Gazi University School of Medicine, Ankara, Turkey.

Communications should be addressed to:
Dr. Yeşilkaya; Pediatrik Endokrinoloji Bilim Dalı;
Gazi Üniversitesi Tıp Fakültesi; Ankara, 06500 Turkey.
E-mail: eyesilkaya@yahoo.co.uk
Received March 14, 2008; accepted July 16, 2008.

© 2008 Published by Elsevier Inc.
doi:10.1016/j.pediatrneurol.2008.07.001 • 0887-8994/08/$—see front matter

enzymes [19,20]. However, oxcarbazepine at higher doses causes an induction of liver enzymes, affects thyroid hormones in a manner similar to that of carbamazepine in children during early phases of treatment, decreases the efficacy of oral contraceptives, and increases the prevalence of polycystic ovaries [16,21-23].

This study investigated the effects of oxcarbazepine monotherapy on levels of γ-glutamyl transferase, 25-hydroxyvitamin D, biochemical bone markers (calcium, phosphorus, alkaline phosphatase, osteocalcin, parathyroid hormone, and calcitonin), and bone-mineral density in prepubertal and pubertal epileptic children without osteopenia or osteoporosis.

Materials and Methods

Thirty-four newly diagnosed pediatric patients (18 prepubertal, and 16 pubertal) with idiopathic partial epilepsy were prospectively enrolled in this study. Pubertal stage was determined according to the system of Marshall and Tanner. We included patients who were not receiving antiepileptic drugs or any other drugs that could affect bone metabolism (e.g., nonsteroidal anti-inflammatory drugs, calcium, vitamin D, or multivitamin preparations), and who were ambulatory, without any neurologic deficits and underlying renal, hepatic, endocrine, cardiac, neurometabolic, or other chronic diseases. Diagnostic tests, including cranial magnetic resonance imaging, tandem-mass spectrophotometry, and urinary and blood amino-acid and organic-acid screening, all produced normal results.

Descriptions of seizure type followed the criteria of the International League Against Epilepsy [24]. The antiepileptic drug dose used was chosen according to generally accepted guidelines [25]. Oxcarbazepine was administered twice daily. Control of epilepsy was good in all patients enrolled, and after the first month of treatment, no patients exhibited more than 2 seizures during treatment.

We calculated daily calcium and phosphorus intake with a 3-day diet history, and all patients demonstrated adequate intake according to recommendations of daily allowance [26]. Height and weight were measured for all children, and all were within normal percentiles for the Turkish pediatric population [27,28]. Hand-wrist radiographs were evaluated for bone maturation. All of these evaluations were performed at the beginning and end of the study. Pubertal stages were determined according to the classification of Tanner and Whitehouse [29]. Patients at stage II and above were considered pubertal. Five subjects who were prepubertal at the onset of the study, but who entered puberty during the study, were excluded.

Among the recruited patients, one was excluded for social reasons, one because of another disease affecting bone metabolism, and 8 because a second antiepileptic drug had to be added to their treatment of persistent epileptic attacks. Finally, serum γ-glutamyl transferase, calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D, osteocalcin, parathyroid hormone, calcitonin, and bone-mineral density were evaluated at baseline and at month 18 in 34 patients.

Blood samples were obtained between 8:00-8:30 AM after an overnight fast, and samples were stored frozen at −70°C until analysis. Levels of serum proteins, γ-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, creatinine, blood urea nitrogen, calcium, magnesium, and phosphate were determined by spectrofluorometric analysis.

Serum 25-hydroxyvitamin D levels were determined using a liquid chromatographic system equipped with a Thermo Finnigan high-performance liquid chromatography system, connected to an ultraviolet (UV-1000) detector (Thermo Electron Corp., Woodstock, GA). Detection was performed at 264 nm. We used a C_{18} analytical column to provide further separation of analytes from other endogenous plasma components before detection.

