

AED EFFECTS ON BONE DENSITY

Antiepileptic Drug-induced Bone Loss in Young Male Patients with Seizures

Andress DL, Ozuna J, Tirschwell D, Grande L, Johnson M, Jacobson AF, Spain W.

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BACKGROUND: Long-term antiepileptic drug (AED) therapy is a known risk factor for bone loss and fractures. Vitamin D deficiency is frequently cited as a cause for bone loss in patients who have seizures.

OBJECTIVE: To determine whether men who have seizures, but who are otherwise healthy, have substantial bone loss in the hip while taking AEDs.

PATIENTS AND METHODS: We prospectively examined femoral neck bone mineral density (BMD) by dual-energy x-ray absorptiometry in 81 consecutive men, aged between 25 and 54 years (mean age, 45 years), who were attending an outpatient seizure clinic. Low BMD values were analyzed for known risk factors for bone loss. Dual-energy x-ray absorptiometry scans were repeated in 54 patients, 12 to 29 months later (mean, 19 months), to assess the rate of change in BMD over time.

RESULTS: Multivariate linear regression analysis revealed that age ($P < 0.001$) and time receiving AEDs ($P < 0.003$) were the two important risk factors associated with low femoral neck BMD. Neither vitamin D deficiency, hypogonadism, cigarette smoking, nor excess alcohol intake was associated with low BMD after correcting for age and time taking AEDs. Longitudinal analysis of femoral neck BMD revealed that only those in the youngest age group (25-44 years) showed significant declines in femoral neck BMD (1.8% annualized loss; 95% confidence interval, -3.1 to -0.9; $P < 0.003$) while receiving AED therapy. There was no evidence that a specific type of AED was more causally related to bone loss in this group, although most patients were taking phenytoin sodium (PHT) or carbamazepine (CBZ) during the longitudinal assessment.

CONCLUSIONS: Long-term AED therapy in young male patients who have seizures causes significant bone loss at the hip in the absence of vitamin D deficiency. Dual-

energy x-ray absorptiometry scanning of the hip is useful in identifying patients who are particularly susceptible to rapid bone loss while taking AEDs.

Evaluation of Bone Mineral Metabolism in Children Receiving Carbamazepine and Valproic Acid

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Dual energy x-ray absorptiometry (DXA) was used to assess lumbar spine (L2-4) and femoral neck bone mineral density (BMD) in 36 children taking either carbamazepine (CBZ) or valproic acid (VPA) for longer than 1 year, for generalized idiopathic epilepsy. Patients were matched with controls. Biochemical parameters of bone mineral metabolism were also measured. BMD values at both the femur neck and lumbar spine in both the CBZ and VPA groups were not significantly different from that of the control group. Serum levels of calcium were subnormal, and alkaline phosphatase levels were high in the CBZ group. Urinary calcium levels were significantly lower in both groups than in the control group ($P \leq 0.05$) and also significantly lower in the VPA group than in the CBZ group ($P \leq 0.05$). There were no other significant biochemical changes in either group. In conclusion, the results suggest that VPA and CBZ monotherapies have minimal effects on bone mineral metabolism, but routine monitoring of risk and consideration of prophylactic vitamin D supplementation is important.

Effect of Antiepileptic Drugs on Bone Density in Ambulatory Patients

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BACKGROUND: Long-term AED use causes multiple abnormalities in calcium and bone metabolism that have been most extensively described in institutionalized patients. The objective is to determine the effect of AED on vitamin D levels and bone density in ambulatory patients and to compare the effects of enzyme-inducing and -non-inducing AED and of single versus multiple therapy on bone density.

METHODS: A cross-sectional evaluation was conducted of 71 patients (42 adults and 29 children/adolescents) receiving AED therapy for at least 6 months who presented to neurologists at a tertiary referral center. Bone mineral density (BMD) as well as serum 25 hydroxyvitamin D (25-OHD) levels were measured. A detailed questionnaire assessing calcium intake as well as previous and current intake of AEDs was administered to all patients.

RESULTS: More than 50% of adults and children/adolescents had low 25-OHD levels, but this finding did not correlate with BMD. AED therapy decreased BMD in adults. Generalized seizures, duration of epilepsy, and polypharmacy were significant determinants of BMD, more so at skeletal sites enriched in cortical bone. Subjects taking enzyme-inducing drugs such as PHT, phenobarbital (PB), CBZ, and primidone (PRM) tended to have lower BMD than those taking noninducers such as VPA, lamotrigine (LTG), clonazepam (CZP), gabapentin (GBP), topiramate (TPM), and ethosuximide (ESM).

