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Original Research Article

Levetiracetam monotherapy effect on serum calcium and serum vitamin D in patient of epilepsy

Anubha Garg*, Surekha Dabla, Sandeep Nagenhalli, Sanjay Fotedar

Department of Medicine, Pt. B. D. Sharma PGIMS, Rohtak, Haryana, India

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***Correspondence:**
Dr. Anubha Garg,
E-mail: anubhag741@gmail.com

ABSTRACT

Background: Objective of the study was to determine the Levetiracetam monotherapy effect on serum calcium and serum vitamin D levels in tertiary care hospital in Haryana, India.
Methods: A total of 110 patients with epilepsy, were enrolled to the study for one year between April 2013 to August 2014. All male patients aged 15-60 years and premenopausal females with epilepsy were included in the study. The study was a interventional prospective study design. The antiepileptic drug levetiracetam was administered starting from a dose of 20 mg/kg and dose was titrated according to the clinical response. During the follow up period, the subjects were asked about the seizure frequency and other side effects. The patients were be subjected to questionnaires based proforma. Baseline investigations, Hemogram, renal and liver function tests, calcium, phosphate, vitamin D and bone mineral density and T scores were noted. All investigations were repeated after one year of levetiracetam monotherapy.
Results: The mean age of onset of seizures in the study group was 23.22±6.62 years. 58% (n=29) were seizure free after 1 year of levetiracetam monotherapy, 28% patients had adequate control and 14% patients had poor control of their seizure episodes. There was an insignificant change in Hemoglobin, total leukocyte count, platelet count, renal parameters and Liver enzymes from baseline over a year of levetiracetam therapy. Serum calcium levels increased insignificantly from baseline levels of 9.68±0.59 mg/dl to 9.72±0.56mg/dl. Vitamin D levels increased from baseline of 39.35±14.91ng/ml to 39.84±14.07 ng/ml. Bone mineral density increased insignificantly from baseline of 0.92±0.13 g/cm^2 to 0.93±0.13 g/cm^2.
Conclusions: Present study has shown an overall beneficial effect on serum calcium, Vitamin D level, bone mineral density and T scores on DEXA scan.

Keywords: Epilepsy, Monotherapy, Seizure control, Vitamin D

INTRODUCTION

In patients with epilepsy, chronic therapy with conventional enzyme inducing antiepileptic drugs (EIAED's) causes abnormalities in calcium metabolism. These including hypocalcaemia, hypophosphatemia, elevated levels of serum alkaline phosphatase, serum parathyroid hormone and reduced serum levels of biologically active vitamin D metabolites. These changes cause radiologic evidence of rickets, and histological evidence of osteomalacia.[1-4]

These patients are also at high risk for pathological fractures due to reduction in the bone mineral density. These EIAED's which include phenytoin, carbamazepine, primidone, phenobarbitone and benzodiazepines cause decrease in bone mineral density by hepatic induction of cytochrome P450 enzymes

leading to increased metabolism of vitamin D.[5] LEV was approved as one of the broad spectrum AEDs with good efficacy and safety in various types of epilepsies.[6,7] The effect of LEV on vitamin D and bone mineral density is unclear. Therefore, the purpose of our study was to find out the effects of levetiracetam monotherapy on bone mineral density and vitamin D level in patients with epilepsy.

METHODS

This study was performed in department of medicine PGIMS Rohtak, Haryana, India to observe the effects of Levetiracetam monotherapy on Serum Calcium, Serum Phosphate and Serum Vitamin D levels and on Bone Mineral Density and T-score by DEXA Scan.

A total of 110 patients with a diagnosis of epilepsy on the basis of history as well as the clinical examination, which fulfilled the inclusion criteria, were enrolled to the study. The duration of study was for one year between April 2013 to August 2014. Out of these 42 patients recurrent episodes of seizures and were compelled for change from levetiracetam to other AED, and hence excluded. 18 patients were lost to follow up, so a total of 50 patients with epilepsy attending the Neurology clinic at Pandit B. D. Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India were included in the study group after obtaining an informed consent. All male patients aged 15-60 years and premenopausal females with epilepsy were included in the study.

