WOMEN AND MIGRAINE

News about the connection between oral contraceptives (OC) and migraine could mean some women have a greater risk for stroke. Dr. Gretchen E. Tietjen, MD, of the Department of Neurosciences at the Medical College of Ohio, presented these findings at the American Association for the Study of Headache annual fall symposium.

Dr. Tietjen reviewed literature studying migraine as a risk factor for stroke, the use of OC and risk of stroke, and the combination of migraine and OC use and the risk of stroke. Migraine and OC use are both independent risk factors for stroke, but women who take OC and experience migraine are at a greater risk. The research revealed that the risk of stroke with OC use is related to the estrogen content of the pills. "There's a lot of good recent data that's been published in reputable journals that have shown that low, meaning 30–40 μg estrogen-containing oral contraceptives, combined OC, really have no real increased risk of ischemic stroke," Dr. Tietjen said. "The older contraceptive pills that were higher doses of greater than 50 or 100 μg, look like there was a risk of stroke with those." Women with migraine, on the other hand, have a two to three times greater risk of stroke. Women who experience migraine with aura have an even greater risk: "Looking at women that have strokes, migraine looked like it was a risk factor, particularly migraine with aura. Those people were six times as likely to have a stroke as women without migraine," said Dr. Tietjen.

These independent risk factors for stroke have a dangerous relationship, because OC use can cause onset of migraines. To minimize the danger of combining these two risk factors, women with migraines are recommended to avoid OC pills containing estrogen.

In another study on migraines, women reporting onset increased by 56% in the 1980s. Greater public awareness of migraine and stress factors, such as increase in single parenting, more women in the workplace, and diets with fasting, are all suggested as possible causes for this jump. "In the 1980s more women were divorced, joining the workforce, or the sole child care provider," said author Walter A. Rocca, MD, MPH, of the Mayo Clinic in Rochester, Minnesota. "These changes may have increased the stress in these young women, and in turn the stress may have triggered more women to have migraines for the first time."

According to a study published in the October 22 issue of *Neurology*, researchers at the Mayo Clinic examined medical records from 1979–1981 and again from 1989–1990 to track onset of migraine (N=1,342). Using the 1988 International Headache Society classification system for headache disorders, more migraines were reported at the second examination than at the first. "Patients have been progressively more frequent in consulting their physicians about headaches," said study author Jerry Swanson, MD, also of the Mayo Clinic. "And we have also observed that the time period between having a first migraine attack to consulting a physician shortened during the 80s." The medical records were obtained from the records-linkage system of the Rochester Epidemiology Project in Olmsted County, Minnesota, which links information from the local health care providers.

Women 20–29 years of age had the highest increase in migraine headaches. For every 100,000 women in this age group, researchers identified 600 first-time cases of migraine in the first phase. In the second phase nearly 1,000 of every 100,000 women in the same age group reported onset of migraines. Smaller increases were also noted in male patients. In the first phase, 200 male patients 20–29 years of age reported onset of migraines, while 250 patients from the same age group reported onset in the second phase.

The possible causes for the increased reporting of migraines (public awareness and various stress factors) do not conclusively indicate increase in incidence of migraine; the increased reporting could be a result of changes in medical services or changes in definition of migraine and diagnostic techniques. However, Dr. Rocca stated, "We suggest that there may be a real increase in migraine. This real increase may be related to increasing stress. It has been previously shown that stress can trigger migraine in individuals who are sensitive to it." Further study is needed to determine real increase of incidence. Dr. Rocca said, "It would be desirable to continue to follow our population in more recent years and to study whether the trend is continuing. Also, the association between stress and migraine in young women could be studied using analytic epidemiology techniques."

Many people still never report their migraines, although these increasing numbers indicate that awareness of migraine treatment is increasing. Nearly 68% of women and 57% of men with migraines never consult a doctor. "In recent years there have been significant changes in how migraines are treated," said Dr. Swanson. "Migraine is a medical illness that physicians can help treat. I encourage everyone with migraine symptoms to seek treatment." CNS

LAMOTRIGINE FOR PARTIAL SEIZURES IN PERIDATROC EPILEPSY

Lamotrigine (Lamictal, Glaxo Wellcome) is safe and effective for the adjunctive treatment of partial seizures in children, according to a report in the November issue of *Neurology*. Lamotrigine significantly reduced the frequency of all partial seizures and the frequency of secondarily generalized partial seizures in treatment-resistant patients, compared to placebo.

