Calcium and bone metabolism in patients with epilepsy taking Phenytoin or Oxcarbazepine

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Aim: Long-term use of antiepileptic drugs may negatively affect calcium metabolism. The aim of the present study was to compare the side effects of two drugs frequently used in epilepsy treatment on calcium and bone metabolism.
Methods: This study involved a total of 30 patients taking oxcarbazepine treatment (Group 1), 30 patients taking phenytoin treatment (Group 2) for epilepsy, and 30 healthy control subjects. Serum Calcium, Parathormone (PTH), 25-hydroxyvitamin D (25-OHD_3), osteocalcin, and deoxypyridinoline (DPD) levels in a 24-hour urine sample were compared between three groups.
Results: There were no significant differences in sex (p=0.65) and age (p=0.28) between the three groups and also there were no significant differences in duration of drug use between Group 1 and Group 2 (p=0.40). Calcium (p_1=0.004; p_2=0.004) and 25-OHD_3 (p_1=0.009; p_2=0.009) levels were found to be statistically lower in Group 2 than in Group 1 or Group 3. PTH (p_1=0.009; p_2=0.006), osteocalcin (p_1=0.003; p_2=0.007), and DPD (p_1=0.005; p_2=0.003) levels were found to be statistically higher in Group 2 than in Group 1 or Group 3.
Conclusion: Oxcarbazepine has fewer side effects on calcium and bone metabolism than phenytoin.

***Keywords*:** calcium and bone metabolism, Oxcarbazepine, phenytoin.

Introduction

Epilepsy is one of the most common neurological diseases of the brain. The prevalence of epilepsy is 5-10/1,000 and the incidence rate is approximately 50/100,000 (1). Epilepsy mostly appears in children and the elderly (2).

Antiepileptic drug treatments are based on the suppression of seizures and control of symptoms because pathophysiological mechanism in epilepsy cannot be fully understood yet (3). This situation calls for long time treatment, and in some patients, lifelong treatment. Antiepileptic drugs have significant side effects on bone and calcium metabolism (4). Chronic antiepileptic drug treatment causes osteopenia, osteoporosis, and osteomalacia, and affects major regulators of calcium, PTH, 25-OHD_3, and osteocalcin levels (4-6).

Phenytoin is an older antiepileptic drug, in use since 1938 (7). Oxcarbazepine is a new antiepileptic drug (8). In this study, we compared the side effects of the two drugs on calcium and bone metabolism.

Methods

A total of 60 patients diagnosed with epilepsy (Groups 1 and 2) and 30 healthy control subjects (Group 3) were included in this study. Patients were divided into two groups: Group 1 patients were using phenytoin and Group 2 patients were using oxcarbazepine.

Inclusion criteria:

- age range of 18-49 years;
- able to do daily activities;
- regular eating;
- female patients have regular menstrual cycle and are premenopausal;
- taking antiepileptic drugs for a minimum of three months.

Exclusion criteria:

- using drugs affecting calcium metabolism;
- hypo-hyperthyroidism;
- chronic renal failure or chronic liver diseases;
- using oral contraceptives;
- using more than one antiepileptic drugs.

After 12-14 hours of fasting, venous blood samples were obtained from subjects for biochemical and hemogram studies. Complete blood cell counts and automated differential counts were determined using the automated hematology analyzer Abbott CELL-DYN 3700. Calcium levels were measured using UV photometric method via a modular Hitachi DP autoanalyser. 25-OHD_3 levels were measured using high-preference UV detector liquid chromatography (HPLC) method in isocratic pump system. Osteocalcin levels were measured using the ELISA method. PTH levels were measured using chemiluminescence immunoassay method in DPC Immulite analyzer. DPD levels were measured from the urine samples taken in the morning using HPLC method in analyzer with florescence detector. The institutional ethics committee approved the study protocol.

Statistical analysis

Statistical Package for the Social Sciences for Windows (version 17.0) was used for all the data analyses. Numerical parameters were defined as means ± standard deviations. Comparison of proportions between categorical variables was done by use of the Chi-Square test. The Kruskal-Wallis test was used to assess differences in the mean values between three or more groups. Conversely, mean differences between two groups were assessed by use of Mann-Whitney U test. Spearman correlation was used to determine linear associations between numeric variables. Statistical significance threshold was set at $P \leq 0.05$.

Results

A total of 90 subjects were included in the data analysis. Patients were divided into two groups. Group 1 (n=30) included patients using phenytoin, while Group 2 (n=30) included patients using oxcarbazepine. Group 3 (n=30) included healthy control subjects. The groups were determined to be homogenous in terms of demographic characteristics and treatment duration (Table 1). Mean age

of group 1 was 40.9 ± 16.5 years, group 2 was 38.8 ± 5.3 years, and group 3 was 40.7 ± 4.6 years. There were no significant differences in sex (p=0.65) and age (p=0.28) among the three groups. Duration of treatment was 47.0 ± 6.6 months in group 1 and 45.0 ± 11.2 months in group 2. There were no significant differences in the duration of treatment between the two groups (p=0.40). Demographic findings and duration of treatment of groups are shown in Table 1.

