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Association of antiepileptic drugs, vitamin D, and calcium supplementation with bone fracture occurrence in epilepsy patients

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ABSTRACT

The aim of this study is to determine whether calcium and vitamin D supplementation reduces the risk of bone fractures in adult epilepsy patients. Records were obtained on 7716 patients with epilepsy prescribed antiepileptic drugs (AED) from the Veteran Affairs Hospital in Lexington, Kentucky. We performed a single center, retrospective cohort study to examine the proportion of fractures in 3303 patients on AED who took supplements compared to patients on AED not taking supplements. Patients prescribed long-term AEDs taking calcium and vitamin D were as likely to have fractures as those who did not take these supplements (11.7% vs. 9.9%, $\chi^2 = 0.59$, $p = 0.44$). Phenytoin use was associated with a statistically significant increased risk of fractures OR = 1.55 (1.10–2.24). Thus, in this group of patients with epilepsy on AED, bone fractures were not prevented in individuals taking calcium and vitamin D supplementation.

1. Introduction

Skeletal fractures are a common co-morbidity in patients with epilepsy. Population studies demonstrate a two-to-six fold increase in fracture rate in epilepsy patients compared to the general population [1–3]. Approximately 39% of fractures are spontaneous and unrelated to trauma or seizures [4], though a significant proportion result from peri-ictal activity [4,5].

Anti-epileptic drugs (AEDs) may contribute to fractures through several mechanisms including, but not limited to, hepatic induction of cytochrome p450 isozymes with increased catabolism of vitamin D, impaired absorption of calcium, calcitonin deficiency, and interference with vitamin K metabolism, all of which alter bone health [6]. Dysregulation of calcium and vitamin D metabolism in patients on chronic AED therapy is a well-recognized phenomenon dating to the 1960s and 1970s [7–9]. Early reports suggested that impaired bone mineralization mediated the pathologic correlation of increased fracture rates in patients on AED therapy [10,11]. More recent published reports implicate secondary hyperparathyroidism and use of enzyme inducing anti-epileptic drugs (EIAED) with resultant increased bone turnover rates in the pathogenesis of AED-related increased fracture risk [12–14].

The standard treatment in patients without epilepsy at risk for fracture occurrence is calcium and vitamin D supplementation. There is controversy over hormone replacement therapy and bisphosphonate use in patients with epilepsy [15] as some of these therapies are not appropriate for use in all epilepsy populations. Hormone replacement therapy is only appropriate for use in women. The estrogen component can be pro-epileptic in those with epilepsy, and their use may increase cardiovascular disease [16]. Bisphosphonates with its potential teratogenicity are used cautiously in pre-menopausal women [17]. Additionally, most of these therapies have not been tested in men. While fracture prevention in epilepsy patients includes seizure prevention to reduce fractures related to trauma [18,19], additional measures are required. Few studies have examined the effects of calcium and vitamin D supplements on fracture incidence in patients on concomitant AEDs. These studies show that a wide range of vitamin D and calcium intake is needed to maintain normal vitamin D serum concentra-

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Table 1
Study participant demographics and characteristics. A total of 3303 patients were included in this study, the mean age of the participants was 55.7 years (SD 13.3), the majority of patients were male (92.4%), 4.9% (n = 162) of patients were taking vitamin supplements, the mean time on supplements was 2 years (SD 1.7), the mean time on AED was 2.8 years (SD 2.4), and 5.8% (n = 329) of patients had at least one fracture.

	All (n = 3,303)	At least one fracture (n = 329)	No fractures (n = 2,974)	
Age[a]				
Mean, years (SD)	55.7 (13.3)	56.2 (14.0)	55.7 (13.3)	NS
Gender				
% Male	92.4	92.4	92.4	NS
Supplement use				
N (%)	162 (4.9)	19 (5.8)	143 (4.8)	p = 0.44
Time on supplement				
Mean, yrs (SD)	2.0 (1.7)	3.9 (2.3)	1.7 (1.4)	p = 0.0007
Time on AED				
Mean, years (SD)	2.8 (2.4)	3.6 (2.6)	2.7 (2.3)	p < 0.0001

[a] Age at which treatment with AED began.

tions and bone density. However, supplementation has not been shown to decrease the risk of fractures [20–23].