The study was an interventional prospective study design. Patients with seizures due to systemic illnesses, renal disorders, on other antiepileptic drugs which are known to affect bone metabolism and bone mineral density, those on steroids, thiazide diuretics, calcium supplements, bisphosphonates or vitamin D due to other medical reasons, post-menopausal females and other known endocrine disorders like thyroid and parathyroid disorders were excluded from the study. The antiepileptic drug levetiracetam was administered in patients enrolled into the study, starting from a dose of 20 mg/kg and dose was titrated according to the clinical response. Patients were followed up for a period of one year. During the follow up period, the subjects were asked about the seizure frequency and other side effects. The patients were be subjected to questionnaires based proforma. The following investigations were done at baseline and after follow up at 1 year. Hemoglobin(g/dl), blood Urea (mg/dl), Serum Uric Acid (mg/dl), Serum Creatinine (mg/dl), Serum Calcium (mg/dl), Serum Phosphate (mg/dl), S. Alkaline Phosphatase (U/L), S. Bilirubin (mg/dl), S. Albumin (g/dl), 25 OH Vitamin D (ng/mil), DEXA BMD and DEXA T-SCORE. Only patients with normal vitamin D levels were enrolled. A T score of -2.5 or lower was defined as osteoporosis. All patients with osteoporosis were excluded from the statistical analysis. The data collected at the end of the study was analyzed. The values at baseline and after one year of the study were compared using student paired 't' test and analyzed using the SPSS software version 20.0 and open EPI v.3.02. A 'p' value of <0.05 was considered as statistically significant.

RESULTS

The mean age of the study group was 25.5±6.94 years (Table 1), M: F ratio 0.78:1. Type of seizure: 60% (n=30) of all patients in the study had a history suggestive of generalized tonic clonic seizure and 22% (n=11) with history of focal seizure with dyscognition. Remaining 18% (n=9) had focal seizures Age of onset of seizures and seizure control: The mean age of onset of seizures in the study group was 23.22±6.62 years. 23 (46%) were in the 11-20 years age group of onset, 18 (36%) in 21-30 years group and 9 (18%) were in 31-40 years of age group of onset of seizure activity.

Table 1: Seizure control with age of onset.

Age of seizure onset	11-20 Years	21-30 Years	31-40 Years
Seizure free	13 (56.5%)	14 (77.7%)	2 (22.3%)
Adequate control	7 (30.4%)	4 (22.3%)	3 (33.3%)
Poor control	3 (13.1%)	0 (0%)	4 (44.4%)
Total	23 (100%)	18 (100%)	9 (100%)

Efficacy of levetiracetam

Effect of levetiracetam monotherapy in seizure control

Efficacy was measured as seizure free, ≥50% seizure reduction (adequate control), <50% seizure reduction (poor control). Out of a total of 50 patients, 58% (n=29) were seizure free after 1 year of levetiracetam monotherapy, 28% patients (n=14) had adequate control and rest 14% patients (n=7) had poor control of their seizure episodes.

Effect of levetiracetam monotherapy on type of seizure

60% of GTCS and 63.3% of patients of focal seizures with dyscognition were seizure free with levetiracetam

monotherapy. Similarly, 33.33% of GTCS, 18.18% of focal seizures with dyscognition and 22.23% of focal seizure patients had adequately controlled seizures. Poor control was seen in 33.3% of focal seizure patients 18.18% of focal with dyscognition and 6.66% of GTCS.

Efficacy of levetiracetam in status epilepticus

In present study, 30% (n=15) had an episode of status epilepticus at presentation. 13 out of 15 (86.67%) patients who presented with status epilepticus and started on levetiracetam monotherapy were seizure free at the end of one year.

Seizure control of levetiracetam with age of onset

In age group of 11-20 years of seizure onset, 56.5% had adequate control of seizures. 30.4% and 13.1% were seizure free and poorly controlled of their seizures respectively. In age group of 21-30 years of seizure onset, 77.7% were seizure free with 22.3% having adequate control. 44.4% of patients with onset in 31-40 years age group were poorly controlled of their seizures with 33.3% and 22.3% being adequately controlled and seizure free respectively after one year of levetiracetam monotherapy (Table 1).

Dose of levetiracetam

Levetiracetam was initiated in the study group with a starting dose of 20mg/kg and the dose was titrated depending on the clinical response. The mean dose of levetiracetam was 1490±391.09 mg.

Hemogram, renal and liver function tests

There was an insignificant increase in Hemoglobin, total leukocyte count and platelet count. There was an insignificant increase in renal parameters blood urea and serum creatinine.

