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INSIDE

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More Good News for Stroke Prevention — Statins and ACE Inhibitors Really Work!

ABSTRACTS & COMMENTARY

By Matthew E. Fink, MD

Vice Chairman, Professor of Clinical Neurology, Weill Cornell Medical College; Chief, Division of Stroke and Critical Care Neurology, NewYork-Presbyterian Hospital

Dr. Fink reports no financial relationship relevant to this field of study.

Synopsis: *The SPARCL study showed that 80 mg per day of atorvastatin reduced the overall incidence of recurrent stroke, and a meta-analysis of several large studies of ACE inhibitors showed a reduction in all stroke types, as well as a reduction in overall cardiovascular mortality.*

Sources: Amarenco P, et al (SPARCL). High-Dose Atorvastatin after Stroke or Transient Ischemic Attack. *N Engl J Med*. 2006;355:613-615; Dagenais GR, et al. Angiotensin-Converting-Enzyme Inhibitors in Stable Vascular Disease without Left Ventricular Systolic Dysfunction or Heart Failure: A Combined Analysis of Three Trials. *Lancet*. 2006;368:581-588.

UNTIL NOW, NEUROLOGISTS HAVE RELIED ON LARGE STUDIES OF patients with coronary atherosclerosis and hyperlipidemia who were treated with statins and were found, as a secondary outcome, to have a reduced risk of ischemic stroke. While the role of cholesterol as a stroke risk factor has remained controversial, the benefit of statins in reducing the risk of ischemic stroke has been compelling. Other mechanisms than reduction of LDL cholesterol have been postulated, such as the antithrombotic, anti-inflammatory, and plaque-stabilizing effects of statins.

Now, Amarenco and colleagues have reported for the first time convincing evidence regarding the efficacy of atorvastatin in a direct study of secondary prevention of ischemic stroke in a selected population of patients with stroke or TIA. In a double-blind, placebo-controlled trial of atorvastatin 80 mg. per day, 4731 patients who had a stroke or transient ischemic attack (TIA) within one to 6 months had low-density lipoprotein cholesterol

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levels (LDL) of 100 to 190 mg/dL, and no known coronary disease, were enrolled in the study, and followed for a median of 4.9 years. During the trial, the mean LDL cholesterol was reduced to 73 mg/dL among patients receiving atorvastatin and 129 mg/dL in those receiving placebo. Two hundred sixty-five patients (11.2 %) receiving atorvastatin and 311 patients (13.1%) receiving placebo had a fatal or nonfatal stroke (5-year absolute RR = 2.2%; adjusted hazard ratio, 0.84; 95% CI = 0.71-0.99; P = 0.03). The 5-year absolute risk reduction for all cardiovascular events was 3.5% (HR = 0.80; 95% CI = 0.69-0.92; P = 0.002). There was a small increase in hemorrhagic stroke, and elevated liver enzymes were more common in the atorvastatin group.

In a complementary study reported in *Lancet* by Dagenais and colleagues, the benefit of using an angiotensin-converting-enzyme inhibitor (ACEI) to prevent stroke in a population of patients with stable coronary artery disease was supported by a meta-analysis of 3 large clinical trials (HOPE, EUROPA, PEACE) that looked at cardiovascular outcomes and total mortality in 29,805 patients randomized to treatment with an ACEI (ramipril, perindopril, trandolapril). In prior studies of patients with overt heart failure, use of an ACEI did not demonstrate a significant reduction in stroke risk. The lack of efficacy was attributed to the relatively low blood pressures that these patients had at time of enrollment. Because high blood pressure is such a powerful risk factor for stroke, use of an ACEI without a significant lowering of blood pressure would not be expected to have much benefit.

Degenais et al's analysis, however, demonstrated that when the findings of the studies were combined, ACEI significantly reduced all-cause mortality (7.8% vs 8.9%, P = 0.0004), cardiovascular mortality (4.3% vs 5.2%, P = 0.0002), and all stroke (2.2% vs 2.8%, P = 0.0004). The baseline mean blood pressures, before treatment, ranged from 134-139 systolic and 78-82 diastolic, and were reduced during treatment by 4-6 systolic and 3-4 diastolic.

COMMENTARY

We are entering a Golden Age for stroke prevention and treatment, and these 2 studies will add to our confidence as neurologists, that we can really help our patients who have had a stroke, or are at high risk for a stroke.

The study by Amarenco et al confirms other data that statins reduce stroke risk. Using 80 mg of atorvastatin, there was a large reduction in LDL cholesterol levels and a relative risk reduction for stroke of 16%, with a relative risk reduction for all major cardiovascular events of 20%. We are still not sure if the mechanism of stroke reduction is lowering of LDL, and it is likely that there are multiple mechanisms at play. In any case, statin treatment has a profound effect, and should be an important part of our armamentarium to prevent stroke.

