

EFFECTS OF LEVETIRACETAM AND TOPIRAMATE ON BONE HEALTH IN ADULTS, USING BONE SPECIFIC BIOMARKERS

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Abstract:

Purpose: Adverse drug reactions [ADRs] are important to monitor, when medications are administered for chronic illnesses such as epilepsy/migraine particularly with recently approved widening indications for antiepileptic drugs [AEDs]. Therefore it is essential to recognize potential of these AEDs to induce bone loss, as an adverse effect. Since osteoporosis is one of the well-known complications following administration of older generation AEDs our aim was to quantify and compare the effects of newer AEDs - levetiracetam [LEV] and topiramate [TPM] monotherapy, on bone health using bone biomarkers viz. - serum cross laps, osteocalcin, vit. D and parathormone [PTH].

Method: 76 patients with epilepsy/migraine between 18-45 years of age, receiving LEV or TPM monotherapy for < 1 month with no co-morbid conditions were included. Serum samples were collected at baseline, 3rd and 6th month. Samples were analyzed for serum cross laps, osteocalcin, Vit D and PTH using Electrochemiluminescence. The levels of bone biomarkers were compared across time.

Results: The mean age of patients was 28.60 ± 6.60 [Mean \pm SD] years with 60.78% females. Patients who received TPM complained of bone related side effects which was significantly greater compared to LEV. There was no significant difference in levels bone biomarkers over a period of six months and did not notice any difference between LEV and TPM.

Conclusion: Use of LEV and TPM as monotherapy in treatment of epilepsy/ migraine over a period of six months was not associated with adverse influence on bone health.

Key words: Bone biomarkers, Epilepsy, Levetiracetam, Migraine, Topiramate

Introduction

Many studies in the past have reported a significant decrease in bone mineral density [BMD] and increase in the fracture risk in

patients treated with enzyme inducing antiepileptic drugs [AEDs] like phenytoin [PHT]^[1], carbamazepine [CBZ]^[2], and phenobarbitone [PB]^[3]. During the last

decade, large number of newer AEDs have been approved for use by FDA in the treatment of epilepsy [4] either alone or in combination with conventional AEDs as well as for various non-epileptic conditions like migraine [5], drug abuse [6]. Therefore, while the outcome of potential long term adverse effects of older enzyme inducing AEDs on bone loss is well known [7], there are spar published clinical studies on newer AEDs.

Levetiracetam [LEV] and topiramate [TPM] are frequently used in patients with epilepsy or migraine and their short term adverse effect profile is available through clinical trials. However, studies on their effects on bone health are lacking. Therefore, the purpose of this study was to quantify and compare the effects of newer AEDs – LEV and TPM monotherapy, on bone health in patients with epilepsy [PWE] or migraine using bone specific biomarkers.

Materials and Methods

In this prospective study, we recruited 76 patients, between the age group of 18-45 years, with confirmed diagnosis of epilepsy or migraine, who received either LEV or TPM monotherapy. Exclusion Criteria : 1. Patients with motor function disorder; 2. Patients with disease affecting their bone and mineral metabolism [such as 1^o hyperparathyroidism, paget's disease, multiple myeloma, liver and kidney disorder, thyroid disease, malabsorption disorder, diabetes and malignancy]; 3. Patients those on medications which would affect their bone and mineral metabolism [such as vit D, calcium, anabolic steroids, bisphosphonates, calcitonin, glucocorticoids and diuretics]; 4. Patients with history of fractures, bone pain, joint pain, osteoporosis, osteopenia; 5. Obese and alcoholics; 6. Pregnant, lactating and post-menopausal women. A written and informed consent was obtained from each study participant. The study was conducted in accordance with ICH-GCP Guidelines, following approval from Institutional Ethics Review Board [IERB].

The demographic characteristics, disease data like duration, date of diagnosis and

details of treatment data with LEV and TPM along with adverse drug reactions [ADR] if any was recorded. Fasting serum samples were collected for analysis of hematological parameters hemoglobin [Hb], Albumin and total proteins and reports on biochemical investigations such as calcium [Ca⁺²], phosphorous [PO⁴⁻] and alkaline phosphatase [ALP] levels was recorded. These were analyzed once on the day of enrolment and were considered as baseline data. Only those patients in whom the lab values were within the normal range were further subjected for analysis of baseline bone biomarkers. Serum samples were collected on the day of enrolment i.e. at baseline and followed up at 3rd and 6th month of treatment. Serum measurements included Vit D, parathormone [PTH], bone formation marker- osteocalcin and bone resorption marker- serum cross laps or C-terminal telopeptide of type I collagen [CTX]. The serum sample for Vit D, PTH, CTx and osteocalcin was stored at -80C until analysis. Measurements of all bone biomarkers were carried out using Electrochemiluminescence [Elecsys cobas e411 by Roche] technique at Central Research Lab, Rajarajeshwari Medical College and Hospital, Bangalore.