The authors, Michael S. Duchowny, MD, director of the comprehensive epilepsy program at Miami Children's Hospital in Florida, and colleagues, studied 201 children with diagnoses of partial seizures of any subtype. All of the children were receiving stable conventional regimens of antiepileptic therapy at several sites around the United States and France. Patients were randomized to add-on lamotrigine or placebo after a baseline observation period

to confirm four or more seizures in each of two consecutive 4-week periods. Then there was a 6-week dose escalation period, followed by a 12-week maintenance period. Patients were between 2- and 16-years-old in the US, and between 2- and 12-years-old in France. "The big part of the study is that the drug shows good efficacy," said Dr. Duchowny. "There was a significant reduction in the number of partial seizures and the adverse effect profile is very acceptable."

Commonly reported adverse events for the lamotrigine patients included vomiting, somnolence, infection, ataxia, dizziness, tremor, and nausea. Placebo patients commonly reported vomiting, somnolence, and infection with a similar frequency as the lamotrigine patients. Both groups had similar withdrawal rates, and two lamotrigine patients had to be hospitalized for skin rash, which is consistent with reports on the drug. "The rash risk was acceptably small and no greater than for other anti-epileptic drugs," said Dr. Duchowny. "We didn't find a high rate [of rash] with it."

Lamotrigine reduced all types of partial seizure by 44% vs 13% during placebo treatment in the maintenance phase. For lamotrigine patients, the frequency of secondarily generalized seizures was also reduced, and there was a 50% improvement and more seizure-free days vs placebo. CNS

CEP-1347 SHOWS THERAPEUTIC POTENTIAL FOR TREATING PARKINSON'S PATIENTS

CEP-1347 (Cephalon) may have therapeutic potential in treating Parkinson's disease by decreasing the loss of nigro-striatal dopamine neurons caused from what is thought to be an apoptotic process.

Cephalon boasts that this molecule works "through a novel mechanism of action." Specifically, CEP-1347 promotes neuronal survival by inhibiting the activation of c-jun N-terminal kinase, which is a key kinase in some forms of stress-induced neuronal death and possibly apoptotis.

The molecule has already proved successful in a study of nonhuman primates conducted by scientists from the National Institute for Neurological Disorders and Stroke as well as in both rat primary neuronal cultures and in neuronally differentiated human SH-SY5Y cells exhibiting dopaminergic neuron characteristics.

In the study involving nonhuman primates, results showed that CEP-1347 successfully protected dopamine neurons from a 1-methyl-4phenyul tetrahydropyridine (MPTP) induced neurotoxity. The study tested 14 cynomologus monkeys. Each was administered a single weekly dose of MPTP for 10 weeks. Eight of these primates were also administered CEP-1347, and six of these primates were administered vehicle injections. At the end of week 10, each group was measured by the interval of time to develop parkinsonism, disability level, global motor activity, putaminal homovanillic acid concentration, and cell density. The CEP-1347 group scored significantly better on all measures compared with the vehicle group.

Dr. Tom Chase, one of the investigators involved in this study said, "CEP-1347 represents an innovative approach to treating Parkinson's disease."

He added, "If effective in man, CEP-1347 would allow us to move beyond symptomatic treatment to therapy that could modify the course of Parkinson's disease."

This in not the only potential of CEP-1347. According to Jeffrey Vaught, PhD, president of research and development at Cephalon, there are many neurodegenerative diseases that CEP-1347 may benefit, including Alzheimer disease and Huntington's disease. "CEP-1347 is the first of several molecules that will be able to attack neurodegenerative diseases," he said.

He compared CEP-1347 to current therapies, saying, "Today's therapies for treatment of Parkinson's are good, but symptomatic. The patient will continue to get worse. CEP-1347 represents the first molecule intended to intercept the process of neuronal death. For the first time, we have a chance to halt the progression of the disease and offer physicians an option that is something more than simply symtomatic therapy."

The best aspects of the drug is that it's a once-a-day product and, according to prior testing, is very safe. Since the elderly, who may have other medical problems, compose a large percentage of patients who would benefit from this drug, the potential of CEP-1347 far exceeds other therapies.

Cephalon is currently testing CEP-1347 in healthy adults, the elderly, Parkinson's patients, and Alzheimer patients. This phase 1 testing began in July of 1999 and is expected to be complete by the spring or summer of next year. It's purpose is to determine the safety and pharmacokinetics of the drug. If positive safety results are obtained, Cephalon will begin phase 2 testing shortly thereafter. Phase 2 testing will test CEP-1347 in Parkinson's patients, but, according to Dr. Vaught, Cephalon is also interested in testing the drug in Alzheimer patients and Huntington's patients.

While Vaught predicted that the drug will not be available for a minimum of 2 to 3 years, he said the most important thing for physicians to know is: "There's hope." CNS

RESEARCHERS TARGET ENZYME LINKED TO ALZHEIMER DISEASE

Scientists say they have targeted β-secretase, one of two key enzymes that lead to Alzheimer disease (AD). β-secretase attacks the brain by snipping a cell's protein, leading to the release of toxic shards that can kill nerve cells in the brain. The discovery was made by Dr. Citron and his colleagues at Amgen, a Thousand Oaks, California-based biotechnology company. Their report is featured in the October 22 issue of *Science*.

