Epilepsy & Behavior 55 (2016) 84–86

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Brief Communication

Preliminary evidence for gender effects of levetiracetam monotherapy duration on bone health of patients with epilepsy

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ARTICLE INFO

Article history:
Received 8 November 2015
Revised 12 December 2015
Accepted 16 December 2015
Available online xxxx

Keywords:
Levetiracetam
Bone
Mineral
Density
Osteopenia
Osteoporosis

ABSTRACT

Enzyme-inducing antiepileptic drugs AEDs have adverse effects on bone mineral density (BMD), whereas studies on levetiracetam (LEV), a nonenzyme-inducing agent, have showed conflicting results. The aim of this study was to further elucidate the role of LEV in bone health. A sample of forty-six patients with epilepsy (mean age: 35.7 years, range: 20.2–64.2 years, 39.1% males) on LEV monotherapy for at least one year (range: 1.5–14.5 years, median 5.5 years) underwent femoral neck (FN) and lumbar spine (LS) BMD measurements. The T- and Z-scores were calculated. Results showed that 15.2% of the patients were identified with osteopenia and none with osteoporosis. Pearson's correlations revealed a negative but not significant association of LEV duration with bone-related measurements (range of rhos: from −0.004 to −0.23), except for LS T-scores. In terms of FN BMD measurements, Z-scores, and T-scores, longer LEV therapy duration had adverse but not significant effects on bone health after adjusting for age and gender. With regard to LS BMD measurements, Z-scores, and T-scores, men taking LEV for at least 5.5 years had better, although not significant, bone health compared with men with shorter LEV exposure, after adjusting for age. The opposite was found in women, although differences did not reach significance. These preliminary results are indicative of a differential effect of LEV therapy duration in men and women, which could presumably account for the incongruity of the already published studies. Also, LS assessments were more sensitive to these gender differences. Future larger studies should validate these results.

1. Introduction

Epilepsy is one of the most common chronic neurological diseases affecting people from birth to old ages. Its consequences extend to all facets of human health (i.e., physical, mental, and social) and are derived both from the condition itself and its treatment. Specifically, the metabolic changes of bones associated with chronic antiepileptic drug (AED) treatment has been parsimoniously studied. More importantly, only about one-third of neurologists retain high levels of awareness of the fact that AEDs are associated with the reduction of bone mineral density (BMD) and, thus, may increase the risk for factures induced by osteopenia or osteoporosis [1]. Patients with epilepsy are 2–6 times more prone to fractures than the general population, with only 35% attributed to the seizures [2,3]. Enzyme-inducing AEDS (e.g., carbamazepine, oxcarbazepine, phenobarbital) have been associated with fracture risk in contrast to the nonenzyme-inducing AEDs (e.g., lamotrigine, tiagabine, topiramate) which have shown no significant association [3]. The pathogenesis of BMD reduction due to AEDs has been extensively described elsewhere [3].

With regard to levetiracetam (LEV), a nonenzyme-inducing AED, evidence is scarce. In rats, a low dose was associated with reduced biomechanical strength of the femoral neck [4]. In a recent retrospective cohort study, duration of exposure to newer nonenzyme-inducing AEDs (including LEV) was associated with higher T-scores (hip, femoral neck, and lumbar spine) compared with nonusers, and patients were less likely to receive the diagnosis of osteoporosis [5]. These findings were corroborated in a study by Koo et al. examining the effects of about 1 year of LEV monotherapy on bone health [6]. On the contrary, another study showed that 70% of patients (12/17) on LEV monotherapy at least for 2 years had decreased BMD (9 were found with osteopenia and 3 with osteoporosis) [7].

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http://dx.doi.org/10.1016/j.yebeh.2015.12.025
1525-5050/

The aim of this study was to expand the literature on the issue of LEV therapy and bone health by investigating a small sample of patients with epilepsy on LEV monotherapy. The study was approved by the hospital's Scientific and Ethical committee.

2. Materials and methods

In this retrospective cohort study, 46 consecutive outpatients with epilepsy treated with LEV monotherapy for at least 1 year underwent BMD measurement. Patients receiving drugs other than LEV (e.g., antidepressants) were excluded. All patients gave their informed consent. The mean age was 35.7 years (range: 20.2–64.2 years, median: 35.8 years). The sample consisted of 18 males (39.1%) and 28 females (60.9%). Mean duration of treatment was 6.5 years (range: 1.5–14.5 years, median: 5.5 years).

Bone mineral density of the lumbar spine (LS) and the femoral neck (FN) was measured using a Norland Excell Plus-XR-36 densitometer (Norland Medical Systems, Fort Atkinson, WI, USA) by dual-energy X-ray absorptiometry (DXA). Osteopenia was defined as a BMD T-score at one site between −1 and −2.5, and osteoporosis was determined as a BMD Z-score at one site less than −2, or as BMD T-score at one site less than −2.5 [8].