The reference range values for various biomarkers were used for comparison [osteocalcin = 11.00-43.00 ng/ml, β serum crosslaps = 0.010-5.94 ng/ml and PTH = 15.00-65.00 pg/ml] between values prior to and after administration of LEV or TPM. The reference range for Vit D levels was considered deficient if <10 ng/ml; insufficient if 10-30ng/ml and sufficient if 30-100ng/ml as recommended by WHO.

In this study, our sample size indicated that, we need to recruit 80 patients with 80% power, 95% CI with dropout rate of 10% over 6 month treatment duration. Statistical analysis was performed using SPSS version 19. Data are presented as mean \pm standard deviation [SD] and median. Comparison of continuous variables between groups was carried out using Mann Whitney U test and Fischer's Test. The significance level was set at $P < 0.05$.

Results

Demographic characteristics of study subjects

The mean age of patients was 28.62 ± 6.60 years [median 28, range 18-45 years] and 50 [60.78%] were females. Majority were of low income group. 60.53% were unemployed, among which 47.3% were housewives and 13.15% were students.

Total of 32 [42.10%] patients received LEV for epilepsy and 44 [57.90%] patients received TPM for either epilepsy or migraine. All patients were on monotherapy with either LEV [500-2000 mg/day] or TPM [25-100 mg/day] and were well within the limit of maintenance doses. None of the patients used alternative or complimentary medicines for either epilepsy or migraine.

Bone Biochemical Indices

Among patients who received either LEV or TPM, there was no significant difference in the levels of osteocalcin, β serum cross laps

and PTH over a period of six months. The baseline values of Vit D were low, and further declined at the end of six month treatment but did not show significant change either with LEV or TPM over a period of time. The levels of PTH were well within the range, but we noticed significant difference between LEV and TPM at 6th month [$P=0.04$] treatment duration. When the analyzed over a period of six months using Fischer's test this did not show statistically significant difference [Table 1]. Gender and age related effects of LEV and TPM on bone biomarkers was done among patients with epilepsy and migraine. Patient's age was classified into three different groups namely Group A-15-25 yrs, Group B-25-35 yrs and Group C > 35 yrs for assessment. Comparison between groups was done using Mann Whitney U test. No significant change in any of the biomarkers was observed either with gender or age.

Table 1: Median values of various bone biomarkers at each visit in patients receiving LEV and TPM monotherapy

Bone Biomarkers	Visits	LEV Median values	TPM Median values	Comparison between groups at each point of time [#]	Comparison over a period of time between LEV and TPM*
Bone formation marker – Osteocalcin [ng/ml]	0	21.36	18.15	0.07	0.18
	3	21.62	16.28	0.06	
	6	24.24	19.25	0.12	
P Value over a period of time*		0.37	0.17		
Bone resorption marker - β Serum cross laps [ng/ml]	0	0.417	0.360	0.37	0.25
	3	0.344	0.341	0.76	
	6	0.413	0.432	0.96	
P Value over a period of time*		0.42	0.59		
Vit D [ng/ml]	0	15.71	15.00	0.88	0.49
	3	13.70	14.23	0.63	
	6	12.64	15.67	0.86	
P Value over a period of time*		0.78	0.88		
PTH [pg/ml]	0	26.08	28.69	0.29	0.75
	3	32.50	29.99	0.07	
	6	33.18	30.62	0.04*	
P Value over a period of time*		0.19	0.37		

#Mann Whitney U test and *Fischer's test. Significance was set at $P < 0.05$

Discussion

The older AED's [eg: carbamazepine, phenytoin, phenobarbitone] are often prescribed for use in patients with epilepsy in routine practice. However such use in addition to several systemic ADRs are reported to adversely affect bone and mineral metabolism, leading to osteoporosis and hence increase in fracture risk, which requires appropriate management^[8]. Therefore, when choosing an AED for long term treatment, it is important to understand its potential secondary adverse effects in general including those on bone health. The use of newer AEDs is on rise with a claim that they have better acceptable pharmacological profile and their use has been increasing for both routine treatment of epilepsy either alone or in combination with conventional AEDs. However the adverse outcome on their use on bone health with the use of newer AEDs is limited. Hence the present study was designed to examine their effects on bone health using bone biomarkers.