Dagenais et al's paper in *Lancet* also adds to our list of effective treatments by confirming that ACEI, as a category of antihypertensive medications, reduce stroke risk with even very small reductions in blood pressure. Many of us have felt that this group of agents might have a selective benefit over other antihypertensive medications because of the widespread presence of ACE receptors in the brain, and the ability of ACEI to maintain cerebral perfusion in the setting of severe heart failure. Dagenais et al's meta-analysis lends more support to this hypothesis, and gives us a compelling reason to select an ACEI over other medications when treating our stroke patients who have hypertension.

Of interest, the World Congress of Cardiology has recently proposed the development of a combination pill that would contain aspirin, a statin, and an ACEI to prevent cardiovascular disease. Such a combination pill would have a very positive impact in reducing stroke risk, since all 3 agents have now been shown to significantly reduce the risk of ischemic stroke. ■

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MANAGING EDITOR: Robert Kimball.
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Genetic Risk Factors for Myopathies Induced by Lipid-Lowering Drugs

ABSTRACT & COMMENTARY

By Dana Leifer, MD

Associate Professor, Neurology, Weill Medical College, Cornell University

Dr. Leifer reports no financial relationship relevant to this field of study.

Synopsis: *Patients with myopathies induced by lipid-lowering drugs, including statins and fibrates, have an increased rate of genetic muscle disorders.*

Source: Vladutiu, GD, et al. Genetic Risk Factors Associated with Lipid-Lowering Drug-Induced Myopathies. *Muscle Nerve*. 2006;34:153-162.

Guidelines for control of hyperlipidemia have become increasingly strict, and the number of patients who are candidates for lipid-lowering therapy has correspondingly been growing. The recently published SPARCL study (reviewed in the previous article) will likely lead to a further increase in the number of patients treated with statins, and neurologists are increasingly likely to encounter patients suffering from statin-induced side effects, especially myopathy. Moreover, these side effects appear to be dose-related, and are likely to be more of a problem as doses of statins are increased to reach lower LDL targets. Even a few years ago, when strict control of LDL was less prevalent, statin-induced myopathy was a significant and under-recognized problem, as pointed out by Dobkin (*Neurorehabil Neural Repair*. 2005;19:259-263).

In this background, the paper by Vladutiu and colleagues is important because it found that 17 of 136 patients with muscle pain associated with use of lipid-lowering drugs, such as statins and fibrates, had one of 3 metabolic muscle disorders. Fifteen patients were taking statins, 2 were taking gemfibrozil, and one was taking fenofibrate. One patient was taking a statin and gemfibrozil. Patients underwent muscle biopsies, and were tested for a variety of metabolic muscle disorders. Seven patients had genetic evidence for myoadenylate deaminase deficiency, 5 were carriers for McArdle disease, one had CPT II deficiency, 3 were carriers for CPT II deficiency, and one had McArdle disease and myoadenylate deficiency carrier status by genetic testing. Only one patient, a homozygote for CPT II deficiency, had muscle-related symptoms prior to statin treatment. The incidence of mutant alleles was 4-fold higher in the patients with myopathy compared to a control group on lipid-lowering therapy with no symptoms ($P < 0.0001$).

Of note, 15 of the 17 patients with genetic myopathies had elevated CK levels, ranging from 4 to 10 times the upper limit of normal, so an elevated serum CK should be found in most, but not all, patients with drug-induced symptoms associated with genetic myopathies. In addition, biochemical analysis of the muscle biopsies revealed that 47% of all of the patients had reduced levels of muscle coenzyme Q10.

COMMENTARY

The work of Vladutiu et al suggests that susceptibility to the side effects of lipid-lowering drugs may have a genetic basis in some patients. As a practical matter, identification of a genetic basis for myopathy may not alter treatment at the moment because the main options, using alternative drugs, lowering doses of offending agents, and emphasizing strict diet control to lower lipids, would be tried even without the knowledge of an underlying genetic problem. There is evidence, however, that some patients who have the genetic disorders associated with myopathies induced by lipid-lowering drugs respond to specific treatments, so some patients may actually benefit from identification of their defect. Moreover, an awareness of the underlying genetic abnormalities may be important in counseling some patients and their families and, in the future, in developing and applying effective alternative treatments for the underlying muscle disorders and for hyperlipidemia.

