

Ischemic Stroke Triggers Race Against the Clock

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

For every hour an acute ischemic stroke is untreated, the human forebrain loses 120 million neurons, 830 billion synapses, and 447 miles of myelinated fiber—the equivalent of 3.6 years of normal aging.

The numbers lend a new urgency to the phrase “time is brain,” said Dr. Jeffrey Saver, who created the quantitative analysis of neural death in stroke (*Stroke* 2006;37:263-6).

“The figures stagger and motivate,” wrote Dr. Saver of the University of California, Los Angeles Stroke Center. “For patients experiencing acute ischemic stroke, and for the physicians [and others] treating them, every second counts.”

Dr. Saver used an extensive literature review to estimate total counts for neurons, synapses, and myelinated fiber length in the forebrain.

He then used published data to estimate the impact of the duration of infarct growth, infarct volume, and time to treatment on these structures.

He concluded that the forebrain contains an average of 22 billion neurons, 157 trillion synapses, and 84,500 miles of myelinated fibers. The accepted estimate for the rate of neuronal loss in the neocortex alone (which

is 86% of the forebrain) is about 31 million per year during normal aging, he said.

The impact of an untreated large vessel ischemic stroke is sudden and severe. Every untreated minute results in the loss of 2 million neurons, 14 billion synapses, and 7.5 miles of myelinated fibers, Dr. Saver said. On a per-second basis, the damage is 32,000 neurons, 230 million synapses, and 218 yards of myelinated fiber. Thus, such a stroke, at an average duration of 10 hours, can age the brain 36 years, destroying 1.2 billion neurons, 8.3 trillion synapses, and 4,470 miles of myelinated fibers.

Every untreated minute of a large vessel ischemic stroke destroys 2 million neurons, 14 billion synapses, and 7.5 miles of myelinated fiber in the forebrain.

In an accompanying editorial, Dr. Steven R. Levine suggested that transient ischemic attacks might actually be microstrokes that inflict permanent—although clinically undetectable—neural damage.

“Even after a few seconds of the focal cerebral ischemic process, tens of thousands of neurons and hundreds of millions of synapses are lost—if the time function is linear,” said Dr. Levine of Mount Sinai School of Medicine, New York.

Dr. Levine suggested that the unanswered clinical question then becomes: “Are these very brief episodes then really ‘microstrokes’ invisible to the neurological examination or current imaging modalities, with very subtle, if any, detectable parenchymal or functional change?” (*Stroke* 2006;37:10). ■

OSA-Hypopnea Syndrome: Atrial Overdrive Pacing Not Useful

BY MARTHA KERR
Contributing Writer

Atrial overdrive pacing proved ineffective in most cases of obstructive sleep apnea-hypopnea syndrome, while nasal continuous positive airway pressure showed strong efficacy, according to a comparison study by Greek researchers.

Dr. Emmanuel N. Simantirakis and colleagues at Heraklion (Crete) University Hospital, Greece, implanted dual chamber pacemakers in 16 patients with moderate or severe sleep apnea, documented sleep-related bradycardias, and normal ventricular function (*N. Engl. J. Med.* 2005;353: 2568-77).

Patients had a mean baseline apnea-hypopnea index of 49 and had at least two self-reported syncopal episodes in the preceding year. Diagnosis of obstructive sleep apnea-hypopnea syndrome was confirmed on polysomnography.

All pacemakers were initially programmed to initiate atrial pacing when the heart rate fell below 40 beats per minute. After 48 hours, half of the patients had their pacemakers programmed for atrial overdrive pacing, with pacing at a rate greater than 15 beats per minute or greater than their normal nocturnal heart rate.

The rest of the patients remained on backup atrial pacing plus nasal continuous positive airway pressure (n-CPAP).

One month later, the groups

switched therapies. The researchers then followed the patients for another month.

Atrial overdrive pacing had virtually no effect on the average apnea-hypopnea index at 1 month, which rose from 49 at baseline to 49.2. The increase was not statistically significant. In contrast, n-CPAP significantly improved the average apnea-hypopnea index after 1 month of therapy, which fell from 49 at baseline to 2.7.

The arousal index, desaturation index, and all other variables measured except total sleep time showed improvements with n-CPAP, while atrial overdrive pacing had no measurable effect on the variables, the researchers said.

“We were unable to show any beneficial effect of pacing in reducing the number of episodes of apnea or hypopnea per hour,” the investigators wrote.

