Antiepileptic Drugs Act Differently in the Aged

BY MARK BLOOM
Contributing Writer

Boston — Antiepileptic drugs can affect elderly patients quite differently from the ways they do a younger population, Thomas R. Browne, M.D., said at a meeting on epilepsy in the elderly sponsored by Boston University.

Pharmacokinetic principles can shift from the center in a variety of ways for older patients, who have double the rate of partial seizures as middle-aged patients, said Dr. Browne, professor of neurology at Boston University.

With age, body fat content increases, while liver and kidney function decrease. The result may be a decrease in volume of distribution with a corresponding increase in plasma concentration with antiepileptic drugs (AEDs) that are water soluble, such as levetiracetam.

Conversely, with drugs that are lipid soluble, such as phenytoin and carbamazepine, there may be an increase in volume of distribution with a corresponding decrease in plasma concentration.

Also, protein binding decreases, which can lead to a higher free level of drugs. Oxidative metabolism and renal excretion may decrease, leading to increased concentration.

Finally, Dr. Browne said, there are many drug-drug interactions that can either increase or decrease the blood level of the AED, resulting in more toxicity for a given blood level of the AED. Following pharmacokinetic principles, the drug of choice for the elderly would have minimum protein binding, minimal oxidative metabolism, minimal renal excretion or predictable renal effects, and minimal toxicity, especially neurotoxicity, according to Dr. Browne.

There are several neurotransmitter changes with age: some that increase the seizure threshold and some that decrease it. "But there is no overriding picture

Cymbalta—an effective way to manage diabetic peripheral neuropathic pain (DPNP)

Effective—multidimensional relief of DPNP

McGill Short-Form Pain Questionnaire (SF-MPQ)—Sensory Portion—assesses multidimensional pain:

Cymbalta significantly reduced multidimensional pain

Mean Change from Baseline to Endpoint (12 weeks)

-6.18
-2.23
-7.08

Cymbalta 120 mg/day (n=100)
Cymbalta 60 mg/day (n=97)
Placebo (n=91)

Mean baseline scores=15.3-16.8

- Most common adverse events for Cymbalta vs placebo during controlled clinical trials for DPNP included: nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia.
here,” he said. “The changes in epilepsy in the old are not readily explained by an increase in GABA [gamma-aminobutyric acid] or an increase in AMPA [alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid],” according to Dr. Browne.

Changes in the absorption processes in older patients may occur but with no consistent pattern, Dr. Browne said. They include pH, gastric motility, decreased transit times that enhance absorption, and a decrease in blood flow.

When elderly patients are absorbing drugs by nasogastric tube, there is decreased motility and adsorption of lipid-soluble drugs. One way to solve this is to use a drug in suspension or solution, particularly levetiracetam. But, the absorption may increase so much if they are switched from phenytoin that clinicians have to be alert to toxicity, he added. Among elderly patients, Dr. Browne said, total body water and lean body mass both decrease, whereas fat mass increases.

So the volume of distribution of water-soluble drugs decreases, and the volume of distribution of lipid-soluble drugs increases. Clinicians can remember that the plasma concentration of a drug is equal to the dose divided by the volume of distribution.

Increased protein binding is one reason why patients may experience toxicity on so-called therapeutic levels of drugs, he said. “The plasma albumin concentration—albumin is the protein that binds drugs—decreases by 5%-10%. Because there is less plasma binding, there is a higher free level of drug.”

In the liver, there is a 40%-50% decrease in blood flow between young adults and the elderly.

There is also a 15%–20% decrease in oxidative metabolism between young and old adults in drugs that use the cytochrome P450 system for oxidation and inactivation. “Unfortunately, there is no magic formula, no test for exactly how much P450 is reduced, unlike creatinine clearance.” Dr. Browne said.
Cymbalta® (duloxetine hydrochloride) Delayed-Release Capsules

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta’s enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to its inactive metabolites, its enteric coating may be compromised by gastric emptying delays due to concomitant systemic illness. Gastric emptying delays due to concomitant systemic illness may make it more likely that duloxetine or its inactive metabolites would be exposed to the upper duodenum or stomach. Phenytoin should be avoided in patients on warfarin. Seizures in the elderly are often due to strokes, and people who have strokes may be taking warfarin. Yet warfarin and phenytoin can have a biphasic interaction. Elderly patients should be monitored closely by a neurologist, professor of neurology at Boston University.

Gabapentin and levetractam, both excreted by the kidney, are better choices for new-onset patients because they don’t affect warfarin.