Regarding the reduced levels of coenzyme Q10 in the muscle biopsies, similar findings have been reported in some prior studies of patients with statin-induced muscle symptoms. The issue of coenzyme Q10 levels is a potentially important one because coenzyme Q10 and cholesterol synthesis both depend on the pathway that is blocked by the inhibitory action of statins on HMG coA reductase, so some of the deleterious effects of statins on muscle may be related to drug-mediated lowering of the coenzyme Q10 level. It is possible that pre-existing genetic disorders could make some patients more sensitive to the effects of low coenzyme Q10 levels. Preliminary data suggest that coenzyme Q10 may ameliorate statin-induced muscle pain, but there is no sufficient evidence to recommend its use on a routine basis. ■

Cluster Headaches

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, NewYork-Presbyterian Hospital, Cornell Campus

Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: *Cluster headache may be accompanied by a variety of neurological manifestations, and responds well to triptans and oxygen therapy.*

Source: Schurks M, et al. Cluster Headaches: Clinical Presentation, Lifestyle Features, and Medical Treatment. *Headache*. 2006;46:1246-1254.

USING INTERNATIONAL HEADACHE SOCIETY CRITERIA to establish a diagnosis of cluster headache (CH), 246 such patients were recruited from the Headache Clinic at the University Hospital in Essen, Germany, to characterize the clinical features and medical treatment of CH. Student's t-test, the Chi-square test, and Fisher's exact test were used for statistical analysis.

Most (77.6%) were men and had episodic (74.7%) rather than chronic (16.7%) CH. Nine percent were newly diagnosed, with no established pattern. Mean age of onset was 36.9 years for both men and women. Strictly unilateral pain, albeit changing sides between attacks, was seen in 97.2%. Seventy-nine percent were always strictly unilateral and 2.8% were bilateral, remaining predominantly one-sided but radiating to the contralateral side. Pain was usually sharp (61.8%) or pulsating (31.3%), and usually lasted 45-180 minutes (67.9%). Twenty-four percent experienced attacks of 2-45 minutes in duration and, in 7.3%, it lasted longer than 3 hours. Cranial autonomic features, including ptosis, miosis, ipsilateral facial sweating, nasal congestion and/or rhinorrhea were present in almost all (98.8%), with many experiencing restlessness during the attack (67.9%) and photophobia and phonophobia (61.2%). Twenty-three percent experienced migrainous aura of fortification spectra, tunnel vision, hemiparesis, hemisensory symptoms, dysarthria, or dysphasia, and physical activity worsened the pain in 21.7%. Men and women shared these clinical characteristics.

Alcohol consumption was more frequent in patients with episodic than chronic CH and, in 53.5%, alcohol (red wine [70.5%] or beer [23%]) triggered an attack, usually within 1 hour (65.2%), with a shorter latency in men than women. Sixty-six percent were current smokers, and 29% had never smoked.

Acute abortive therapy most often comprised triptans (77.6%) and oxygen (71.1%), with 71.7% and 76.6% experiencing relief, respectively. Ergots (32.1%) and lidocaine nasal spray (22.8%) were used less frequently, and almost 60% used unproven medication, including nonsteroidals, caffeine, and opioids. Prophylactic medication was used in 84.6%; usually verapamil (70.3%, with 65.3% efficacy) or corticosteroids (57.7%, with 73.2% efficacy). Lithium was effective in 37%, but valproic acid in only 20%. Once properly recognized and diagnosed, appropriate treatment is usually effective for CH.

COMMENTARY

More recently described treatments for CH include hypothalamic stimulation, where 13 of 16 intractable CH patients were pain-free or almost so, with no persistent side effects, following 23 months of follow-up, and the remaining 3 were improved (Neurology 2006;67;150-2). Among 53 CH patients who had experimented with psilocybin or lysergic acid diethylamide (LSD), 22 of 26 noted that psilocybin aborted attacks, 25 of 48 noted that it terminated the cluster period, and 18 of 19 reported that it extended their remission period (Neurology 2006,;66;1920-2). Cluster period termination was reported in 7 of 8 LSD users, and extended remission in 4 of 5. Clozapine, testosterone, and pramipexole have also been reportedly successful. Clearly, more research is needed to determine the most effective and safe treatments for this disabling and common disorder.

Is Ginkgo Biloba Comparable to Donepezil for Treating AD?

ABSTRACT & COMMENTARY

By Norman Relkin, MD

Associate Professor, Clinical Neurology and Neuroscience, NewYork-Presbyterian Hospital, Cornell Campus

Dr. Relkin is on the speaker's bureau for Pfizer, Eisai, and Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: *In this study, ginkgo biloba was just as effective as donepezil in treating Alzheimer's disease.*

Source: Mazza M, et al. Gingko Biloba and Donepezil: A Comparison in the Treatment of Alzheimer's Dementia in a Randomized Placebo-Controlled Double-Blind Study. *Eur J Neurol*. 2006;13:981-985.

