CPAP May Lower Stroke Risk for Apnea Patients

BY SHARON WORCESTER
Southeast Bureau

SALT LAKE CITY — Studies consistently show a link between obstructive sleep apnea and stroke, with the most recent data showing that sleep apnea is an independent risk factor for stroke and death.

The cumulative data in regard to sleep apnea and stroke suggest that patients with sleep apnea should be treated with continuous positive airway pressure (CPAP) or other measures, Dr. Vahid Mohsenin said at the annual meeting of the Associated Professional Sleep Societies.

The evidence supporting the efficacy of CPAP is overwhelming—with good compliance, efficacy is about 90%—and the expectation is that treatment will reduce the risk of stroke, although more research is needed to confirm this, said Dr. Mohsenin, professor of medicine and director of the Yale Center for Sleep Medicine, Yale University, New Haven, Conn.

In fact, a guideline from the American Heart Association/American Stroke Association Stroke Council for the primary prevention of ischemic stroke was updated earlier this year to incorporate new information about stroke prevention, including data on the role of sleep-disordered breathing in stroke. The guideline was initially published in 2001.

Although the guideline stops short of making specific treatment recommendations, and instead states that treatment should be individualized, it does address patient evaluation. It is reasonable that patients and their bed partners be questioned about symptoms of sleep-disordered breathing and that appropriate patients be referred to a sleep specialist for further evaluation, the guideline states.

This is particularly important if the patient has drug-resistant hypertension or certain risk factors for stroke, such as abdominal obesity and hypertension (Stroke 2006;37:1583-633).

In making its recommendation, the AHA/ASA Stroke Council cited data from several studies, including a case-control study of 181 patients, which showed an association between excessive daytime sleepiness (likely caused by obstructive sleep apnea) and stroke (odds ratio 3.07).

The council also cited a 10-year observational study of more than 1,600 men, which showed that those with severe obstructive sleep apnea-hypopnea had an increased risk of fatal and nonfatal cardiovascular events including stroke, compared with healthy individuals (OR 2.87 and 3.17, respectively).

The guideline noted that there are a number of biologically plausible mechanisms for a link between sleep apnea and stroke; Dr. Mohsenin agreed.

Several studies suggest that the mechanism by which sleep-disordered breathing increases stroke risk is by "leading to or worsening hypertension and heart disease and possibly by causing reductions in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, hypercoagulability, inflammation, and paradoxical embolism in patients with patent foramen ovale," the guideline states.

But the real question, Dr. Mohsenin said, is whether there is an independent association between sleep apnea and stroke, and a recent study on which he was an author shows that there is indeed such an association.

In the observational cohort study of 697 patients with obstructive sleep apnea and 325 controls (mean apnea-hypopnea index of 35 vs. 2 in the patients and controls, respectively), obstructive sleep apnea was found to have a statistically significant association with stroke or death (hazard ratio of 1.91) after adjustment for numerous factors, including age, sex, race, smoking status, alcohol consumption, body mass index, diabetes, hyperlipidemia, atrial fibrillation, and hypertension.

A trend analysis also showed a significant dose-response relationship between sleep apnea severity at baseline and development of a composite end point of stroke or death from any cause (N. Engl. J. Med. 2005;353:2034-41).

While randomized controlled trials are needed to firmly establish a causal link between sleep apnea and stroke—to "put the last nail in the coffin and say, 'ok, sleep apnea is indeed a cause of stroke in a high-risk patient population,' " as Dr. Mohsenin put it, the findings increasingly suggest this is the case. Also, sleep apnea occurs as commonly in transient ischemic attack as it does in stroke, further underscoring the need for sleep apnea treatment in affected patients, he noted.

Additionally, a number of studies have shown that sleep apnea is associated with worse functional outcomes in stroke patients, Dr. Mohsenin said.

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Data increasingly suggest that a causal link exists between sleep apnea and stroke, Dr. Vahid Mohsenin says.

Patients with stroke who have sleep apnea have been shown to have more delirium, depression, impaired functional capacity, longer rehabilitation time, and longer hospitalization, he said.

"Sleep apnea does affect the outcome of stroke," he said, noting that in some studies these effects lasted out to 12 months.

Patients who have had a stroke should be evaluated for sleep disordered breathing, he advised.