Serum osteocalcin concentrations were measured with DSL-6900 radioimmunoassay kits from Diagnostic Systems Laboratories, Inc. (Webster, TX), with a sensitivity of 0.6 ng/mL and intra-assay and interassay coefficients of variation of 7.4% and 6.7%, respectively. Serum parathyroid hormone concentrations were measured with DSL-8000 radioimmunoassay kits, with a sensitivity of 12 pg/mL and intra-assay and interassay coefficients of variation of 5.7% and 4.5%, respectively. Serum calcium concentrations were measured spectrophotometrically using a DAX Technicon 48 (Bayer Corp., Tarrytown, NY) with O-cresolphthalein complexone. Serum phosphorus concentrations were measured spectrophotometrically with a DAX Technicon 48, using ammonium heptamolybdate. Serum alkaline phosphatase concentrations were measured spectrophotometrically with a DAX Technicon 48, using the methods of the American Association of Clinical Chemistry and International Federation of Clinical Chemistry. Serum concentrations of monohydroxy-carbamazepine (the active metabolite of oxcarbazepine) were determined at months 3 and 18 of therapy, using high-performance liquid chromatography.

Bone-mineral density was assessed using dual-energy x-ray absorptiometry (Norland XR-36 analyzer, Norland Corp., Fort Atkinson, WI) in the lumbar spine at levels $L_{2\text{-}4}$ and in the femur neck. Drug-induced osteopenia was defined as a z score of −2.0 or more [30]. Approval for this study was obtained from the Gazi University Faculty of Medicine Ethics Committee. Informed consent was received from parents.

Statistical Analysis

Analysis of all data was performed using the SPSS 11.5 packet program (SPSS Corp., Chicago, IL). Continuous variables were expressed as means ± standard deviations, and categorical variables as percentages. Repeated-measures analyses of variance were used to evaluate serum parameters, except for bone-mineral density and levels of parathyroid hormone. Comparisons within groups were performed with a paired-samples t test. Basal and month 18 bone-mineral density and parathyroid hormone levels were compared using the Wilcoxon test. Statistical significance was set at $P < 0.05$.

Table 1. Clinical characteristics of patients receiving oxcarbazepine

	Dosage of OXC (mg/kg/day)				Type of Epilepsy		Puberty Stage		DSC (μg/mL)	
N	25	30	35	40	P	G	Prepubertal	Pubertal	Month 3	Month 18
34	6	10	12	6	34	0	18	16	21.09 ± 6.33	24.50 ± 6.98

Abbreviations:
DSC = Drug serum concentration
G = Generalized
OXC = Oxcarbazepine
P = Partial

Results

The clinical characteristics of patients are given in Table 1. At month 18, levels of serum calcium, phosphorus, alkaline phosphatase, osteocalcin (only in prepubertal patients), parathyroid hormone, calcitonin, and bone-mineral density were different from the initial values. However, these differences were not statistically significant. Serum gamma glutamyl transferase, 25-hydroxyvitamin D, and osteocalcin values at month 18 in control subjects were statistically significant compared with those of at month 0 ($P < 0.05$) (Table 2).

At the end of 18 months of oxcarbazepine treatment, 2 prepubertal patients and 1 pubertal patient manifested osteopenia, with declines in z score of bone-mineral density from −1.84, −1.68, and −1.80 to −2.12, −2.11, and −2.12, respectively. Among the 3 patients who developed osteopenia, 2 had slightly increased levels of parathyroid hormone, osteocalcin, and alkaline phosphatase, whereas calcitonin and 25-hydroxyvitamin D levels were similar. One had a slightly increased level of parathyroid hormone, with no difference in osteocalcin and calcitonin levels. A minimal decrease in 25-hydroxyvitamin D level was detected.

There were no correlations between levels of serum γ-glutamyl transferase, calcium, phosphorus, alkaline phosphatase, parathyroid hormone, osteocalcin, calcitonin, and 25-hydroxyvitamin D and bone-mineral density val-