GINKGO BILOBA HAS BEEN USED BY PRACTITIONERS OF Eastern medicine for centuries to boost memory and other health purposes. Although it is not approved in the

United States to treat memory loss, it is available over-the-counter, and often advertised as a memory-enhancing agent. Several past placebo-controlled trials failed to demonstrate consistent benefit when Gingko was used to treat memory loss in the elderly or in patients with dementia due to Alzheimer's disease (AD). However, few studies have compared Ginkgo directly to the medications currently approved for treating dementia.

Mazza and colleagues carried out a randomized, controlled, clinical trial of Gingko extract EGB-761 (160 mg/day) vs donepezil (5 mg/day) and placebo in 76 patients with mild-to-moderate AD. The average age of study participants was 68.5 years, their mean MMSE was 18.7, and roughly equal numbers of males and females participated. The study, which was conducted in Italy, used the Kurz test as its primary cognitive outcome measure and the Mini-mental state examination and a clinician-based global assessment as additional metrics. A 4-week placebo run-in period was performed to eliminate placebo responders.

Approximately 80% of subjects completed the 24-week study. No major side effects were observed in the Gingko-treated arm. Patients receiving Gingko improved to an equal degree as those given donepezil on the Kurz et al's global assessments. Improvements were statistically significant, relative to placebo and indistinguishable from donepezil. Gingko recipients scored an average of 0.6 MMSE points higher than their baseline after 24 weeks, vs an increase of 1.2 points for the donepezil group and a decline of 0.25 points for those getting placebo. Mazza et al concluded that Gingko biloba special extract EGb-761 may be as effective as a cholinesterase inhibitor in treating mild-moderate stages of AD.

COMMENTARY

EGB-761 is a special extract of Gingko biloba that is purported to have neuroprotective properties. Past clinical trials have hinted at EGb-761's efficacy in the treatment of dementia, but results have been inconsistent. With only 60 persons completing 24 weeks of treatment and only a single time point at which outcome was measured, this new study adds to only marginally to past claims of Gingko's clinical efficacy and does not establish its comparability to cholinesterase inhibitors. Although no difference was found between Gingko and donepezil on the primary outcome measure, the dose of donepezil employed (5 mg) was half of that usually recommended, and the group sizes were inadequate to document a significant difference, given the small effect size. As in past studies, Gingko was very well tolerated and, if larger controlled studies were to demonstrate comparable benefits, Gingko biloba EGb-761 may someday be accepted as a cost effective alternative treatment for AD.

Impulse Control Disorders in Parkinson's Disease: Too Much of a Good Thing?

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

Assistant Professor, Neurology and Neuroscience, Weill Cornell Medical College

Dr. Nirenberg reports no financial relationship relevant to this field of study.

Synopsis: *Treatment of Parkinson's disease with dopamine agonist medications may precipitate impulse-control disorders such as compulsive gambling, buying, and hypersexuality.*

Source: Weintraub D, et al. Association of Dopamine Agonist Use With Impulse Control Disorders in Parkinson's Disease. *Arch Neurol*. 2006;63:969-973.

Recent reports have called attention to the fact that patients with Parkinson's disease (PD) have a higher incidence of impulse control disorders (ICDs) than the general population. These ICDs include compulsive gambling, buying, and hypersexual behavior. Prior studies have linked these disorders to the use of dopaminergic medications, particularly dopamine agonists.

This study reports the results of a cross-sectional screening and assessment study of ICDs in a series of 272 unselected, predominantly male PD patients seen at one of 2 outpatient movement disorders centers over the course of a year. Of these, approximately half (50.4%) were receiving active treatment with a dopamine agonist. Subjects were screened with a battery of open-ended questions regarding the occurrence of current or past compulsive gambling, buying, or sexual behaviors. Those who were positive for one or more of these ICDs then completed a modified Minnesota Impulsive Disorders Interview (MIDI) to confirm the presence of an ICD. A total of 18 subjects (6.6%) were identified who met MIDI criteria for having experienced an ICD during the course of PD. Of these, 11 (4%) had at least one active ICD at the time of screening. Of the 18 subjects who experienced an ICD during the course of PD, this fact had been recognized and recorded in the chart in only 3 (27.3%).

All subjects (18/18) who experienced an ICD during the course of PD had been concurrently taking a dopamine agonist medication; the ICDs subsequently remitted in 6/6 subjects in whom the dopamine agonist was subsequently discontinued or reduced in dose. Affected subjects were also more likely to have a premorbid history of ICDs

(3.5% vs 36.4%). Subjects with ICDs tended to be younger (59.5 ± 9.4 years vs 68.6 ± 10.2 years) and to have had a longer duration of PD (11.2 ± 7.5 years vs 6.9 ± 5.8 years) than those without. In multivariate regression analysis, however, the only significant predictors of an active ICD were current dopamine agonist use and a history of ICD symptoms prior to the onset of PD. Increased risk of ICDs was associated with dopamine agonists as a class, and not with a specific medication.