In addition, patients using long-term CPAP should be reevaluated for residual symptoms of the disorder to ensure adequate treatment and compliance, he added. ■

Ramelteon Is Effective for Some Insomnia Patients

BY DAMIAN MCNAMARA
Miami Bureau

ORLANDO — Ramelteon is effective for a subset of patients with insomnia, according to a presentation at a psychopharmacology congress sponsored by the Neuroscience Education Institute. In addition, because the agent works on melatonin receptors, a potential off-label use is for patients with shift-work disorder.

Ramelteon (Rozerem, Takeda Pharmaceuticals) targets the melatonin receptors MT1 and MT2. The agent is approximately 10 times more potent than melatonin. Other approved drugs promote sleep by increasing γ-aminobutyric acid (GABA), which is normally released by the suprachiasmatic nucleus in the brain.

"Ramelteon is a very interesting drug. It is the first on the market for sleep that does not work on the GABA system," Dr. Wallace B. Mendelson said. The melatonin receptor agonist is a very short-acting drug with a half-life of 1 to 2 hours. "It is very potent for helping people fall asleep but not as effective for those who wake up early. So it's for a subset of patients."

The drug 'is very potent for helping people fall asleep but not as effective for those who wake up early. So it's for a subset of patients.'

The Food and Drug Administration approved ramelteon for treatment of insomnia characterized by difficulty with sleep onset. "It is not a DEA classified substance, only a hypnotic without potential for dependence," said Dr. Mendelson, psychopharmacology consultant for many pharmaceutical companies, including Takeda Pharmaceuticals North America Inc.

A delay to peak therapeutic effect is another distinction of ramelteon, compared with benzodiazepines and newer, nonbenzodiazepine GABA agonists such as zolpidem (Ambien, Sanofi-Aventis) or eszopiclone (Lunesta, Sepracor).

"It can take up to a week for full effect, so caution patients that they may not feel tired right away," said Dr. Mendelson, who is also a consultant, an adviser, and on the speakers' bureau for Sanofi-Aventis and Sepracor Inc.

People with shift-work sleep disorder can experience excessive daytime sleepiness because their body rhythm stays the same but the world changes around them, Dr. Mendelson said.

"No one knows why some people are more susceptible to this, except it is harder to adapt to night-time shift work as you get older."

Pharmacotherapy with a sleep aid might be sufficient for a shift worker who complains only of sleepiness or trouble going off to sleep, Dr. Mendelson said. However, "if they are having trouble with both sleep and waking, it might make sense to try to help them shift to the new time. One way is to use melatonin." Exogenous melatonin can shift circadian rhythms. Melatonin taken in the evening can shift a person's circadian rhythm earlier while melatonin in the morning can shift it later, he said.

"I have a real issue with the quality and standardization of melatonin. It's not consistent, which is why I prefer a drug like Rozerem," Dr. Mendelson said. "Rozerem is not indicated for this, but some research indicates it can shift circadian rhythm with off-label use similar to melatonin."

Another option for circadian rhythm adjustment is bright light therapy. "I like bright light therapy because it's more benign—but it works the opposite." In the morning, the therapy pushes circadian rhythm phase earlier, and at night, it pushes it later.

Insomnia rarely occurs alone, Dr. Mendelson said. "About 80% of insomnia patients you see have some other disorder. The old name was secondary insomnia. Us sleep guys are now calling this comorbid insomnia."

Ramelteon might be an appropriate choice for patients with sleep apnea, Dr. Mendelson said. A significant minority of sleep apnea will present with insomnia as the primary complaint. "We need to carefully diagnose because most of the agents we prescribe for insomnia can make sleep apnea worse, except ramelteon or the tricyclic antidepressants."

The probability of diagnosing a psychiatric disorder increases among patients who complain of insomnia (Sleep Med. 2005;6:549-53). In this study, a survey of 200 general hospital patients indicated 57% reported insomnia and 50% reported at least one psychiatric disorder. Insomnia can play a major role in several psychiatric illnesses, especially depression, Dr. Mendelson said. "Targeting insomnia with sleep aids and behavioral therapy can improve outcomes." Insomnia may also signal depression onset. "On average, 41% of people will have insomnia preceding depression." ■