A Review of the Effect of Anticonvulsant Medications on Bone Mineral Density and Fracture Risk

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ABSTRACT

Background: Osteoporosis and seizure disorders are common diagnoses in older adults and often occur concomitantly.

Objective: The goal of this review was to discuss the current hypothesis for the pathogenesis of anticonvulsant-induced bone density loss and the evidence regarding the risk for osteoporosis and fractures in older individuals.

Methods: A review of the literature was performed, searching in MEDLINE and CINAHL for articles published between 1990 and October 2009 with the following search terms: *anticonvulsant* OR *antiepileptic;* AND *osteoporosis* OR *bone density* OR *fracture* OR *absorptiometry, photon*. Studies within the pediatric population, cross-sectional studies, and studies whose results were published in a language other than English were excluded.

Results: A search of the published literature yielded >300 results, of which 24 met the inclusion and exclusion criteria and were included in this review. Hepatic enzyme induction by certain anticonvulsant medications appears to contribute to increased metabolism of 25-hydroxyvitamin D to inactive metabolites, which results in metabolic bone disease. There is increasing evidence that anticonvulsant use is associated with a higher risk of osteoporosis and clinical fractures, especially among older agents such as phenobarbital, carbamazepine, phenytoin, and valproate. Several observational studies suggest a class effect among anticonvulsant agents, associated with clinically significant reductions in bone mineral density and fracture risk. The use of anticonvulsant medications increases the odds of fracture by 1.2 to 2.4 times. However, only 2 large-scale observational studies have specifically examined the risk among those aged >65 years. This review also identified a randomized controlled trial whose results suggest that supplementation with high-dose vitamin D may be associated with increased bone mineral density in patients taking anticonvulsant medications. However, no randomized controlled trials investigating therapeutic agents to prevent fracture in this population were identified. Consequently, there are no formal practice guidelines for the monitoring, prevention, and management of bone disease among those taking anticonvulsants.

Conclusions: Observational studies suggest an association between use of anticonvulsant medications, reduced bone mineral density, and increased fracture risk. Randomized clinical trials are needed to guide the management of bone disease among those who use anticonvulsants. (*Am J Geriatr Pharmacother.* 2010;8:34–46) © 2010 Excerpta Medica Inc.

Key words: anticonvulsants, bone density, osteoporosis, fractures.

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INTRODUCTION

Osteoporosis and seizure disorders are common diagnoses in older adults and may occur concomitantly. There is a bimodal distribution in the incidence of seizures and epilepsy, peaking in childhood but then increasing again after the age of 60 years.[1] In this older age group, the incidence of unprovoked seizures is 121 per 100,000 per year and the diagnosis of epilepsy nears 40 per 100,000 per year.[1,2] Likewise, the prevalence of epilepsy is 1% among individuals aged >60 years and increases with advancing age.[3] Anticonvulsants may also be prescribed for nonseizure indications such as neuropathic pain.[4]

Accordingly, the number of anticonvulsant prescriptions has increased in this population. In the United States and in European countries, ~1% of community-dwelling older adults are prescribed an anticonvulsant medication.[5–7] The prevalence increases to ~10% among nursing home residents.[8,9] Newer anticonvulsant medications are becoming increasingly more prevalent, although traditional anticonvulsants (eg, phenytoin, carbamazepine, valproic acid) continue to be used in older patients.[10,11]

The incidence of osteoporosis also increases after the age of 60 years.[12] In white populations, ~50% of women and ~20% of men aged >50 years will have a fragility fracture in their remaining lifetime.[13] Hip fractures carry an especially high burden of both morbidity and mortality.[14–16] The incidence of hip fracture is >700 per 100,000 person-years among women and >300 per 100,000 person-years among men, with wide variations within specific population groups, and with exponential increases in risk as age increases.[17] With the aging of the global population, if incidence rates remain stable, the number of hip fractures worldwide is projected to rise from 1.7 million in 1990 to 6.3 million in 2050.[18]

Despite the increasing prevalence and incidence of these diseases with age, few studies have specifically examined the risk of reduced bone mineral density (BMD) and fracture in older adults who use anticonvulsant medications. Data from a Veterans Affairs Cooperative Trial, following 593 patients aged >60 years with newly diagnosed seizures, suggest that the newer anticonvulsant medications, such as lamotrigine and gabapentin, may be better tolerated by older adults, with fewer early terminations due to adverse drug effects compared with the older agent carbamazepine (12.1% for lamotrigine, 21.6% for gabapentin, and 31% for carbamazepine; $P = 0.001$).[19] However, there are limited data regarding the impact of these medications on bone health.

In this article, the current hypothesis for the pathogenesis of anticonvulsant-induced bone density loss is discussed, and the evidence regarding the risk for osteoporosis and fractures in older individuals is reviewed.

METHODS

A review of the literature was performed to search MEDLINE and CINAHL for articles published between 1990 and October 2009 with the following search terms: *anticonvulsant* OR *antiepileptic;* AND *osteoporosis* OR *bone density* OR *fracture* OR *absorptiometry, photon*. Studies within the pediatric population or among patients with neurodevelopmental disorders (eg, cerebral palsy), cross-sectional studies, and studies whose results were published in a language other than English were excluded. References from published articles were scanned for other relevant studies. Studies were evaluated using the Jadad criteria for randomized clinical trials or other published criteria for cohort studies,[20] and data specific to patients aged >65 years were abstracted.

RESULTS

A search of the published literature (using the specified databases and search terms) yielded >300 results, of which 24 met the inclusion and exclusion criteria and were included in this review.

Pathogenesis

Study of the mechanism by which anticonvulsant medications may be associated with metabolic bone disease has concentrated on vitamin D metabolism and bone turnover. The effects of anticonvulsant medications on bone were noted in the 1960s among children with rickets.[21] Observations that adult osteomalacic disease due to anticonvulsant use could be tempered by the administration of vitamin D were made in the 1970s. These observations led to studies on vitamin D metabolism as a mechanism for anticonvulsant-induced bone disease. In the 1970s, Hahn et al[22] reported that vitamin D was metabolized at a more rapid rate when administered to patients with long-term use of phenobarbital. Furthermore, they found that, in a rat model, this rapid metabolism was mediated by increased hepatic hydroxylation activity.[23] Similar results were noted with carbamazepine and oxcarbazepine.[24] Together, these findings suggest that hepatic enzyme induction led to increased metabolism of 25-hydroxyvitamin D to inactive metabolites, which resulted in metabolic bone disease.

Another study further elaborated this hypothesis. Pascussi et al[25] exposed human hepatocytes in tissue