COMMENTARY

Dopamine agonist-related ICDs have potentially devastating financial and psychosocial consequences. They include not only compulsive gambling, buying, and hypersexuality, as examined in this study, but also a wide range of other uncontrolled behaviors, including compulsive eating, hobbyism, and punding (repetitive, purposeless behaviors similar to those seen in the setting of amphetamine or cocaine use). The diagnosis of ICDs in PD is difficult because patients are not always forthcoming about their behaviors, particularly when they are embarrassing or socially inappropriate.

This study provides further evidence that ICDs in Parkinson's disease are an underrecognized, reversible side-effect of dopamine agonists. The findings highlight the importance of routine screening for ICDs in patients treated with dopamine agonists, so that these disorders can be identified and treated before secondary consequences emerge.

α-Synuclein Promoter Variability Affects Risk for Parkinson's Disease

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

Assistant Professor, Department of Neurology, Weill Medical College, Cornell University

Dr. Henchcliffe is on the speaker's bureau for GlaxoSmithKline, Teva/Eisai, and Boehringer Ingelheim.

Synopsis: *α-synuclein mutations leading to Parkinson's disease are extremely rare. However, based upon this study, variability in the gene promoter may account for up to 3% of the risk of Parkinson's disease in the general population.*

Source: Maraganore DM, et al. Collaborative Analysis of Alpha-Synuclein Gene Promoter Variability and Parkinson Disease. *JAMA*. 2006;296:661-670.

This study was conducted by the genetic epidemiology of Parkinson's Disease Consortium, which includes 3 cores (coordinating, statistical, and laboratory) and 18 global sites. Maraganore and colleagues performed allele-length variability analysis of the 3 most common dinucleotide repeat sequence (REP1) alleles (263 base-pairs [bp], 261 bp and 259 bp) of the α-synuclein (SNCA) gene promoter, and of the -770 and -116 bp single-nucleotide polymorphism (SNP) genotypes in Parkinson's disease (PD) patients and controls. The 11 participating sites were chosen on the basis of 1) intent to collaborate and to provide DNA samples for analysis by the consortium laboratory core or 2) provision of existing data determined to have a low genotyping error rate (as judged by re-analysis by the consortium laboratory core of > 20 samples per site, with inter-laboratory reliability > 90%, and required concordance with the Hardy-Weinberg equilibrium). The final analysis comprised 2692 cases and 2652 controls. Genotypes defined by the 263 bp REP1 allele were associated with an increased risk for PD (OR 1.43; 95% confidence interval [CI], 1.22-1.69). Genotypes defined by the 259 bp allele were associated with a decreased risk (OR 0.86, 95% CI, 0.79-0.94) for PD. However, REP1 genotypes were not associated with age of onset or gender. The frequency of haplotypes defined by the REP1, -770, and -116 loci was significantly different in cases compared to controls ($P < 0.001$).

COMMENTARY

SNCA gene mutations were among the first to be linked to autosomal dominant familial PD.[1] Currently, there are 3 known SNCA mutations associated with PD: SNCA 209G>A (Ala53Thr), SNCA 88G>C (Ala30Pro), and SNCA 188G>A (Glu46Lys). In addition, SNCA multiplication leads to familial PD (PARK4), suggesting α-synuclein over-expression as a possible mechanism leading to neurodegeneration. α-synuclein is expressed throughout the brain and is found in Lewy bodies, the characteristic cytoplasmic inclusions found in dopaminergic neurons in PD. Until now, the SNCA mutations described have been extremely rare and considered of doubtful, practical significance for PD patients seen in office practice. In the present study, Maraganore et al have extended the potential significance of the SNCA gene in PD beyond monogenetic Mendelian inheritance. Their findings suggest that the 263 bp SNCA REP1 allele is a susceptibility gene for PD in a large cohort of familial and sporadic PD cases worldwide. This will clearly stimulate further investigation to confirm and better define the level of attributable risk and to further investigate association with specific disease characteristics, such as age of onset. Maraganore et al estimate that SNCA REP1 locus variability may explain approximately 3% of the risk for PD in the general population, pointing to significant clinical implications. If correct, interventions targeting

SNCA expression might be useful for primary prevention of PD. SNCA, therefore, joins other proposed PD susceptibility genes, such as the tau H1 haplotype, variations in gene sequences of monoamine oxidase B, and glucocerebrosidase (better known for its role in Gaucher's disease), among others. Moreover, despite problems associated with this study design, Maraganore et al have established an important paradigm for research in genetics of complex disorders like PD, and have demonstrated the value of a worldwide collaborative effort, providing large numbers of clinically and genetically characterized subjects. ■

Reference

1. Farrer MJ. Genetics of Parkinson's Disease: Paradigm Shifts and Future Prospects. *Nat Rev Genet*. 2006;7:306-318.

Cardiac Surgery and Cerebrovascular Disease: What are the Risks, Options?