It is well established that the process of bone remodeling takes 3 weeks to 3 months and hence the alterations if any, in serum markers may be noticed only after a month of the treatment, as well as the effect of the drug accordingly on the bone can be noticed only after the completion of one remodeling cycle^[9]. Therefore we evaluated influence of newer AEDs on bone biomarkers over six month treatment period.

Demographic Profile

In the present study we included subjects between 18 - 45 years (median age of 28 years), of age to avoid influence of physiological impairment of bone health among older patients and are prone for sustaining fracture compared to younger age^[10]. Studies elsewhere addressing bone health have also considered similar selection criteria in their patients in relation to age^[11]. Majority [60.53%] of our study patients were unemployed, which is in contrast to a study by Baker, 1997^[12] who reported a rate

of 23% and Han le in 2011^[13] reported 27% among patients with epilepsy and migraine respectively. The possible reason for such difference in finding could be that most of our patients were housewives.

Bone Biomarker Levels

In our study, the median levels of bone biomarkers over a period of six months remained within the normal range and also did not show significant change in their levels when compared between patients who received LEV and TPM over a period of six months. Thus indicating that neither of the AEDs have any adverse influence on bone biomarkers at 6 months.

Despite safety profile of LEV monotherapy on bone health, there are several issues in respect to clinical interpretation. We noticed a trend in reduction of Vit D levels over 6 months in patients receiving LEV and the reason for this could be that there was an increase in mean values of PTH over a period of six months. We also noticed a trend towards increase in the median levels of osteocalcin over a period of 6 months. This insignificant trend in the reduction of vit D levels over 6 months could be confirmed on long term studies by Dual X ray absorptiometry [DEXA]. The observed trend might be difficult to explain based on short term studies

The studies in the past have shown controversial results with regards to effects of LEV on bone health. Two studies using LEV, suggest that it affected bone strength and bone mineral density [BMD]. However, among these - one was animal study^[14] and the other was a retrospective study, which had a limited sample size and did not control the potential cofounders^[15] which could influence bone health, hence results were inconclusive.

Recently Koo and his colleagues^[16] have published longitudinal study in drug naïve patients who received LEV treatment with follow up of 24 months. The assessment of various values for biomarkers of bone metabolism [calcium, phosphorous, bone

specific alkaline phosphatase, Vit D, PTH, osteocalcin, serum crosslaps and insulin like growth factor and BMD] were compared between baseline and at the end of one yr. This study did not show any adverse influence of LEV on bone strength and metabolism. The results of our study are similar and add supportive evidence to these findings

With regards to the effects of TPM on bone health our study did not show any adverse effects on bone health over a period of six months. A study reported by Kyoung Heo^[11] and colleagues investigated the effects of TPM monotherapy on bone mass and metabolism in premenopausal women with epilepsy. The study compared the effects of older AEDs and TPM for their effects on bone health over one year with inclusion and exclusion criteria similar to our study. The bone metabolism markers they used were total calcium, bicarbonate, vit D, PTH, insulin like growth factor, bone specific alkaline phosphatase, osteocalcin, and β serum cross laps [C terminal telopeptide of type I collagen –CTx]. The samples were analyzed at baseline and at 16 weeks. The results showed that the use of TPM was associated with lower PTH and bicarbonate concentrations along with mild hypocalcaemia and bone turnover, suggesting that TPM may have adverse influence on bone when used on long term basis which was in contrast with our study.

In a study by Imran Ali^[17] and his colleagues evaluated bone health in patients who received TPM monotherapy for more than six months by examining biochemical and radiological markers of bone metabolism like Vit D, osteocalcin and BMD. These authors noted osteopenia in 53% of the patients treated with TPM which is again in contrast with our study.

Conclusion

Our results demonstrate that the use of LEV and TPM monotherapy for a period of six months in the treatment of epilepsy or migraine did not induce adverse influence

on bone health. A possible limitation of our study is that patients were followed up for a short duration. Therefore, it is suggested that studies to evaluate longer duration effects of LEV and TPM monotherapy on bone health are necessary.

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Conflict of Interest: None

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