Table 2. Laboratory data of children treated with OXC

OXC (n = Patients)	Pretreatment (Month 0)	Month 18	*P* Value
GGT*			
Prepubertal (n = 18)	21.61 ± 7.33	28.89 ± 10.76‡	0.035
Pubertal (n = 16)	16.25 ± 6.09	23.81 ± 9.22‡	0.033
Total (n = 34)	19.09. ± 7.21	26.50 ± 10.24‡	0.003
Calcium* (mg/dL)			
Prepubertal (n = 18)	9.69 ± 0.31	9.55 ± 0.50	NS
Pubertal (n = 16)	9.51 ± 0.25	9.30 ± 0.50	NS
Total (n = 34)	9.61 ± 0.30	9.43 ± 0.51	NS
Phosphorus* (mg/dL)			
Prepubertal (n = 18)	4.63 ± 0.33	4.77 ± 0.46	NS
Pubertal (n = 16)	4.49 ± 0.55	4.53 ± 0.71	NS
Total (n = 34)	4.57 ± 0.45	4.66 ± 0.59	NS
ALP* (IU/L)			
Prepubertal (n = 18)	277.06 ± 64.48	289.28 ± 82.40	NS
Pubertal (n = 16)	234.38 ± 86.35	239.19 ± 87.19	NS
Total (n = 34)	256.97 ± 77.45	265.71 ± 87.16	NS
25-Hydroxyvitamin D* (ng/mL)			
Prepubertal (n = 18)	28.41 ± 8.70	25.59 ± 5.87	NS
Pubertal (n = 16)	27.37 ± 9.10	24.64 ± 6.52	NS
Total (n = 34)	27.92 ± 8.76	25.14 ± 6.11‡	0.016
Osteocalcin* (ng/mL)			
Prepubertal (n = 18)	23.08 ± 8.31	25.35 ± 4.17	NS
Pubertal (n = 16)	23.29 ± 4.64	26.64 ± 4.92‡	0.015
Total (n = 34)	23.18 ± 6.73	25.96 ± 4.51‡	0.013
Parathyroid hormone† (pg/mL)			
Prepubertal (n = 18)	39.24 ± 10.23	39.32 ± 12.63	NS
Pubertal (n = 16)	35.32 ± 14.55	37.02 ± 10.00	NS
Total (n = 34)	37.40 ± 12.41	38.10 ± 11.20	NS
Calcitonin* (pg/mL)			
Prepubertal (n = 18)	5.13 ± 2.31	5.28 ± 2.15	NS
Pubertal (n = 16)	6.37 ± 2.00	6.41 ± 2.06	NS
Total (n = 34)	5.71 ± 2.23	5.81 ± 1.83	NS
#Bone-mineral density (z score)			
Prepubertal (n = 18)	−0.09 ± 1.36	−0.11 ± 1.43	NS
Pubertal (n = 16)	−0.04 ± 0.75	−0.18 ± 0.75	NS
Total (n = 34)	−0.06 ± 1.10	−0.14 ± 1.14	NS

Values are expressed as mean ± SD.
* Repeated-measures analysis of variance, group versus baseline.
† Wilcoxon test, group versus baseline.
‡ Statistically significant difference between month 18 and baseline ($P < 0.05$).

Abbreviations:
ALP = Alkaline phosphatase
GGT = γ-Glutamyl transferase
NS = Nonsignificant
OXC = Oxcarbazepine

ues (data not shown). There were no correlations between increased osteocalcin levels and decreased 25-hydroxyvitamin D levels and bone-mineral density (data not shown). There were no correlations between decreased 25-hydroxyvitamin D levels and decreased bone-mineral density (data not shown).

Discussion

In this study, we longitudinally investigated bone-mineral density and biochemical bone markers in prepubertal and pubertal epileptic children with normal results of initial biochemical and hormonal analyses, who began to receive oxcarbazepine monotherapy. We found a significant increase only in serum osteocalcin levels and a significant decrease in serum 25-hydroxyvitamin D levels, but these were not correlated with a decrease in bone-mineral density during 1.5 years of oxcarbazepine drug therapy.

Osteocalcin is an important organic substance of bone formation [31], and its serum levels change in pathologies where bone metabolism is altered [1,4,32]. Recently, serum osteocalcin levels were found to be different (although to a statistically insignificant degree) in adult epileptic patients during oxcarbazepine treatment, and this difference was attributed to the decrease in 25-hydroxyvitamin D levels, as with patients undergoing carbamazepine therapy [4]. Likewise, we found increased osteocalcin levels in pubertal and prepubertal patients, and this difference reached statistical significance in the pubertal patients. On the other hand, increased osteocalcin levels after 18 months of treatment were not correlated with low 25-hydroxyvitamin D levels and low bone-mineral density z scores in our patients. Puberty is the period when bone mineralization occurs most rapidly, and skeletal mass has approximately doubled by the end of puberty [33,34]. Therefore, a pubertal gain in bone mass is crucial. In a recent study, carbamazepine was found to manifest its effects on osteocalcin levels via decreased 25-hydroxyvitamin D, independent of puberty [9]. Our results, on the other hand, indicate that increased osteocalcin levels are related to increased bone formation rather than decreased 25-hydroxyvitamin D.