ABSTRACTS & COMMENTARY

By Dara G. Jamieson, MD

Associate Professor, Clinical Neurology, Weill Medical College, Cornell University

Dr. Jamieson is a consultant for Boehringer Ingelheim and Merck, and is on the speaker's bureau for Boehringer Ingelheim, Merck, Ortho-McNeil, and Pfizer.

Synopsis: *The neurological risk of cardiac surgery is still not well characterized, but post-operative strokes occur in 3-9% of patients. A decrease in intra-operative blood pressure and increased cardiopulmonary bypass time may result in watershed infarcts. Carotid stenting followed by cardiac surgery is an option for patients with coexistent disease.*

Sources: Newman MF, et al. Central Nervous System Injury Associated with Cardiac Surgery. *Lancet*. 2006;368:694-703; Gottesman RF, et al. Watershed Strokes after Cardiac Surgery: Diagnosis, Etiology, and Outcome. *Stroke*. 2006;37: 2306-2311; Oscar M, et al. Synchronous Carotid Stenting and Cardiac Surgery: An Initial Single-Center Experience. *Catheter Cardiovasc Interv*. 2006;68:424-428.

CENTRAL NERVOUS SYSTEM INJURY AFTER CARDIAC surgery includes ischemic stroke, encephalopathy, delirium, and neurocognitive decline. Prediction of risk and understanding of mechanism of injury should lead to improved post-operative outcome. Newman and colleagues reviewed studies that evaluated neurological consequences of cardiac surgery and outlined issues and controversies in the field. Questions that need further study include: 1) Does off-pump cardiac bypass surgery decrease post-operative complications and 2) Is neurocognitive decline related to the surgery? While atrial fibrillation is associated with increased post-operative neurological abnormalities, its contribution to post-operative cognitive decline is less certain. Do genetics, pre-existing cerebrovascular disease, and anesthesia factors also predict risk? The review in *Lancet* described issues for further investigation without reaching specific conclusions about risk reduction.

The multiple mechanisms for strokes associated with cardiac surgery include emboli from the heart and/or aorta and cerebral hypoperfusion. Improved cardio-pulmonary bypass techniques with arterial filtration and membrane oxygenation have decreased embolic risk, but intraoperative hypoperfusion may still lead to watershed infarcts, with poor outcome. The deleterious effect of more subtle changes in cerebral perfusion pressure has not been established. Watershed-distribution infarcts are seen more frequently in patients after cardiac surgery than in the general stroke population.

The study by Gottesman and colleagues evaluated 98 patients who had an MRI, including diffusion-weighted imaging (DWI), to evaluate a stroke occurring up to 10 days after cardiac surgery. The reviewers of the 98 MRI films and 109 CT films were blinded to the patient clinical information. Prospective data entered into the Cardiac Surgery Stroke database included pre-operative blood pressure. Intra-operative blood pressure was defined as mean arterial pressure (MAP) while on cardiopulmonary bypass (CPB), excluding blood pressure measurements for patients operated on an off-pump. Change in MAP was calculated by subtracting the intra-operative average measurement from the pre-operative blood pressure value.

Watershed infarcts were noted bilaterally on 48% of DWI studies and 22% of CT scans, with unilateral watershed infarcts on 68% of DWI studies and 37% of CT scans. Patients with bilateral watershed infarcts were more likely to have undergone an aortic procedure and to have had longer CPB time. Bilateral watershed infarcts were more likely to result in an increased length of hospital stay. Poor outcome was associated with bilateral infarcts, with these patients more likely to be discharged to a long-term care or rehabilitation facility, or to die in hospital.

Patients with an intra-operative drop in MAP of at least 10 mm/Hg were 4.06 times (adjusted odds ratio; 95% CI, 1.03, 15.98) more likely to develop bilateral watershed strokes than those patients who had a smaller or no drop in blood pressure. A decrease of 10 mm MAP was the dichotomized threshold for a larger watershed stroke vol-

ume. Increase in CPB time did not reach significance as an effect on the development of bilateral watershed infarcts.

Preoperative carotid duplex results were available for 84 patients. No significant interaction was found between change in blood pressure and presence of bilateral carotid disease (defined as > 60% stenosis bilaterally) in the development of bilateral watershed infarcts. However, the small sample size limited the conclusion.

