



Impact of Levetiracetam on Bone Health - A Descriptive Study

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ABSTRACT

In recent years there has been increasing evidence suggesting that epilepsy and its treatment can have adverse effects on bone mineralization and calcium metabolism. Levetiracetam is one of the second generations AED used as an adjunctive for partial seizures. Only little is known about the impact of levetiracetam on bone health. Hence we decided to measure the bone markers namely serum calcium, phosphorus, and alkaline phosphatase in newly diagnosed epileptic patients starting on levetiracetam monotherapy before and 6 months after the treatment. 60 newly diagnosed epileptic patients of primary cause starting on levetiracetam are included in the study. Serum calcium, phosphorus, alkaline phosphatase was measured before and 6 months of levetiracetam monotherapy and were compared. Serum calcium and phosphorus were significantly decreased (Mean=9.17±0.48vs9.01±0.51) (p value<0.01) and (Mean=3.61 ±0.46vs3.49±0.47) (p value<0.01) where as alkaline phosphatase were significantly increased (Mean-79.47±13.15 vs. 84.27±12.53) (p value <0.01) after 6 months of levetiracetam monotherapy which indicates reduced bone mineral density. There is an evident impact of levetiracetam on bone health resulting in reduced calcium and phosphorus and elevated alkaline phosphatase levels.

Keywords: Alkaline phosphatase, Calcium, Epilepsy, Levetiracetam, Phosphorus.

INTRODUCTION

Seizure disorder is one of the leading neurological disorders that we encounter in clinical practice. Approximately 5–10% of the population will have at least one seizure, with the highest incidence occurring in early childhood and late adulthood.¹ Epilepsy is a heterogeneous symptom complex—a chronic disorder characterized by recurrent seizures. Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons.² since seizures and epilepsy are heterogeneous; they have to be classified for selecting appropriate drug therapy and providing information regarding the prognosis. The International League against Epilepsy in 1981 divided seizures into partial and generalized.³

Levetiracetam (LEV) is a second generation antiepileptic drug, structurally similar to the nootropic drug piracetam.⁴ Levetiracetam have proved to be effective and have a favourable tolerability profile as an adjunctive for partial seizures in both adult and pediatric patients. There has been increasing evidence that it may also be used in patients with generalized absence or myoclonic seizure.⁵

Bone is a mineralized connective tissue with hydroxyapatite made up of calcium and inorganic phosphates as its mineral component. These hydroxyapatite confers to bone the strength and resilience required by its physiological role.⁶ Serum

Alkaline Phosphatase is an important marker of bone formation and its level increases in glucocorticoid excess as well as in osteoporosis.⁷ Since there is no single marker for assessing the bone is available, estimation of calcium, phosphorus and the enzyme alkaline Phosphatase can be used to detect the disturbances in bone metabolism.⁸

Since there are evidences pointing that treatment with novel antiepileptic drug such as Valproic acid, phenytoin may reduce the bone density.⁹⁻¹¹ Levetiracetam is a new generation anti-epileptic drug whose side effects and benefits are not fully explored. Therefore we decided to estimate the serum levels of bone markers namely calcium, phosphorus and alkaline phosphatase in epileptic Patients on Levetiracetam monotherapy at the time of initiation of therapy and 6 months later so as to evaluate the early effects of this drug on bone metabolism.

MATERIALS AND METHODS

We conducted a descriptive study including 60 newly diagnosed epileptic patients of primary cause starting on Levetiracetam monotherapy in the age group 18 to 45 years attending our PIMS Neurology OPD during the period of January 2012 to August 2013. We excluded patients over 45 years of age, patients with H/O liver and Kidney disorders, thyroid and parathyroid disorders, bone disorders like rickets, osteomalacia. Patients currently on steroids due to other medical reasons were also excluded from the study. After getting written and informed



consent and comforting the patients, samples were collected on the day of starting the therapy and 6 months later. Serum was separated and serum calcium was estimated using Arsenazo III method and serum phosphorus by UV endpoint method with Ammonium Molybdate and Serum alkaline Phosphatase by Enzymatic method using autoanalyser (Cobas integra 400).

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation and median. 'Wilcoxon Signed Rank Test', a non parametric test was used to compare the median value. p value of ≤ 0.05 was accepted as statistically significant. SPSS version 17.0 software was used.

RESULTS AND DISCUSSION

In our study, out of 60 epileptic patients, 31 were males (51.7%) and 29 were females (48.3%). Mean age groups of the patients were 27 ± 7 years. The baseline characteristics are shown in table 1.