CONCLUSIONS: Epilepsy and its therapy, including the newer drugs, are risk factors for low bone density, irrespective of vitamin D levels. Skeletal monitoring with the institution of appropriate therapy is indicated in patients receiving prolonged AED therapy.

COMMENTARY

Altay et al. evaluated a well-defined group: all were Turkish children (aged 4–18 years) with primary generalized epilepsy receiving CBZ or VPA monotherapy for longer than 1 year. There was a control group of children matched for age. The longest duration of therapy is not noted. The children were said to have had normal diets and normal activity. None had mental or physical disabilities or abnormal neurologic or imaging examinations. One-time assessments of morning fasting calcium, phosphorus, alkaline phosphatase, parathyroid hormone, calcitonin, osteocalcin, AEDs, and urinary calcium and phosphorus levels were obtained. Bone age and maturation were determined by wrist radiographs, and BMD by DEXA at lumbar spine and femoral neck.

They found that both patient groups had high alkaline phosphatase and increased osteocalcin and believed this was due to AED use. They did not find evidence of demineralization but did not have histopathologic results to confirm this. They suggested that additive risk factors (immobilization, physical disability, inactivity, poor calcium intake, comedications that have additional calcium risk, long term treatment) could contribute significantly to symptomatic bone disease.

Farhat et al. reported a cross-sectional look at 42 adults (22 male, 20 female patients) and 29 children/adolescents (17 male, 12 female patients) from a Beirut epilepsy clinic. Patients with other metabolic disease or taking medications affecting bone turnover were excluded. Numbers of patients in subgroups were small. Calcium intake was low in all groups. Most had normal activity level. Vitamin D levels were low in children and adults. BMD was low in adults. The age distribution and hormonal status of female cohorts are not specified. No measures of bone turnover were obtained. Although patients were classified as taking single or multiple drugs, inducing or noninducing therapy, the historical profiles of exposure and exposure length were not considered. For the adults, this exposure was 9 ± 10 years for individuals aged 33 ± 12.2 years; thus this may be a considerable factor to consider. They had no control population from their region. They thought that the lack of vitamin D level and BMD correlation confirmed a non-vitamin D mechanism of action of the AED on the skeleton. BMD was decreased by up to 7% compared with standard adult controls, suggesting greater future osteoporotic fracture risk.

Andress et al. evaluated 81 men aged 25–54 years from the Seattle VA Seizure Clinic. (How much sunshine is available compared with Turkey and Iran?) Serum calcium, phosphate, alkaline phosphatase, and luteinizing hormone were obtained. Historical data included smoking, alcohol, diet, comedications, and fractures. BMD scans were performed 12 months apart. Regression analysis was performed. Subgroups were analyzed additionally based on age: 25 to 44 years, 28 patients; 45 to 49 years, 30 patients; 50 to 54 years, 23 patients. The youngest group showed significant change in BMD, losing 1.8% per year (0.1% to 4.3%), and this group had received AEDs for the shortest time. The two older groups also showed BMD loss, but it was not statistically significant. They believed that the older patients had “stabilized their bone loss.” They thought bone loss was a direct effect of AED on bone turnover, possibly by stimulating osteoblasts and that the younger skeleton may be more susceptible.

All three of these reports offer important observations on this difficult and poorly understood problem. All the studies were small groups, and none were long-term longitudinal. Ideally patients could be studied in the “perfect study,” which could be designed to be a large multicenter study that entered

patients at time of initiation of AEDs. A baseline BMD and measurement of markers of bone turnover could be made and then repeated studies on a regular basis for up to 10 years, with an accurate intake and follow-up history of diet, nutrition, comorbid disease, and comedication, AEDs, geographic location, and fracture history. Individuals with BMD changes should have bone biopsies considered. This study should be powered adequately for subgroup analysis to include sex, age, and AED groupings.

What we know is that our patients do develop osteopenia, probably at younger ages than the general population. We can screen our at-risk patients with dual energy x-ray absorptiometry and initiate treatment to prevent fractures and morbidity. We must learn more to attempt to prevent the development of the problem in our young patients.

by Patricia E. Penovich, M.D.