The findings of the study, however, may not apply in general to all patients with the obstructive sleep apnea-hypopnea syndrome, they cautioned.

The failure of atrial overdrive pacing to improve symptoms “suggests that overdrive pacing is likely to have a very limited role in this setting,” Dr. Daniel J. Gottlieb of Boston University said in an accompanying editorial (*N. Engl. J. Med.* 2005;353:2604-6).

“Phenotypes will be identified in which modification of neuromuscular factors will play a useful therapeutic role,” he added. ■

Armodafinil Improves Daytime Wakefulness in CPAP Users

BY BRUCE JANCIN
Denver Bureau

DENVER — The investigational drug armodafinil significantly increased daytime wakefulness in patients with obstructive sleep apnea who experienced excessive sleepiness despite regular nighttime continuous positive airway pressure therapy, according to the results of two phase III clinical trials presented at the annual meeting of the Associated Professional Sleep Societies.

Based on these findings, as well as data from two other phase III trials involving patients with shift work sleep disorder or narcolepsy, the drug’s manufacturer, Cephalon Inc., has filed a new drug application seeking approval to market armodafinil (Nuvigil) as a wakefulness-promoting agent in patients with any of three disorders: obstructive sleep apnea-hypopnea syndrome, narcolepsy, or shift work sleep disorder.

Armodafinil is a single-isomer formulation of Cephalon’s Provigil (modafinil), which has a markedly shorter half-life than the newer enantiomer.

Dr. Jed E. Black reported on 392 patients with excessive daytime sleepiness as defined by a baseline Epworth Sleepiness

Scale score of 10 or more despite good adherence to continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea-hypopnea syndrome. Participants were randomized to armodafinil at 150 mg, 250 mg, or placebo once daily in the morning in this 12-week, double-blind multicenter trial.

Patients on both doses of armodafinil showed significantly improved daytime wakefulness, compared with placebo patients, as measured with the Maintenance of Wakefulness Test at weeks 4, 8, and 12.

Moreover, at each assessment, blinded physicians rated the armodafinil-treated patients as showing significantly more clinical improvement. For example, at the final visit, physicians rated 71% of patients in the 150-mg armodafinil group and 74% in the 250-mg group as showing at least minimal clinical improvement on the Clinical Global Impression of Change (CGIC) scale compared with 37% of patients taking placebo.

From a mean baseline Epworth Sleepiness Scale score of 15.5, the armodafinil group (both dosages combined) improved by a mean of 5.5 points, compared with 3.3 points in the placebo group. The armodafinil-treated patients rated their global fatigue as improved by a mean of 1.2

points from a baseline of 4.9 on the Brief Fatigue Inventory; that was twice as great a gain as in the placebo arm, said Dr. Black of Stanford (Calif.) University.

Armodafinil had no adverse effects on nighttime sleep as assessed by polysomnography, nor did it affect CPAP use, which continued at an average of 7 hours per night throughout the study.

Results were similar in a separate phase III trial reported by Max Hirshkowitz, Ph.D. This double-blind study included 259 patients with obstructive sleep apnea-hypopnea syndrome randomized to 150 mg of armodafinil or placebo for 12 weeks. These patients were experiencing excessive daytime sleepiness despite averaging nearly 7 hours per night of CPAP.

Once again, armodafinil resulted in significantly improved objective and subjective measures of wakefulness. In this trial, however, 150 mg/day of armodafinil also significantly improved the quality of long-term episodic memory, although it didn’t affect measures of attention or speed of memory, according to Dr. Hirshkowitz of the Michael E. DeBakey Veterans Affairs Medical Center, Houston.

In both trials, the adverse events that were more common with armodafinil

12-Week Improvement on Epworth Sleepiness Scale

5.5 points

Armodafinil (150 or 250 mg)

3.3 points

Placebo

Note: Based on data for 392 patients with excessive daytime sleepiness.
Source: Dr. Black

than placebo were mild to moderate headache, nausea, insomnia, dizziness, and anxiety. Headache and nausea, the two most frequent adverse events, were dose related. Headache, for example, occurred in 21% of patients on 250 mg/day of armodafinil in the first trial, in 15% of those on 150 mg/day in both trials, and in 7%-8% of patients on placebo.

Both phase III clinical trials were sponsored by Cephalon Inc. ■