Epilepsy Research 116 (2015) 59–66

Contents lists available at www.sciencedirect.com

Epilepsy Research

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

Enzyme-inducing antiepileptic drugs and fractures in people with epilepsy: A systematic review

Lisa-Ann Fraser[a,*], Jorge G. Burneo[b], J. Alexander Fraser[b]

[a] Department of Medicine, Division of Endocrinology and Metabolism, Western University, London, ON, Canada
[b] Department of Clinical Neurological Sciences, Division of Neurology, Western University, London, ON, Canada

ARTICLE INFO

Article history:
Received 17 March 2015
Received in revised form 15 June 2015
Accepted 5 July 2015
Available online 8 July 2015

Keywords:
Epilepsy
Enzyme-inducing antiepileptic drugs
Fracture
Bone mineral density

ABSTRACT

Objective: People with epilepsy (PWE) have an increased fracture risk, independent of seizures. Antiepileptic drugs are thought to increase this risk, particularly those that induce the hepatic cytochrome P450 enzyme system. We aimed to determine whether PWE treated with enzyme-inducing antiepileptic drugs (EIAEDs) have decreased bone mineral density (BMD), or increased fracture incidence, versus those treated with non-EIAEDs.
Methods: We searched MedLine, EMBase, CENTRAL, and CINAHL prior to November 2014 for all studies comparing fracture risk, or BMD change, in PWE treated for ≥1 year with EIAEDs versus non-EIAEDs.
Results: Thirteen observational studies met eligibility criteria. These studies, representing 68,973 adult PWE, were significantly heterogeneous, making meta-analysis impossible. Study results were split, with 5 studies showing decreased BMD in EIAED users, 5 studies showing no effect of EIAED on BMD, 2 studies showing increased fracture incidence in EIAED users, and 1 study showing no difference in fracture risk. The largest study (n = 63,259), which was also the most methodologically rigorous, showed an increased hazard ratio of 9–22% for any fracture, and 49–53% for hip fracture, in EIAED users.
Significance: The literature is divided regarding the bone effects of EIAEDs; however, current best evidence supports an increased fracture risk in PWE treated with an EIAED compared to those treated with non-EIAEDs. A single article dominated our review, and other large methodologically rigorous studies are needed to confirm or refute its results. Further small studies, with limited power to control for multiple potentially confounding variables, are not likely to help.

Introduction

Antiepileptic drugs (AEDs) have long been recognized as an important risk factor for osteoporosis-related fragility fractures (Cummings et al., 1995). People with epilepsy (PWE) already have an increased fracture risk related to seizure-associated trauma and to falls associated with the motor and cerebellar side-effects of AEDs (Beghi, 2009; Zaccara et al., 2008); however, there also seems to be a bone fragility associated with certain AEDs that confers an increased fracture risk independent of these considerations (Cummings et al., 1995; Souverein et al., 2006a).

One theory holds that cytochrome P450 enzyme-inducing antiepileptic drugs (EIAEDs) may have increased fracture risk compared to non-EIAEDs by altering vitamin D metabolism, leading to serum calcium abnormalities and subsequent osteoporosis (Kulak et al., 2004; Pack et al., 2005, 2011; Krishnamoorthy et al., 2010). Against this theory are several studies that have not identified any impact on serum calcium levels or vitamin D indices (Pack et al., 2011), or even any difference in fracture risk, between EIAEDs and non-EIAEDs (Souverein et al., 2006a). Because osteoporotic fractures increase morbidity and decrease quality of life regardless of age or sex (Papaioannou et al., 2009; Bliuc et al., 2009; Holvik et al., 2010; Piirtola et al., 2008), and because the 5-year mortality rate after osteoporotic fracture in patients over age 50 is as high as 23.5% (Ioannidis et al., 2009), any differential effects of enzyme inhibition on bone heath are highly relevant to neurological practice.

We performed a systematic review of the literature to examine whether EIAEDs cause increased fractures or decreased bone mineral density (BMD) in PWE, compared to PWE on non-EIAEDs. No prior systematic reviews have addressed this specific question. By summarizing the current available literature, we aimed to define any additional fracture risk imparted by EIAEDs in PWE and to clarify areas in need of further study.

* Corresponding author. Tel.: +1 5196466245; fax: +1 5196466067.
E-mail addresses: Lisaann.Fraser@sjhc.london.on.ca (L.-A. Fraser), Jorge.Burneo@lhsc.on.ca (J.G. Burneo), Alex.Fraser@lhsc.on.ca (J.A. Fraser).

http://dx.doi.org/10.1016/j.eplepsyres.2015.07.003
0920-1211/

Methods

We conducted a systematic review according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Appendix 1) (Stroup et al., 2000).

Information sources and search

We searched MedLine, EMBase, EBMR (Cochrane), Web of Science, and BIOSIS, from inception to November 2014 for all comparative studies examining fracture risk or BMD change in PWE taking an EIAED for at least one year. Studies were included if they compared patients on an EIAED to similar patients taking non-EIAEDs. No age, gender, publication date, or language restrictions were applied. Reference lists of relevant articles were also searched. Our search strategy was reviewed by a research librarian with experience in systematic reviews. A list of subject headings and keywords used to search the various databases is presented in Appendix 2.