Antiepileptic drugs (such as carbamazepine) exert their negative effects on bone metabolism by decreasing 25-hydroxyvitamin D levels secondary to liver-enzyme induction [4,7,35], although this conclusion is still disputed [5,9]. Although their structures are similar, oxcarbazepine (a new-generation antiepileptic drug) has less induction effect on liver enzymes than carbamazepine [13,19]. On the contrary, in a recent adult study, oxcarbazepine decreased 25-hydroxyvitamin D levels to the same extent as carbamazepine, and the levels of 25-hydroxyvitamin D did not change, even when the two drugs were exchanged. Mintzer et al. [4] suggested that oxcarbazepine may induce P450C1 and P450C24, the enzymes responsible for the metabolism of 25-hydroxyvitamin D. Similarly, we detected decreased 25-hydroxyvitamin D levels in epileptic children receiving oxcarbazepine. Moreover, this decrease reached statistical significance when pubertal and prepubertal patients were analyzed together. Therefore, although oxcarbazepine is a weak liver-enzyme inductor, it is thought that oxcarbazepine exerts a negative effect on bone metabolism by liver enzyme induction [4]. Hence, we measured serum γ-glutamyl transferase levels (as an indicator of liver enzymes), but we did not confirm this hypothesis, because we did not find a correlation between increased γ-glutamyl transferase levels and decreased 25-hydroxyvitamin D levels. This study suggests that although oxcarbazepine increases gamma glutamyl transferase levels, decreased 25-hydroxyvitamin D cannot be readily explained by liver-enzyme induction.

Measurement of bone-mineral density is the gold standard for diagnosing osteopenia or osteoporosis [36]. The reduction in z scores of bone-mineral density was associated with the use of a number of enzyme-inducing antiepileptic drugs [7,9,37]. Although enzyme-inducing antiepileptic drugs are often thought to be the primary agents associated with the reduction of z scores of bone-mineral density, Vestergaard et al. [38] demonstrated that an increase in fracture risk was evident in both liver-inducing antiepileptic drugs (carbamazepine and phenobarbital) and in noninducer antiepileptic drugs (valproic acid). Farhat et al. [39], in a study of 29 pediatric patients and 42 adult patients, examined the effects of enzyme-inducing antiepileptic drugs (including phenobarbital, phenytoin, carbamazepine, and primidone) and noninducing agents (valproate, lamotrigine, and topiramate). Although vitamin D levels correlated poorly with bone-mineral density, they indicated that serum concentrations of 25-hydroxyvitamin D had decreased in adult and pediatric patients using either enzyme-inducing antiepileptic drugs or noninducing antiepileptic drugs. There is no information in the literature that oxcarbazepine affects bone-mineral density. As best we can determine, for the first time in the literature, we observed a slight decrease in bone-mineral density in both prepubertal and pubertal patients undergoing oxcarbazepine monotherapy. In light of our findings, the effect of oxcarbazepine on bone mass cannot be readily explained by decreased vitamin D metabolism, because we could not detect a correlation between bone-mineral density and 25-hydroxyvitamin D levels. Oxcarbazepine probably exerts an effect on osteoblast-osteoclast interactions, rather than an effect on serum 25-hydroxyvitamin D levels. This hypothesis should be confirmed in further histologic studies [4].

Although our results indicate that oxcarbazepine does not exert a significant effect on bone metabolism in children, we detected osteopenia in 3 patients (with pretreatment z scores less than -1.5) at month 18. Considering the results of Tekgül et al. [5] (patients with a z score of less than -1.5 before treatment were prone to developing osteopenia during antiepileptic drug monotherapy) and the fact that these drugs are used for long

periods, it is apparent that such patients should be followed carefully.

Although several mechanisms were proposed, the exact mechanism of antiepileptic drug-induced osteopenia remains unclear [5]. It was reported that other mechanisms might exist by which antiepileptic drugs lead to changes in bone composition other than liver-enzyme induction, including effects on bone cells [40], intestinal calcium absorption [41], increased urinary loss of calcium [3], inhibition of the cellular response to parathyroid hormone [7], hyperparathyroidism [7,40], and calcitonin deficiency [7]. Although we did not find statistically significant changes in calcium, alkaline phosphatase, parathyroid hormone, and calcitonin levels; we observed decreased calcium levels, and increased alkaline phosphatase and parathyroid hormone levels, in pubertal cases. However, in this study, we could not clarify which mechanism predominated.

A limitation of our study involved the absence of a control group for ethical reasons. However, this limitation may be ignored, because baseline values were used as controls within the design of the study. Moreover, we could not perform this study within a single season because of its longitudinal nature, but because the sun is quite strong in Turkey even in winter, we assumed that 25-hydroxyvitamin D measurements were not affected [31].