Liver enzymes Aspartate and Alanine transaminase and alkaline phosphatase decreased insignificantly from baseline over a year of levetiracetam therapy (Table 2).

Table 2: Complete hemogram, renal and liver functions.

Investigation	Baseline	1 Year	P value
Hemoglobin (g %)	12.30±1.64	12.54±1.35	p>0.05
Total leucocyte count (cells/ mm^3)	8142±2569.054	8210±2419.753	p>0.05
Absolute platelet count (lakh/mm^3)	2.95±0.9	3.04±0.71	p>0.05
Blood Urea (mg/dl)	28.24±10.79	30.17±8.03	p>0.05
S. Creatinine (mg/dl)	0.85±0.19	0.88±0.19	p>0.05
AST (U/L)	41.44±15.03	35.56±8.86	p>0.05
ALT(U/L)	37.3±14.58	32.94±8.8	p>0.05
S. Alkaline Phosphatase(U/L)	88.24±19.6	84.96±16.5	p>0.05
Serum Albumin(g/dl)	4.35±0.36	4.39±0.31	p>0.05
S.Phosphorus (mg/dl)	3.66±0.56	3.66±0.54	p>0.05

Table 3: Serum calcium and vitamin D.

		Baseline	AT 1 Year	P value
Serum Ca2+ (mg/dl)	Total	9.68±0.59	9.72±0.56	p>0.05
	Males	9.54±0.46	9.66±0.51	p>0.05
	Females	9.79±0.66	9.76±0.60	p>0.05
Serum vitamin D	Total	39.35±14.91	39.84±14.07	p>0.05
	Males	41.27±15.92	42.36±14.90	p<0.05
	Females	37.84±14.18	38.58±12.72	p>0.05

Serum calcium

Serum calcium levels at baseline were 9.68±0.59 mg/dl. Females had a mean calcium level of 9.79±0.66 mg/dl and males had a mean of 9.54±0.46 mg/dl. The serum calcium levels after one year of levetiracetam treatment increased to 9.72±0.56mg/dl. The change was statistically insignificant (p>0.05). The mean for females and males was 9.76±0.60 mg/dl and 9.66±0.51 mg/dl which was statistically insignificant (p>0.05) (Table 3).

Serum vitamin D

Serum Vitamin D level at baseline was 39.35±14.91ng/ml. The serum Vitamin D level after one year of levetiracetam treatment increased to 39.84±14.07

ng/ml. The change was statistically insignificant (p>0.05). Females had a baseline mean of 37.84±14.18ng/ml with an insignificant increase to 38.58±12.72ng/ml (p>0.05). Males had a mean of41.27±15.92ng/ml at baseline. There was a significant increase in vitamin D levels in males to 42.36±14.90ng/ml after one year (p<0.05) (Table 3).

Bone mineral density (BMD)

Bone Mineral density (BMD) of L1-L4 lumbar vertebrae using DEXA scanner at baseline was 0.92±0.13 g/cm^2. Mean BMD in males and females were 0.88±0.14 g/cm^2 and 0.95±0.10 g/cm^2. After one year of levetiracetam monotherapy, BMD increased to 0.93±0.13 g/cm^2 but the change was statistically insignificant (p>0.05). Mean BMD in males increased to 0.90±0.12 g/cm^2 but decreased in females to 0.94±0.13 g/cm^2 which were statistically insignificant (p>0.05) (Table 4).

DEXA T Score

T score at L1-L4 lumbar vertebrae using DEXA scanner at baseline was -1.08±0.52. T score in males and females at baseline were -1.13±0.40 and -1.04±0.60 respectively. After one year of levetiracetam monotherapy, T score increased to-1.03±0.48 which was statistically insignificant (Table 4).

Table 4: DEXA scan: bone mineral density (BMD) and T score.

		Baseline	At 1 year	P value
BMD (g/cm^2)	Total	0.92±0.13	0.93±0.13	p>0.05
	Males	0.88±0.14	0.90±0.12	p>0.05
	Females	0.95±0.10	0.94±0.13	p>0.05
T score	Total	-1.08±0.52	-1.03±0.48	p>0.05
	Males	-1.13±0.40	-1.05±0.46	p<0.05
	Females	-1.04±0.60	-1.02±0.51	p>0.05

Effect of high dose of levetiracetam on calcium, vitamin D, bone mineral density and T score

We categorized the study group into those who received <1500 mg of levetiracetam per day as low dose and ≥1500 mg as high dose treatment group. 54% (n=27) and 46% (n=23) were in the high dose and low dose groups respectively. The effect of dose of levetiracetam on the mean change of calcium and Vitamin D were not statistically significant (p>0.05) (Table 5). There was no significant baseline change in bone mineral density and T scores in either low or high dose levetiracetam treatment groups.