This study emphasized the utility of DWI, as compared to CT scanning, in the post-operative evaluation of the cardiac surgery patient. The decrease from the pre-operative to the intra-operative MAP appeared to be a more important risk factor for watershed infarction than was the absolute intra-operative blood pressure value. A prolonged CPB time also appeared to increase risk for watershed infarction. Limitations of the study included the lack of standardization of neurological evaluation. The intra-operative blood pressure measurement was episodic, and duration of hypotension may also factor into stroke risk. Further evaluation of the risk factors for intra-operative stroke, including stenosis of cerebral vessels should improve outcome after cardiac surgery.

Coexistent carotid stenosis and cardiac disease increases risk for intra-operative stroke, but operative management prior to cardiac surgery is controversial. Synchronous or staged surgical procedures may be considered, but carotid stenting is an option to decrease stroke risk. Oscar and colleagues reported their experience with 30 patients who received carotid stenting, followed immediately by cardiac surgery, from 1995 through 2005. The patients were 80% male, with an average age of 72 years; about 77% of patients had hypertension. Five patients had a previous stroke or TIA. Carotid stenting was performed on > 70% symptomatic or > 80% asymptomatic carotid stenosis. Patients were pre-treated with aspirin alone, and were given bolus heparin during the carotid stenting. Immediately after the stenting, the patients underwent coronary artery bypass grafting with or without valve replacement. Three in-hospital deaths were due to non-neurological complications. No strokes occurred in-hospital or after a mean follow-up of 18 months. The synchronous carotid stenting and cardiac surgery had low neurological risk and is an acceptable strategy for appropriate high-risk patients. ■

CME Questions

15. Patients with myopathy associated with lipid-lowering drugs were found to have all of the following disorders except for:
a. CPT II deficiency.
b. McArdle disease.
c. myoadenylate deaminase deficiency.
d. Becker muscular dystrophy.

16. Gingko biloba extract EGb-781:
a. is approved in the United States to treat Alzheimer's disease.
b. has consistently shown benefit for treating memory loss in past placebo-controlled trials.
c. yields improvements in the cognition of AD patients that are greater than donepezil.
d. is well-tolerated at a dose of 160 mg/day.

17. Impulse-control disorders in Parkinson's disease are most closely associated with:
a. levodopa.
b. COMT inhibitors
c. dopamine agonists.
d. anticholinergic medications.

Answers: 15. (d); 16. (d); 17. (c)

CME Objectives

The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs; and

• To discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

Announcement

The 12th Annual "Clinical Neurophysiology: Principles and Practice" December 27, 28, 29, 2006, New York City. Presented by the Cornell University Medical College Department of Neurology. Contact: Fatima Castro, Department of Neurology, The New York Hospital-Cornell Medical Center, 525 East 68th Street, Rm. K-615, New York, NY 10021; Telephone: (212) 746-2320; Fax: (212) 746-8984. Email: frcastro@med.cornell.edu

The 3rd Annual Update Symposium on Clinical Neurology and Neurophysiology, Feb. 19-21, 2007, Tel Aviv, Israel. Presented by Weill Cornell University Medical College Department of Neurology and Tel Aviv Medical Center. Information:
www.neurophysiologysymposium.com ■

In Future Issues:

Update on Creutzfeldt-Jakob Disease

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

The Indictment of Pharma Industry Marketing Practices

A team from UCSF recently reviewed company documents that were entered into the public record as a result of litigation over the promotion of gabapentin (Neurontin) between 1994 and 1998. The result, a rather scathing indictment of the pharmaceutical industry's marketing practices, is published in the August 15 *Annals of Internal Medicine*.

The authors had access to thousands of pages of inside company documents from Pfizer, Parke-Davis, and Warner-Lambert regarding the marketing of gabapentin during a time that the drug was a blockbuster, with sales in the hundreds of millions of dollars.

The primary focus of the litigation was the promotion of off-label indications of gabapentin by Parke-Davis. The paper highlights the company's marketing strategy, which included identifying groups of physicians for targeted marketing. Local champion physicians were identified and trained as "peer-to-peer selling" program leaders. The company also identified physician thought leaders in academic medicine who were given large honoraria, research grants, and educational grants to promote the drug. Resident physicians were also targeted, and large sums of money were given to residency programs. Medical education was one of the cornerstones of the marketing plan.

Physician lectures, teleconferences, and other meetings were set up discuss treatment of epilepsy, but also to discuss off-label use of the drug. Parke-Davis employees frequently surreptitiously listened in on these meetings electronically, in part to gauge the effectiveness of the presentation. Physician moderators were paid well for their participation.

