VA Study Compares Epilepsy Treatments in Elderly

Newer antiepileptic agents were better tolerated and more effective than the older carbamazepine.

BY BRUCE JANCIN
Denver Bureau

BRECKENRIDGE, COLO. — Lamotrigine and gabapentin are the newly-crowned evidence-based first-line treatments for new-onset epilepsy arising in the elderly, according to the findings of a major new Veterans Affairs trial.

Both drugs significantly outperformed carbamazepine in VA Cooperative Study 428, a multicenter randomized double-blind clinical trial involving 593 veterans with new-onset seizures after age 60.

Lamotrigine showed a consistent trend for more favorable outcome measures compared with gabapentin, although many of these differences did not achieve statistical significance. Both newer drugs significantly outperformed carbamazepine, Mark C. Spitz, M.D., reported at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

The primary end point in the study was retention in the trial on the assigned drug after 12 months. The rates were 58% for patients randomized to lamotrigine, 49% with gabapentin, and 37% with carbamazepine.

The drugs were roughly equally effective at controlling seizures. Rather, the difference in outcome was due to disparities in tolerability. Despite the fact that older veterans are a notoriously uncomplaining group that tends to stick with a problematic assigned treatment well beyond the point when others would bail out, more than 27% of the carbamazepine group dropped out of the trial due to intolerable side effects, compared with 17% on gabapentin and 10% on lamotrigine, noted Dr. Spitz, professor of neurology at the University of Colorado, Denver.

Older veterans are a notoriously uncomplaining group, yet more than 27% of the carbamazepine group dropped out due to intolerable side effects.

Target doses in the study were 150 mg/day of lamotrigine, 1,500 mg/day of gabapentin, and 600 mg/day of carbamazepine. Physicians were permitted to deviate from the standard titration schedules based upon a patient's signs and symptoms in a way that mirrored common clinical practice. This was done in 30% of cases.

There was a nonsignificant trend for less neurologic toxicities with the newer drugs. The significant differences in systemic toxicity involved weight gain and loss, water retention, and hypersensitivity-type skin rashes. Skin rash occurred in 10% of patients on carbamazepine, 5% on gabapentin, and—to the great surprise of Dr. Spitz and the other investigators—in a mere 2.7% of lamotrigine-treated patients.

"This is very interesting. Everybody is worried about the black box warning with lamotrigine. But as it turns out, hypersensitivity reactions were significantly more common with carbamazepine," he said.

Three percent of carbamazepine-treated patients experienced skin rash requiring hospitalization, compared with none of the gabapentin group and 0.5% on lamotrigine. The sole death in the trial occurred in a patient on carbamazepine who developed Stevens-Johnson syndrome with multiorgan failure.

Because lamotrigine carries a black box warning about serious rashes including Stevens-Johnson syndrome, its titration schedule was more protracted than were those of the other agents. Patients started with 25 mg at bedtime for 2 weeks, then 25 mg b.i.d. for 2 weeks, followed by 50 mg b.i.d. for 2 weeks, and then 75 mg b.i.d.

"The concept of titrating slowly with lamotrigine to minimize the chance of rash is a rule I follow very closely," Dr. Spitz said.

The trial was designed a decade ago, at a time when investigators viewed carbamazepine as the best-proven antiepileptic drug for the elderly.

The goal was to learn whether the then-new gabapentin and lamotrigine were clinically advantageous.

Today, phenytoin is the agent most often prescribed for epilepsy in the elderly. Indeed, a recent VA system-wide study showed 80% of veterans with epilepsy diagnoses are on phenytoin, a finding Dr. Spitz finds disconcerting because of the drug's narrow therapeutic range, complex pharmacokinetics, associated accelerated bone loss, and reduced hepatic clearance in the elderly.

"We've known for many years that although phenytoin isn't a bad drug in general, there's good evidence that phenytoin isn't a good drug for old people," he said.

The primary results of VA Study 428 will soon be published.

The trial—one of the largest ever to focus on new-onset epilepsy in the elderly—includes numerous secondary end points expected to provide follow-up analyses for years to come. The study has already provided data serving to debunk widespread misconceptions regarding the nature of seizure disorders arising in older people. ■

New-Onset Epilepsy Can Resemble Dementia in Some Elderly Patients

BY MARK BLOOM
Contributing Writer

BOSTON — Epilepsy in the elderly often presents as complex partial seizures that can resemble sudden-onset dementia, A. James Rowan, M.D., said at a meeting on epilepsy in the elderly sponsored by Boston University.