The aim of the current retrospective, cohort study is to determine whether calcium and vitamin D supplementation reduces bone fracture risk in adult epilepsy patients on AEDs, and to investigate the association between AED use and fractures in this population. We hypothesized that individuals with epilepsy on AEDs and calcium and vitamin D supplementation would have reduced fracture rates compared to epilepsy patients on AEDs alone. Limitations exist in our ability to implicate particular AED use with fracture occurrence in part due to potential delayed AED effects on bone health.

2. Patients and methods

2.1. Study population

In accordance with an approved Institutional Review Board protocol, the patient database at the Veteran Affairs Medical Center (VMAC) in Lexington, Kentucky was retrospectively reviewed between October 1998 and March 2007. Records were obtained on 7716 patients with epilepsy on AEDs. 3303 patients included in the study had data concerning supplemental calcium and vitamin D use with concurrent AED use for at least one month during the review period. Information about medication intake prior to 1998 was unavailable in the database, and we assumed that patients had no previous exposure to AEDs or supplements. Of the 3303 patients included in this study, the mean age of the participants was 55.7 years (SD 13.3), the majority of patients were male (92.4%), 4.9% (n = 162) of participants were taking vitamin supplements, the mean time on supplements was 2 years (SD 1.7), the mean time on AED was 2.8 years (SD 2.4), and 5.8% (n = 329) of patients had at least one fracture.

2.2. Study design

This was a single center, retrospective cohort study. Our cohort consisted of epilepsy patients in the database with information concerning both calcium and vitamin D supplementation and AED use. To limit inclusion of individuals with a prior increased fracture risk, patients were excluded if a documented fracture occurred prior to documented supplement use. We defined time on AED and supplement use as the calculated difference in the first and last date that the VAMC pharmacy dispensed the medication. We assumed continuous medication use during this time interval. Patients on phenobarbital were not included in this study since this medication is known to be associated with bone fractures.

2.3. Clinical information

This cohort of patients with epilepsy is composed of patients on monotherapy and polytherapy. Women with epilepsy were included in the analysis regardless of menopausal status. The AEDs included in the analysis were: carbamazepine, clonazepam divalproex, gabapentin, lamotrigine, levetiracetam, phenytoin, primidone and topiramate. Phenobarbital was not included in the study.

2.4. Statistical methods

We used the chi-square test to compare the proportion of bone fractures in patients on AEDs taking supplements compared to that of patients on AEDs not taking supplements. Logistic regression and calculated odds ratios were used to assess the influence of age, gender, time on AED, and time on supplement on fracture occurrence in association with AED and supplement use. To assess the effect of individual AEDs on fracture risk, logistic regression models were fit controlling for gender, supplement use, age at first AED use, and time on AED. For patients who took more than one AED between 1998 and 2007, the AED of interest selected was the drug used at the time of the fracture.

3. Results

3.1. Identified patients

A total of 7716 patients with epilepsy taking AEDs and documented medical care at the VMAC in Lexington, Kentucky were identified. Of these, 3303 patients had adequate data documentation available for calcium and vitamin D supplementation and were included in the study. Three-hundred twenty-nine patients had at least one fracture after their first recorded supplement use (see Table 1). Patients whose fractures occurred before their first recorded supplement use (n = 30) were excluded from further analyses.

Calcium and vitamin D users were significantly older than nonusers when they began taking AED (59.3 years vs. 55.5, years p < 0.0002), were older when they were seen for their first fracture (65.0 years vs. 58.4 years, p = 0.05), and with a female preponderance (25.3% vs. 6.7%, p < 0.0001).

3.2. Supplementation outcomes

Patients on long-term AEDs who took calcium and vitamin D were as likely to have fractures as those who did not take these supplements (11.7% vs. 9.9%, χ^2 = 0.59, p = 0.44). Adjusting for age at first recorded AED use, gender, and time on AED, calcium and vitamin D users were less likely than nonusers to have fractures