Parke-Davis also developed speaker's bureaus and created academic neurologic lecture series for the neurology community. Department chairs and clinical training program directors were frequently on the speakers lists of these programs. The company also gave unrestricted grants through third-party medical education companies which allowed speakers to legally discuss off label use of gabapentin and to grant CME credits.

A Parke-Davis memo describes these activities as a "growth opportunity" for off-label use of the drug. Physician advisory boards were also well paid to attend meetings where promotional activities were discussed. Research was also directed by the company, and there are indications that studies that gave favorable outcomes were more likely to be published than studies that were not favorable to the drug.

The company also promoted review articles and letters to the editor of journals regarding gabapentin for as much as the $18,000 per article. The authors point out that activities "traditionally considered independent of promotional intent" such as CME and research were corner-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

stones of marketing efforts, and when run through a third party, were legal marketing forums for off-label uses of the drug. The authors call for new strategies to "ensure a clear separation between scientific and commercial activity" (*Ann Int Med*. 2006;145:284-293). This paper is a must read for anyone involved in formulary management, cost effective prescribing processes, or medical education.

TNF Blockers: Should You Be Concerned?

The use of TNF blockers for treatment of rheumatoid arthritis has always been clouded by the potential risk of lymphoma or solid cancers. A new study suggests that the concern may be unfounded.

Researchers from Harvard and University of British Columbia performed a cohort study pooling data from 1152 RA patients who received a biologic DMARD (the TNF blockers etanercept, infliximab, adalimumab, or anakinra) and 7306 patients who received methotrexate. Both groups of patients had elevated risks of cancer compared to the general population, but the overall hazard ratio for hematologic and solid tumors for patients receiving a biologic DMARDs vs methotrexate was 0.98 (1.11 lymphoproliferative cancers 1.37 for hematologic malignancies, and 0.91 for solid tumors).

The authors conclude that biologic agents are unlikely to have a substantial increase in the risk of hematologic malignancies and solid tumors as compared with methotrexate users (*Arthritis Rheum*. 2006;54:2757-2764).

FDA Actions

The FDA has approved over-the-counter access for Plan B, the so-called morning-after pill. Over-the-counter sales of Plan B have been a contentious issue on Capitol Hill throughout the Bush presidency, and it took a change in leadership in the FDA to bring about the change in position. Plan B will be available for women ages 18 and older without a prescription; however, a prescription is still required for women ages 17 and younger. Plan B is marketed by Duramed, a subsidiary of Barr Pharmaceuticals.

Several SSRI antidepressants have made the switch to generic, including fluoxetine, paroxetine, citalopram, and sertraline. Now the first generic serotonin/norepinephrine reuptake inhibitor has been approved. Venlafaxine (marketed as Effexor) was approved for generic switch in August in 25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg strengths. TEVA pharmaceuticals have exclusivity on the generic for 180 days.

The FDA has approved the use of clopidogrel (Plavix -Bristol-Myers Squibb) in patients with ST segment elevation myocardial infarction (STEMI) who are not going to have coronary artery interventions. The new indication for the drug was based on the findings of 2 studies (COMMIT and CLARITY), which showed improved outcomes with use of the drug in STEMI patients, including those who had initial thrombolytic therapy.

In related news, a somewhat bizarre patent battle over clopidogrel is raging between Bristol-Myers Squibb and Canadian generic maker Apotex. The Canadian company challenged the patent, and introduced generic clopidogrel to the American market on August 8. On August 31, a federal judge in New York issued a restraining order to block distribution of the generic version of the drug; however, she did not require a recall of the generic pills already on the market. Bristol-Myers, which derives 30% of its yearly profit from sales of Plavix, is unsure how much generic product was distributed in 4 weeks; most estimates are approximately 3 months supply. Meanwhile, the patent trial is scheduled to begin in January.

The FDA's Center for Drug Evaluation and Research has issued a warning regarding concomitant use of ibuprofen and aspirin for patients who are taking aspirin for cardioprotection. Functional studies have shown that ibuprofen blocks the effect of aspirin on platelets if the 2 drugs are taken at the same time. Both drugs inhibit cyclooxygenase on platelets. Aspirin's effect is irreversible for the life of the platelet, whereas ibuprofen and other NSAIDs cause reversible inhibition. If ibuprofen is taken before or concomitantly with aspirin, the receptor site is occupied and aspirin is unable to exert its effect. However, if aspirin is taken 30 minutes before ibuprofen or 8 hours after, there is no competitive inhibition. The FDA is recommending that physicians be aware of the timing of ibuprofen and, perhaps, other NSAIDs when used with aspirin, and specifically recommend that aspirin be given 30 minutes prior to ibuprofen or 8 hours later. Recommendations regarding enteric-coated aspirin are unavailable at this time. ■