The incidence of new-onset seizures begins to climb when patients are in their 50s after a decline that begins in childhood and reaches a nadir around age 30, said Dr. Rowan, professor of neurology at the Mount Sinai School of Medicine in New York.

By age 60, the incidence of epilepsy reaches 40 new cases per 100,000 per year, Dr. Rowan said, citing data from W. Allen Hauser, M.D., professor of neurology and neuroepidemiology at Columbia University, New York. The incidence begins an almost exponential climb to age 75, when it hits 139 new cases per 100,000 per year, which is higher than the incidence of epilepsy in infants and children up to age 3.

"Epilepsy is, in fact, a disease of the very young and the very old," Dr. Rowan said.

Yet epilepsy in elderly patients is often quite different from that in children, who typically have generalized tonic-clonic seizures. In the elderly, complex partial seizures are the norm.

Dr. Rowan described the case of a 72-year-old woman whose treatable epilepsy was misdiagnosed as worsening dementia. She was about to be sent to a nursing home.

The woman was admitted to the hospital for a dementia evaluation. She reported having "fuzzy" periods. Her past medical history was unremarkable. A CT scan showed atrophy. ECG and lab results were negative. But in a neurologic consult, she said the "fuzzy" periods were intermittent. She kept asking, "What am I doing here?"

The neurologist felt that something didn't fit, Dr. Rowan said.

A video EEG revealed a complex partial seizure. In the elderly the postictal state following a complex partial seizure may last up to 2 weeks. When she was treated with phenytoin, the symptoms resolved, and she went home. "It was a remarkable turnaround," he said.

If such patients are recognized as having seizures, they can be treated and may enjoy a vastly improved quality of life. Often, he added, they are misdiagnosed with altered mental status, confusion, dizziness, syncope, memory disturbance, or dementia.

Dr. Rowan noted that 50% of all new-onset seizures occur in patients 60 years or older. Although in younger patients the diagnosis of epilepsy is reserved for those who have had at least two seizures, the diagnosis can be made in the elderly after just one seizure; 90% of elderly patients who have had one seizure will have a second unless they are treated.

Among the other differences between epilepsy in the young and the elderly, he added, is that epilepsy in the elderly, while extremely common, is manifested by a low rate of seizures. Yet in the elderly the postictal state after complex partial seizures tends to be prolonged. The period of confusion can last up to 2 weeks, compared with a minute or so in infants and youngsters.

In most cases, epilepsy in the elderly develops secondary to cerebrovascular disease, said Dr. Rowan, with infarctions accounting for nearly 40% of cases. Multivessel atherosclerosis, cerebral hemorrhage, and subarachnoid hemorrhage make up another 10%. Approximately 30% of cases are of unknown etiology. About 20% of cases were Alzheimer's patients. Drugs such as theophylline lower the seizure threshold. ■

Urge Warfarin Users to Avoid Cranberry Juice

BY BRUCE JANCIN
Denver Bureau

BRECKENRIDGE, COLO. — Warfarin plus cranberry juice can add up to big trouble.

A series of five case reports of a suspected clinically significant drug-food interaction between warfarin (Coumadin) and cranberry juice has prompted the United Kingdom's Committee on Safety of Medicines and the Medicines and Healthcare Products Regulatory Agency to warn patients on the oral anticoagulant to limit consumption of cranberry juice or avoid it altogether, Jacci Bainbridge, Pharm.D., said at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

"The volume of cranberry juice in these cases was glasses per day, not gallons and gallons. It was the sort of quantities patients might use to treat a bladder infection or for a body cleansing," explained Dr. Bainbridge of the University of Colorado, Denver.

The drug-food interaction was manifested by a rise in the international normalized ratio to levels far outside the therapeutic range, resulting in a markedly increased risk of bleeding.

Indeed, the INR in one patient soared to in excess of 50 within 6 weeks after starting to drink cranberry juice regularly; the patient died of gastrointestinal and pericardial hemorrhage, the only known fatality to date.

A cranberry juice/warfarin interaction is biologically plausible. Warfarin is metabolized chiefly by cytochrome P-450 in the liver, and the antioxidant flavonoids contained in the juice are known to inhibit the enzyme pathway, Dr. Bainbridge noted. ■