Table 5: Effect of levetiracetam dose on calcium.

	Low dose (<1500mg)	High dose (≥1500 mg)	'p' value
Change in serum calcium (mg/dl)	-0.17±0.57	0	p>0.05
Change in serum vitamin D (ng/ml)	-0.52±1.97	1.30±1.2	p>0.05

Correlations between the Dosage of Levetiracetam and Changes in Calcium, Vitamin D, BMD and T Scores using the Pearson correlation coefficient

There was a statistically insignificant correlation between change in serum calcium levels and dosage of levetiracetam with a correlation coefficient of 0.19 (p>0.05). There was a significant positive correlation between change in serum vitamin dose of levetiracetam with a correlation coefficient of 0.45 (p<0.05). Changes in both bone mineral density and T score did not correlate with dosage of levetiracetam (r=0.00) (Table 6).

Table 6: Correlation with levetiracetam dose.

	Correlation coefficient (r)	'p' value
Change in calcium	0.19	>0.05
Change in vitamin D	0.45	<0.05
Change in BMD	0.00	N.S
Change in T score	0.00	N.S

DISCUSSION

Efficacy was measured as seizure free, ≥50% seizure reduction (adequate control), <50% seizure reduction (poor control). Elinor BM et al, and collegues studied the efficacy and tolerability of levetiracetam in patients with intractable epilepsy and concluded that the levetiracetam was very efficacious with >75% of patients having adequately controlled seizures.[9,10] The findings of present study coincide with the findings of study by Tim B et al, and collegues. Their studies revealed that majority of patients with generalized seizures were seizure free at the end of one year of levetiracetam monotherapy.[11] Regarding status epilepticus, in a study by McTague et al, and colleagues, levetiracetam terminated seizures in 24 of

the 39 patients (62%) with acute repetitive seizures.[12] Levetiracetam terminated seizures in three of the four (75%) patients with status epilepticus.

Regarding serum calcium levels, present findings are same as studies by Koo DL et al, and colleagues who reported that no differences were observed in serum calcium across LEV treatment.[13] Similarly studies by Nissen Meyer et al, observed that neither high or low dose levetiracetam affected calcium levels in study group as compared to controls.[14]

Vitamin D levels increased both in males and females in our study. Ali et al, and collegues concluded that levetiracetam did not have any significant effect on serum 25 (OH) D levels.[15] In another study by Koo DL et al, levetiracetam did not show vitamin D to be decreased.[13] Andras H et al, and collegues assessed various studies and concluded that newer non enzyme inducer AEDs like levetiracetam does not seem to lower vitamin D levels.[16] Chifari R et al, and collegues opined the new AEDs such as topiramate, lamotrigine and levetiracetam seemed not to affect either Vitamin D levels or BMD.[17]

Regarding DEXA T score, present observations were similar to the findings by Nissen Meyer et al, who reported that LEV did not significantly affect BMC and BMD.[14] But low dose LEV inhibited bone formation as assessed by decreased serum osteocalcin levels and decreased BMD and BMC. High-dose LEV had no impact on BMD or BMC. In their study, there was a dose dependent effect of LEV in bone. This effect was due to decrease in estrogen levels by low dose levetiracetam compared to high dose as noted in some studies.[18] In contrast Beniczky and collegues reported that among patients using AED's in monotherapy the incidence of decreased BMD was significantly higher in patients treated with LEV as compared to the remaining patients.

CONCLUSION

From the present study we conclude that levetiracetam as monotherapy does not seem to have adverse effect on bone mineral density or vitamin D levels unlike the conventional enzyme inducing antiepileptic drugs. Our study has shown an overall beneficial effect on serum calcium, Vitamin D level, bone mineral density and T scores on DEXA scan.

As limited studies are available on the effect of levetiracetam as monotherapy on bone mineral density and vitamin D, and present findings were in a small subset of epilepsy patients, further prospective studies in a large number of patients need to be carried out to confirm the findings of our study.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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