The incidence of low BMD (osteopenia, osteoporosis) was measured. The effect of LEV duration on bone health was first examined with Pearson's rho correlation. Then, duration of LEV therapy was grouped according to the median value of 5.5 years forming two groups; the short and the long treatment groups. Analyses of covariance (ANCOVA) were conducted with bone-related measurements as dependent variables (separately), treatment group as predictor, and age and gender as covariates. In case of significant interaction terms, different subgroup analyses were conducted. Adjusted mean bone-related measurements with standard errors were presented. Level of significance was set at 0.05. For all analyses, we used SPSS 22.0 for Windows (SPSS Inc., Chicago, IL).

3. Results and discussion

There were no patients identified with osteoporosis. Two patients (4.3%) had osteopenia based on the FN T-score, three patients (6.5%) had osteopenia based on LS T-score, and two (4.3%) patients had osteopenia according to both T-scores (total patients with osteopenia: 7/46 or 15.2% of the study sample).

Table 1 presents the correlation between duration of LEV therapy and bone measurements. All Pearson's rhos except for LS T-score were negative indicating that increased treatment duration is associated with worse bone health. However, none of the correlations reached statistical significance.

Table 2 presents the adjusted means of bone-related measurement across the short (≤5.5 years of LEV therapy) and long (+5.5 years of LEV therapy) subgroups of LEV therapy. As evidenced, there were no significant differences across the subgroups. With regard to FN measurements, patients in the long treatment group had lower mean values compared with the short treatment group indicating an adverse, but not significant, effect of LEV on bone health. Regarding LS measurement, a significant effect of the treatment group × gender interaction term was found indicating that LS bone measurements are affected differently with respect to gender and duration of treatment. Separate gender analyses disclosed that men in the long treatment group have better bone health than men in the short treatment group, although not statistically significant. On the other hand, women in the long treatment group have worse bone health than women in the short treatment group.

Although this study used a small sample, to our knowledge, this is the first one reporting a diverse effect of LEV on bone health across genders. Study limitations are that previous AEDs effects were not taken into account and that pre-LEV BMD was not assessed. However, given the long LEV exposure and the relatively young age of our patients, this limitation could be minimized. These gender differences especially for LS measurements may account for the incongruity between studies indicating either a beneficial or a detrimental effect of LEV on bone health [5–7]. Also, this study indicated the differential role of FS versus LS measurement with respect to the role of gender, rendering the latter presumably as a more sensitive procedure for assessing bone health in patients receiving AEDs.

Table 1
Pearson's rho correlation between duration of levetiracetam monotherapy and bone-related measurements.

	Pearson's rho, p-value	
	Femoral neck measurements	Lumbar spine measurements
BMD	−0.18, 0.24	−0.13, 0.93
Z-score	−0.23, 0.13	−0.004, 0.98
T-score	−0.22, 0.15	0.01, 0.97

BMD: bone mineral density.

Table 2
Adjusted means for bone-related measurements for short and long duration of levetiracetam therapy groups.

	≤5.5 years of treatment	+5.5 years of treatment	p-Value
Total			
Mean FN BMD ± SE	1.05 ± 0.03	1.02 ± 0.03	0.56
Mean FN Z-score ± SE	0.47 ± 0.22	0.16 ± 0.24	0.35
Mean FN T-score ± SE	0.29 ± 0.22	0.01 ± 0.24	0.39
Men			
Mean LS BMD ± SE	1.22 ± 0.04	1.32 ± 0.06	0.18
Mean LS Z-score ± SE	0.10 ± 0.35	0.93 ± 0.44	0.17
Mean LS T-score ± SE	−0.01 ± 0.36	0.84 ± 0.45	0.17
Women			
Mean LS BMD ± SE	1.24 ± 0.03	1.17 ± 0.03	0.09
Mean LS Z-score ± SE	0.59 ± 0.21	0.04 ± 0.21	0.08
Mean LS T-score ± SE	0.46 ± 0.21	−0.09 ± 0.21	0.07

FN: femoral neck, LS: lumbar spine, BMD: bone mineral density, SE: standard error. Analyses for covariance (ANCOVA) tests after adjusting for age and gender. LS bone measurements were tested separately because of statistically significant effect of the treatment group × gender interaction term.

4. Conclusions

In conclusion, the study was suggestive of the differential effects of bone measurements and gender for assessing bone health in patients receiving LEV. Femoral neck measurements revealed adverse but not significant effects of longer LEV duration on bone health. On the other hand, LS measurements disclosed a putative beneficial effect of longer LEV duration on bone health in men and a corresponding detrimental effect in women. These preliminary findings should be validated by larger studies.

Conflicts of interest

None.

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