Table 1: Baseline characteristics of epileptic patients before starting levetiracetam therapy

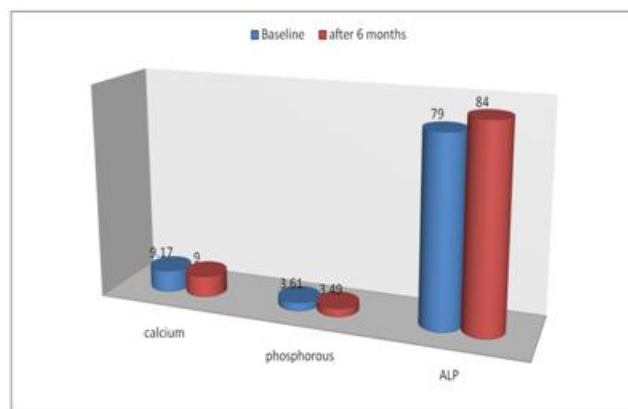
Characteristics	Results
Number of patients	60
Age groups(years)	27 ± 7
Gender	Males = 31(51.7%) Females=29(48.3%)
Calcium levels (mg/dl)	Mean= 9.17 ± 0.48 Median= 9.15
Alkaline phosphatase(IU/L)	Mean= 79.47 ± 13.15 Median= 79

Both serum calcium and phosphorus were found to be significantly decreased and serum alkaline phosphatase was significantly increased after 6 months of levetiracetam monotherapy (table 2 and figure 1).

Table 2: Comparison of serum parameters in epileptic before and after 6 months of treatment using Wilcoxon Signed Ranks Test

Parameters	Baseline	After 6 months	p-value
Serum Calcium (mg/dl)	Mean= 9.17 ± 0.48 Median= 9.15	Mean= 9.01 ± 0.51 Median=9	<0.01*
Serum Phosphorus(Meq/L)	Mean= 3.61 ± 0.46 Median=3.75	Mean= 3.49 ± 0.47 Median=3.6	<0.01*
Serum Alkaline phosphatase(IU/L)	Mean= 79.47 ± 13.15 Median= 79	Mean= 84.27 ± 12.53 Median=85	<0.01*

* p- Value < 0.05- statistically significant



* p-value < 0.01, statistically significant.

Figure 1: Comparison of serum parameters of epileptic patients before and after 6 months of levetiracetam therapy.

DISCUSSION

In recent years there has been increasing evidence suggesting that epilepsy and its treatment can have adverse effects on bone mineralization and calcium metabolism. It is well documented that novel anti-epileptic drugs like Valproic acid and Phenytoin reduces bone mineral density. Only little is known about the impact of newer anti-epileptic drug like levetiracetam on bone health. This made us to measure the levels of bone markers namely calcium, phosphorus and alkaline phosphatase before and after 6 months of levetiracetam monotherapy treatment.

In our study we found that there was a significant decrease in calcium and phosphorus levels before and after 6 months of levetiracetam monotherapy accompanied by elevated alkaline phosphatase levels before and 6 months after the treatment. Serum bone ALP levels reflect osteoblastic activity which is an indicator of bone formation. Its elevated concentration helps to predict the metabolic bone disease and risk of fractures independent of bone mineral density. Reduced serum calcium and phosphorus and elevated ALP level indicates the impending decrease in the bone mineral density which we observed in our epileptic patients receiving levetiracetam monotherapy.

Mechanism by which anti-epileptic drugs affects the bone health is still unclear. There were various postulated mechanisms by which these drugs affect the bone health. Some of these are,

1. Hepatic induction of cytochrome P450 enzymes leading to increased metabolism of vitamin D into inactive metabolites thereby results in reduced calcium levels and reduced bone mineralization.
2. Direct action of AEDs on osteoblasts has been observed.
3. Impaired calcium absorption.
4. Elevated homocysteine.

5. Inhibition of response to PTH.
6. Hyperparathyroidism.
7. Reduced vitamin K levels.¹²

Clinical data on the effects of LEV on skeletal integrity are scarce. In 2007, Nissen-Meyer et al. conducted a preclinical study in rats and observed decreased bone strength at the femoral neck of rats treated with low-dose LEV. But in contrast, bone mineral content and bone mass remained unchanged.¹³ whereas in 2012, Beniczky SA et al., conducted a cross-sectional study among 168 epileptic adults on various anti-epileptic monotherapy and found that reduced bone mineral density was present significantly most often in patients treated with levetiracetam.¹⁴ To evaluate the vitamin D status in children receiving AED including levetiracetam, Nettekoven S et al in 2008 carried out a cross-sectional study in 38 children on AED and found that more than 75% of them were Vit-D deficient and 21% had an inefficient Vit-D status resulting in reduced calcium and its consequences.¹⁵

Xiong N et al., reported that an epileptic pediatric patient developed a significant elevation in serum alkaline phosphatase level (ALP) during LEV monotherapy⁴ and also he observed that the serum ALP level was decreased to normal after LEV discontinuation. Recently in Feb 2013, Borusiak P et al., conducted a multi-centre cross-sectional study on 128 epileptic children receiving anti-epileptic drugs including levetiracetam and observed about 24% had hypocalcaemia and 25% had hypophosphatemia.¹⁶ In contrast, Koo DL, et al suggested that LEV monotherapy may have no harmful effect on bone strength and metabolism for 1 year after their cross-sectional study involving 61 epileptic patients on levetiracetam monotherapy.¹⁷ One of the limitation of our study is that we estimated total ALP activity which includes liver activity also..., so estimation of bone specific ALP will be more precise to exactly measure the bone mineral density.

CONCLUSION

There is an evident impact of levetiracetam on bone health resulting in reduced calcium and phosphorus and elevated alkaline phosphatase levels. Further large prospective studies exploring Vit D status and determination of bone mineral density using DEXA SCAN should be carried out in order to evaluate the exact influence of levetiracetam on the bone health.

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