Phenytoin, Other Antiepileptic Drugs Accelerate Bone Loss

ARTICLES BY
BRUCE JANCIN
Denver Bureau

BRECKENRIDGE, COLO. — Antiepileptic drug usage by older women sharply increases their rate of bone mineral loss, with phenytoin being a particular offender, according to recent data from a landmark American study.

This is a disturbing finding in light of the fact that phenytoin remains the most frequently prescribed antiepileptic drug (AED) in this country, including among older patients, Jose F. Cavazos, M.D., said at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

"If you start a 70-year-old woman on phenytoin and her life expectancy is 15 years, you're going to considerably increase her likelihood of having a hip fracture, compared with women using other anticonvulsants," added Dr. Cavazos of the university's South Texas Comprehensive Epilepsy Center.

Dr. Cavazos noted that a fuller understanding of the scope of the fracture risk associated with specific AEDs was recently provided by an enormous population-based case-control study led by Peter Vestergaard, M.D., of Aarhus (Denmark) University. The investigators compared rates of AED use in 124,655 patients with any fracture and 373,962 controls.

In an unadjusted analysis, all AEDs—both traditional and newer ones—were associated with increased risk of fracture. However, after adjustment for history of corticosteroid use, prior fractures, diagnosis of epilepsy, comorbid conditions, and other potential confounders, the list of AEDs associated with a significantly increased fracture risk was narrowed to phenobarbital, with a 79% increased risk; clonazepam, 27%; carbamazepine, 18%; valproate, 15%; and oxcarbazepine, 14%.

While phenytoin and topiramate were associated with increased fracture rates of 20% and 39%, respectively, these didn't reach significance (Epilepsia 2004;45:1330-7).

The most encouraging finding in this impressive study, according to Dr. Cavazos, was that several newer AEDs emerged as being very unlikely to increase fracture risk. These included tiagabine, with an associated 25% reduced risk of any fracture, compared with non-AED users; vigabatrin, with a 7% decreased risk; and lamotrigine, with a nonsignificant 4% increased risk.

In discussing the overall osteoporosis risk in older women associated with AED use, Dr. Cavazos cited data from the Study of Osteoporotic Fractures (SOF), a National Institutes of Health–sponsored prospective study involving 9,704 elderly community-dwelling women.

Phenytoin is the most frequently prescribed AED in this country, including among older patients.

DR. CAVAZOS

In a recent secondary analysis of SOF data, Kristine E. Ensrud, M.D., of the University of Minnesota, Minneapolis, and her associates classified the women either as continuous users of AEDs during the study period, intermittent users, or nonusers. Serial measurements showed an adjusted average annual rate of decline in total hip bone mineral density of 0.70% in the nonusers, 0.87% in intermittent users, and 1.16% in continuous AED users.

The same highly significant pattern of increased bone loss with continuous use of AEDs was repeated at the calcaneus.

Extrapolating from the bone mineral density findings, Dr. Ensrud and her colleagues estimated that without intervention, continuous use of AEDs by women aged 65 years and older would increase their risk of hip fracture by 29% over 5 years (Neurology 2004;62:2051-7).

The SOF analysis also demonstrated that continuous use of phenytoin was associated with an adjusted 1.8-fold greater rate of bone loss at the calcaneus and a 1.7-fold greater bone loss at the hip, compared with non-AED users. ■

Look for Catamenial Epilepsy Pattern

BRECKENRIDGE, COLO. — Seizures in many epileptic women exhibit a stereotypic menses-related pattern that may have important treatment implications, Jose F. Cavazos, M.D., said at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

How common is this catamenial exacerbation of seizures? In one recent study led by Andrew G. Herzog, M.D., of Harvard Medical School, Boston, 87 women with localization-related epilepsy charted their seizures in three menstrual cycles. Fully 39% showed one of three predefined catamenial patterns of seizure exacerbation during at least two of the three cycles.

The three patterns characteristic of catamenial epilepsy were perimenstrual or periovulatory exacerbations during normal cycles, and exacerbations during the second half of anovular cycles (Ann. Neurol. 2004;56:431-4).

The implication is that for the many women whose seizures follow a catamenial pattern, anticipatory short-term increases in antiepileptic drug dosing may help. Or patients can add an adjunctive anticonvulsant such as acetazolamide or a benzodiazepine for 3-4 days. Several days of clomiphene are another possibility, according to Dr. Cavazos of the university's South Texas Comprehensive Epilepsy Center.