Table 1. Demographic data of patients by groups

	Group 1	Group 2	Group 3	P-value
Age (years)	40.9 ± 16,5	38.8 ± 5.3	40.7 ± 4.6	0.28
Gender (M:F)	18: 12	17: 13	16: 14	0.65
Duration of treatment (months)	47.0 ± 6.6	45.0 ± 11.2	-	0.40

Biochemical parameters of the three groups are shown in Table 2. Patients using phenytoin have lower calcium (p_1=0.004; p_2=0.004) and 25-OHD_3 (p_1=0.009; p_2=0.009) levels and higher PTH (p_1=0.009; p_2=0.006), osteocalcin (p_1=0.003; p_2=0.007) and DPD (p_1=0.005; p_2=0.003) levels than patients using oxcarbazepine and control group. These values were found to be statistically significantly higher or lower in the patients using phenytoin.

Table 2. Effects of Phenytoin and Oxcarbazepin on biochemical parameters

	Group 1	Group 2	Group 3	P_1 values*	P_2 values	P_3 values
Ca (mg/dl)	8.99 ± 0.19	9.47 ± 0.34	9.33 ± 0.26	**0.004**	**0.004**	0.170
PTH (pg/ml)	56.79 ± 14.82	39.53 ± 13.40	40.71 ± 12.52	**0.009**	**0.006**	0.796
25-OHD_3 (µg/L)	26.20 ± 4.52	34.55 ± 8.92	35.98 ± 8.42	**0.009**	**0.009**	0.442
Osteocalcin (ng/ml)	9.40 ± 5.07	5.03 ± 1.50	4.97 ± 1.33	**0.003**	**0.007**	0.988
Dpd (pmol/L)	319.57 ± 85.41	155 ± 44.98	159 ± 40.25	**0.005**	**0.003**	0.344

*P_1: Oxcarbazepin and phenytoin, P_2: phenytoin and control, P_3: Oxcarbazepin and control.

Discussion

Phenytoin is the one of oldest AED being used since 1938. It is generally preferred for tonic-clonic seizures and status epilepticus treatment (7). Phenytoin induces the hepatic CYP450 enzyme system. Published studies have shown that AEDs which induce the hepatic CYP450 enzyme system are most commonly related with side effects on bone and calcium metabolism. Phenytoin causes vitamin D_3 deficiency and secondary hyperparathyroidism (9). This situation increased bone turnover. After 1 or 2 years of treatment, lower bone mineral density values were measured (10). In our study we found low vitamin D_3 levels and high PTH levels in the patients using phenytoin. Our findings are consistent with the literature.

Osteocalcin is produced by osteoblasts. Serum osteocalcin levels increase in situations such as puberty, osteoporosis, osteomalacia, or metastatic bone diseases. Bone turnover is thus increased (11). In our study, high osteocalcin levels were found. This shows that phenytoin increases bone turnover.

There are many studies showing the relationship between phenytoin treatment and hypocalcemia and hypophosphatemia. Phenytoin induces the CYP450 enzyme system and increases vitamin D_3 catabolism. Overcatabolism of vitamin D_3 causes hypocalcemia and hypophosphatemia (12-14). We found low calcium levels in the patients using phenytoin but did not measure phosphate levels. Low calcium levels are consistent with the literature.

Deoxypyridinoline (DPD) creates crosslinks of type 1 collagen and provides resistance of collagen in the bone. DPD is released with the destruction of bone matrix by osteoclasts and is not metabolized in the body. High levels of DPD in the urine show increased bone resorption (13,15). We found DPD levels that were two times higher in patients using phenytoin than the oxcarbazepine and control groups. High DPD levels show that phenytoin increased bone resorption.

Oxcarbazepine is a newer AED. It is generally preferred for partial and secondarily generalized tonic-clonic seizures. Oxcarbazepine is associated with only the CYP3A isoenzyme. Oxcarbazepine is a weak inducer hepatic CYP450 enzyme system which has lower side effects on bone and calcium metabolism than phenytoin. Studies showed that, oxcarbazepine have no effect on calcium and phosphate (16). In our study, we found levels of calcium similar to the control group.

The effects of oxcarbazepine on vitamin D_3 and PTH remain controversial, as some studies suggest that oxcarbazepine decreases vitamin D_3 levels and increases PTH levels (17-18) and others suggest that oxcarbazepine does not affect vitamin D_3 and PTH levels (16,19). In our study, there were no statistically significant differences between the oxcarbazepine group and control group.

Different results of the study may be connected to multiple factors, including dietary calcium, duration of sunlight, seasonal characteristics, clothing style, working area, and religious beliefs.

Conclusion

Oxcarbazepine has fewer side effects on calcium and bone metabolism than phenytoin and is also a very safe drug for long term use. Oxcarbazepine should be considered as a first in the treatment of epilepsy.

Conflicts of interest: None declared.

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