In conclusion, this study indicates that although some changes in bone metabolism ensue during 18-month oxcarbazepine monotherapy, these changes do not cause significant bone loss in children whose initial measurements with regard to bone metabolism are normal before treatment. However, patients with borderline osteopenia before therapy should be followed carefully, bearing in mind that oxcarbazepine treatment can last longer than 18 months, and these slight differences regarding bone loss could be important in these patients.

References

[1] **Erbayat Altay** E, Serdaroğlu A, Tümer L, Gücüyener K, Hasanoğlu A. Evaluation of bone mineral metabolism in children receiving carbamazepine and valproic acid. J Pediatr Endocrinol Metab 2000;13:933-9.

[2] **Halsam** RHA. The nervous system. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson textbook of pediatrics, 16th ed. Philadelphia: W.B. Saunders, 2000:1793-893.

[3] **Keck** E, Gollnick B, Reinhardt D, Karch D, Peerenboom H, Krüskemper HL. Calcium metabolism and vitamin D metabolite levels in children receiving anticonvulsant drugs. Eur J Pediatr 1982;139:52-5.

[4] **Mintzer** S, Boppana P, Toguri J, DeSantis A. Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. Epilepsia 2006;47:510-5.

[5] **Tekgül** H, Serdaroglu G, Huseyinov A, Gokben S. Bone mineral status in pediatric outpatients on antiepileptic drug monotherapy. J Child Neurol 2006;21:411-4.

[6] **Chung** S, Ahn C. Effects of anti-epileptic drug therapy on bone mineral density in ambulatory epileptic children. Brain Dev 1994;16: 382-5.

[7] **Pack** AM, Morrell MJ. Adverse effects of antiepileptic drugs on bone structure: Epidemiology, mechanisms and therapeutic implications. CNS Drugs 2001;15:633-42.

[8] **Feldkamp** J, Becker A, Witte OW, Scharff D, Scherbaum WA. Long-term anticonvulsant therapy leads to low bone mineral density—Evidence for direct drug effects of phenytoin and carbamazepine on human osteoblast-like cells. Exp Clin Endocrinol Diabetes 2000;108:37-43.

[9] **Verrotti** A, Greco R, Latini G, Morgese G, Chiarelli F. Increased bone turnover in prepubertal, pubertal, and postpubertal patients receiving carbamazepine. Epilepsia 2002;43:1488-92.

[10] **Guo** CY, Ronen GM, Atkinson SA. Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. Epilepsia 2001;42:1141-7.

[11] **Grant** SM, Faulds D. Oxcarbazepine. A review of its pharmacology and therapeutic potential in epilepsy, trigeminal neuralgia and affective disorders. Drugs 1992;43:873-88.

[12] **Dam** M, Ekberg R, Løyning Y, Waltimo O, Jakobsen K. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. Epilepsy Res 1989;3:70-6.

[13] **Schmidt** D, Elger CE. What is the evidence that oxcarbazepine and carbamazepine are distinctly different antiepileptic drugs? Epilepsy Behav 2004;5:627-35.

[14] **Beydoun** A, Kutluay E. Oxcarbazepine. Expert Opin Pharmacother 2002;3:59-71.

[15] **Beydoun** A, Sachdeo RC, Kutluay E, McCague K, D'Souza J. Sustained efficacy and long-term safety of oxcarbazepine: One-year open-label extension of a study in refractory partial epilepsy. Epilepsia 2003;44:1160-5.

[16] **Rattya** J, Turkka J, Pakarinen AJ, et al. Reproductive effects of valproate, carbamazepine, and oxcarbazepine in men with epilepsy. Neurology 2001;56:31-6.

[17] **Larkin** JG, McKee PJ, Forrest G, et al. Lack of enzyme induction with oxcarbazepine (600 mg daily) in healthy subjects. Br J Clin Pharmacol 1991;31:65-71.

[18] **Patsalos** PN, Zakrzewska JM, Elyas AA. Dose dependent enzyme induction by oxcarbazepine? Eur J Clin Pharmacol 1990;39:187-8.

[19] **Isojarvi** JI, Pakarinen AJ, Rautio A, Pelkonen O, Myllyla VV. Liver enzyme induction and serum lipid levels after replacement of carbamazepine with oxcarbazepine. Epilepsia 1994;35:1217-20.