Eligibility criteria

Epilepsy was defined as a disorder of recurrent seizures (partial or generalized) requiring ongoing AED therapy. All comparative studies of PWE on an EIAED were included in our initial search. Participants were individuals of any age or sex, diagnosed with epilepsy, who were prescribed an EIAED (including carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, or topiramate) (Perucca, 2005; Diaz et al., 2008) for at least one year. Studies without a comparison group taking a non-EIAED (for at least one year) were excluded. Studies that used AEDs as monotherapy or as adjunctive therapy were all included. Non-EIAED users could not have had any exposure to an EIAED; if an individual was on combination therapy with both an EIAED and a non-EIAED, they were considered an EIAED user for the purposes of this analysis. Our primary outcomes were fracture (at any bone site) and change in BMD (at any site). Secondary outcomes included mortality, seizure control, and reported adverse events.

Study selection, data collection, and risk of bias

Two reviewers (LAF and JAF) independently reviewed the titles and abstracts of all citations identified in the original search. All citations that were deemed potentially relevant by at least one reviewer were then retrieved for full text review. Both published articles and conference abstracts were included. For articles available only in non-English languages, native speakers were sought to interpret, or interpretation computer software was used. Both reviewers independently accessed each full text article and extracted data using a pre-defined data extraction form. After all data extraction was completed by both reviewers, the extracted data were jointly reviewed to ensure accuracy, and inconsistencies were resolved with discussion. When further data or a clarification of methodology was needed, e-mails were sent to the authors of the studies being reviewed.

Study quality was assessed using the Newcastle-Ottawa Scale (NOS), a 9 "star" instrument that incorporates study selection criteria, comparability of groups, and exposure/outcome definitions (Wells et al., 2014). The NOS is useful for providing a semi-quantitative assessment of quality for cohort and case control studies, and is recommended by the Cochrane Collaboration (Higgins and Green, 2011). We categorized quality by groups, with a 7–9 star rating defined as 'good' quality, 4–6 as 'moderate' quality, and 0–3 as 'poor' quality. Cross sectional studies were assessed for quality by each reviewer on a 9-item scale similar to the NOS, but without using the scale directly, as the NOS was not created for this type of study.

Results

Search results

After duplicate articles were removed, 1209 citations were identified in our search and were assessed by the two reviewers for eligibility. Of these citations, 145 underwent full text review, and 13 studies met the pre-defined review criteria, and were performed in a population of adult PWE, making them eligible to include in the final review (Fig. 1). The two reviewers discussed in detail all articles individually assessed during the full-text review (unweighted kappa = 0.71). The two most common specific reasons for excluding a study were failure of the study to separate EIAEDs and non-EIAEDs and failure of the study to restrict inclusion to a population of PWE. There were 26 articles that did not present enough information to meet our eligibility criteria, despite attempts to contact authors for further results or details. The final 13 studies included in our analysis represented a broad range of observational designs: 7 cross sectional, 2 retrospective cohort, 2 prospective cohort, 1 case control, and 1 nested case control study.

Study characteristics and quality assessment

Characteristics of the included studies are shown in Table 1. A total of 68,973 adult PWE were included in the 13 studies: 7 cross sectional studies representing 596 patients (Fuleihan et al., 2008; Heo et al., 2011; Phabphal et al., 2009; Salimipour et al., 2013; Sato et al., 2001; Sivaraaman and Jacobson, 2009; Srivastava and Jain, 2001), 4 cohort studies representing 66,726 patients (Espinosa et al., 2011; Nicholas et al., 2013; Pack et al., 2008; Phabphal et al., 2013), 1 case control study of 78 patients (Stephen et al., 1999), and 1 nested case control study representing 1573 patients (Souverein et al., 2006b). The majority of studies (7 of 13) were from Asia/the Middle East; 3 studies were from North America; and 3 studies were from Europe. Two studies were performed in females only (Heo et al., 2011; Pack et al., 2008), but most included patients of both sexes. Mean age of the included participants ranged from 25 to 76 years, thereby including both pre- and post-menopausal women. The duration of AED use was broad, ranging from 1 to 36 years. The quality of the included studies varied, with 5 studies rated as 'poor', 4 'moderate', and 2 'good'. Two studies existed only in conference abstract form and had limited information on which to base an assessment of quality; therefore, we refrained from assigning a specific numeric quality score to these citations.

Outcomes

Bone mineral density

Of the 10 studies that included bone mineral density as an outcome (Fuleihan et al., 2008; Heo et al., 2011; Pack et al., 2008; Phabphal et al., 2009, 2013; Salimipour et al., 2013; Sato et al., 2001; Sivaraaman and Jacobson, 2009; Srivastava and Jain, 2001; Stephen et al., 1999), 5 ($n = 433$ individuals; 2 cohort, and 3 cross sectional studies) found decreased (or decreasing) BMD values in PWE on EIAEDs compared to non-EIAEDs, whereas 5 studies ($n = 405$; 1 case control, and 4 cross sectional) showed no effect of AED type on BMD (Table 2). The methodology and outcome definitions of these 10 studies were markedly heterogeneous, with some studies reporting a change in BMD over a one year period, and other studies simply measuring BMD once in all patients and then comparing the differences between groups. The BMD values were reported differently between studies as well, with some reporting results as g/cm^2, and others reporting *Z*-scores or *T*-scores. Similarly, BMD was measured