Ridding the brain of β-amyloid (Aβ), a plaque which blankets the brains of AD patients, is what most active scientists say is the key to curing AD. Aβ is formed from Aβ protein fragments, which can be created when the

β-secretase enzyme, which Dr. Citron and his colleagues claim to have located, snips a cell's amyloid precursor protein (APP), and then a second enzyme, γ-secretase, snips the remaining fragment, releasing the toxic Aβ protein. Aβ production, and thus the amyloid plaque, can be thwarted by blocking either the β- or γ-secretase enzymes, both of which have avoided scientific discovery. Locating either of these enzymes is a key step in the fight against AD. "The availability of purified enzyme will accelerate the course of drug discovery because one can generate inhibitors of an enzyme much faster when one has the molecule in isolated form rather than in a mixture with many other compounds," Dr. Citron said.

Dr. Citron and his colleagues began their β-secretase research in 1997. They searched for β-secretase by attempting to locate the gene that directs cells to produce this enzyme. The doctors experimented with 8,600 pools consisting of 100 genes each. They introduced cloned genes into cultured cells that produce β-secretase, checking to see if any of the active genes boosted cellular Aβ production. The experiments were repeated until a single gene was located. The protein encoded by this gene was named "beta-site amyloid precursor protein cleaving enzyme" (BACE). In their report, Dr. Citron and colleagues discuss how BACE cut proteins at exactly the right spot, and no other spot, in trial after trial. "β-secretase specifically cleaves APP at the beginning of Aβ, the protein found in Alzheimer plaques," Dr. Citron said. BACE shows all the properties expected in a β-secretase, and Dr. Citron and colleagues revealed that inhibition of their purified enzyme decreased Aβ production by cultured cells.

Amgen is now searching for compounds that will block β-secretase. Researchers said they hope such compounds will not only prevent amyloid plaque production but also destroy plaque already present in the brain. There is also the question of negative drug side-effects and whether or not these inhibitor drugs will actually improve patient condition. "It will be several years before β-secretase inhibitors will be available for human testing, but other promising drugs may go into clinical trials earlier," Dr. Citron said. CNS

THALAMOCORTICAL DISRHYTHMIA MAY ACCOUNT FOR A VARIETY OF NEUROLOGICAL DISORDERS

A wide range of neurological and psychological disorders, including Parkinson's disease, tinnitus, depression, and obsessive-compulsive disorder, may be caused by a dysfunction in thalamocortical oscillations, according to a study presented at the annual meeting of the Society for Neuroscience in Miami Beach, Florida.

Rodolfo Llinas, MD, PhD, a single cell physiologist and professor of neuroscience at New York University, and colleagues measured the brain activity of nine healthy control subjects and nine patients suffering from chronic, severe, and therapy-resistant Parkinson's disease, tinnitus, neurogenic pain, or depression, using magnetoencephalography (MEG).

The data showed a persistent and abnormal distribution as well as coherence of low-frequency activity over the anterior and posterior areas of the brain in the patient group. Compared with controls, patients showed increased low-frequency θ rhythmicity and a widespread increase of coherence among high- and low-frequency oscillations.

Based on these results and the results of prior studies, Dr. Llinas and colleagues proposed that some neurological and psychological abnormalities occur when protracted hyperpolarization of a specific nucleus causes one part of the thalamus to persistantly oscillate at a frequency ranging in the θ-frequency band. These low frequencies produce harmonics, bringing in high frequencies (γ-frequency oscillations) that generate consciousness. This creates an edge effect such as the ringing in the ears experienced by people suffering from tinnitus. This edge effect can generate a variety of sensations, including sound, pain, and other hallucinations. Depending on the location in the thalamus at which this occurs, a specific disorder is generated. For example, if the low frequency occurs in the motor thalamus, Parkinson's disease is generated because the thalamus is receiving too much inhibition.

Specific areas where Dr. Llinas and colleagues report that they expect to see maximal low-frequency activity are the cingulate, medial prefrontal, and orbitofrontal cortices for neuropsychiatric symptoms; the supplementary motor and cingulate areas for Parkinson's disease; the insular, parietal opercular, and cingular cortices for neurogenic pain; and the medial temporal areas for tinnitus.

It is important to note that low frequencies are not always pathological. Such frequencies occur in healthy individuals during deep sleep and transiently during wakefulness. Factors that distinguish pathological low frequencies from the θ rhythmicity sometimes present under normal waking conditions are: (1) its presence is persistent during the awake state; and (2) it has wide coherence. CNS