[20] **Isojarvi** JI, Pakarinen AJ, Rautio A, Pelkonen O, Myllyla VV. Serum sex hormone levels after replacing carbamazepine with oxcarbazepine. Eur J Clin Pharmacol 1995;47:461-4.

[21] **Cansu** A, Serdaroğlu A, Camurdan O, Hirfanoğlu T, Bideci A, Gücüyener K. The evaluation of thyroid functions, thyroid antibodies, and thyroid volumes in children with epilepsy during short-term administration of oxcarbazepine and valproate. Epilepsia 2006;47:1855-9.

[22] **Klosterskov Jensen** P, Saano V, Haring P, Svenstrup B, Menge GP. Possible interaction between oxcarbazepine and an oral contraceptive. Epilepsia 1992;33:1149-52.

[23] **Lofgren** E, Tapanainen JS, Koivunen R, Pakarinen A, Isojarvi JI. Effects of carbamazepine and oxcarbazepine on the reproductive endocrine function in women with epilepsy. Epilepsia 2006;47:1441-6.

[24] **Commission on Classification and Terminology of the International League Against Epilepsy**. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389-99.

[25] **Scheuer** ML, Pedley TA. The evaluation and treatment of seizures: current concepts. N Engl J Med 1990;323:1468-74.

[26] **Murphy** SP, Poos MI. Dietary reference intakes: Summary of applications in dietary assessment. Public Health Nutr 2002;5:843-9.

[27] **Neyzi** O, Binyildiz P, Alp H. Growth standards for Turkish children: Heights and weights. Courier 1979;29:553-8.

[28] **Neyzi** O, Furman A, Bundak R, Gunoz H, Darendeliler F, Bas F. Growth references for Turkish children aged 6 to 18 years. Acta Paediatr Scand 2006;95:1635-41.

[29] **Tanner** JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity and stages of puberty. Arch Dis Child 1976;51:170-82.

[30] **Fielding** KT, Nix DA, Bachrach LK. Comparison of calcaneus ultrasound and dual x-ray absorptiometry in children at risk of osteopenia. J Clin Densitom 2003;6:7-15.

[31] **Oner** N, Kaya M, Karasalihoglu S, Karaca H, Celtik C, Tutunculer F. Bone mineral metabolism changes in epileptic children receiving valproic acid. J Paediatr Child Health 2004;40:470-3.

[32] **Takeshita** N, Seino Y, Ishida H, et al. Increased circulating levels of gamma-carboxyglutamic acid-containing protein and decreased bone mass in children on anticonvulsant therapy. Calcif Tissue Int 1989;44:80-5.

[33] **Kanbur** NO, Derman O, Sen TA, Kinik E. Osteocalcin. A biochemical marker of bone turnover during puberty. Int J Adolesc Med Health 2002;14:235-44.

[34] **Saggese** G, Baroncelli GI, Bertelloni S. Puberty and bone development. Best Pract Res Clin Endocrinol Metab 2002;16:53-64.

[35] **Tjellesen** L, Gotfredsen A, Christiansen C. Effect of vitamin D2 and D3 on bone-mineral content in carbamazepine-treated epileptic patients. Acta Neurol Scand 1983;68:424-8.

[36] **Elliott** ME, Binkley N. Evaluation and measurement of bone mass. Epilepsy Behav 2004;5 (Suppl.):S16-23.

[37] **Sheth** RD, Wesolowski CA, Jacob JC, et al. Effect of carbamazepine and valproate on bone mineral density. J Pediatr 1995;127: 256-62.

[38] **Vestergaard** P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. Epilepsia 2004;45:1330-7.

[39] **Farhat** G, Yamout B, Mikati MA, Demirjian S, Sawaya R, El-Hajj Fuleihan G. Effect of antiepileptic drugs on bone density in ambulatory patients. Neurology 2002;58:1348-53.

[40] **Hahn** TJ, Scharp CR, Richardson CA, Halstead LR, Kahn AJ, Teitelbaum SL. Interaction of diphenylhydantoin (phenytoin) and phenobarbital with hormonal mediation of fetal rat bone resorption in vitro. J Clin Invest 1978;62:406-14.

[41] **Mosekilde** L, Hansen HH, Christensen MS, et al. Fractional intestinal calcium absorption in epileptics on anticonvulsant therapy. Short-term effect of 1,25-dihydroxycholecalciferol and 25-hydroxycholecalciferol. Acta Med Scand 1979;205:405-9.