To date, there have been no large prospective treatment studies in women with catamenial epilepsy. Reported therapeutic successes are strictly anecdotal, and there is no universally accepted therapy, the neurologist added.

The biologic basis of catamenial epilepsy is grounded in two well-established observations: Estrogens are mildly proconvulsant, whereas progesterones have a slight anticonvulsant effect. Animal studies have shown that a drop in serum levels of the endogenous neurosteroid allopregnanolone, a progesterone metabolite, lower the seizure threshold. But attempts to quell catamenial epilepsy via progesterone therapy have generally been thwarted by the finding that effective doses also result in depressive symptoms and other side effects, Dr. Cavazos continued.

Another etiologic factor in catamenial epilepsy is menstrual cycle–related alteration in hepatic metabolism of antiepileptic drugs. The perimenstrual decrease in sex hormones is associated with increased hepatic enzyme activity, which can result in lower serum anticonvulsant levels, he said.

Discontinuing Valproate May Reverse PCOS in Some Women

BRECKENRIDGE, COLO. — Hormonal evidence of polycystic ovary syndrome in patients on valproate is often reversed by a switch to one of the newer antiepileptic drugs, Jacci Bainbridge, Pharm.D., reported at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

Women with epilepsy are known to have an increased frequency of polycystic ovary syndrome (PCOS), a common complication of valproate therapy. Evidence that the associated adverse neuroendocrine changes are reversible with a change in seizure medication comes from a recent study by investigators at the University of Birmingham (England), said Dr. Bainbridge of the University of Colorado, Denver.

At the annual meeting of the American Epilepsy Society, the British investigators reported on 16 women with generalized epilepsy who had been taking valproate for longer than 2 years. They ranged in age from 16 to 27 years, and nine had been diagnosed with juvenile myoclonic epilepsy. All patients had the elevated testosterone and/or FSH levels that help define PCOS.

Patients were initially switched from valproate to lamotrigine (Lamictal). If their seizures worsened on the new medication, they were switched again, this time to levetiracetam (Keppra). Eleven women finished the study on lamotrigine. All five patients who were switched to levetiracetam became seizure free. Of the 16 patients, 15 lost hormonal evidence of PCOS during the switch from valproate.

Conference director Jose F. Cavazos, M.D., said that rather than doing routine hormone measurements in his valproate-treated patients in an effort to identify those with hyperandrogenism, he relies upon sudden weight gain as an early clinical tip-off to the presence of PCOS. Weight gain in this setting is often due to the insulin resistance that is one of the first manifestations of PCOS.

There are some data to suggest that there is a dose-dependent relationship between the use of valproate and PCOS. It may be possible to use the drug at lower doses without increasing the risk of the hormonal/metabolic disorder. That's welcome news because valproate remains a useful drug in certain circumstances.

"Patients with refractory primary generalized epilepsy are going to end up on multiple medications—and one of them is often Depakote [valproate]," noted Dr. Cavazos of the University of Texas at San Antonio.

Seizures can entail hypothalamic storm, with resultant long-term adverse effects on the hypothalamic-pituitary-ovarian axis. One outcome can be premature ovarian failure, which is more common in women with epilepsy. This helps explain the relatively low birth rate among women with epilepsy, he said.

Dr. Cavazos mentioned one study in which investigators evaluated 50 consecutive women with epilepsy aged 38-64 years whose seizures began prior to aged 41. A control group included 82 age-matched neurologically normal women. Of the women with epilepsy, 14% had onset of menopause prior to 42 years, compared with just 4% of controls (Epilepsia 2001;42:1584-9).

In another study, Cynthia L. Harden, M.D., of Columbia University, New York, demonstrated that seizure frequency and lifetime number of seizures were associated with earlier age at menopause, according to Dr. Cavazos.

She surveyed 68 women with epilepsy whose mean age at menopause was 47.8 years. The 15 women classified as having a low-seizure-frequency history had a mean age at menopause of 49.9 years, compared with 47.7 years in the intermediate-seizure-frequency group and 46.7 years in the 28 women with high seizure frequency. The age difference was statistically significant.

Potential confounders, including the use of the older enzyme-inducing antiepileptic drugs, smoking history, and number of pregnancies, didn't significantly affect the results (Neurology 2003;61:451-5). ■