Sleep Aid Suppresses Reflux-Related Awakening

BY MARY ANN MOON

Zolpidem, a frequently prescribed sleep aid, suppresses nocturnal awakenings that are an important CNS response to acid reflux events.

By enabling users to sleep through reflux events, the drug has the unintended effect of increasing esophageal exposure to stomach acid. This in turn opens the door to gastroesophageal reflux disease (GERD) complications such as erosive esophagitis, stricture formation, Barrett's esophagus, and esophageal adenocarcinoma, said Dr. Gregg Gagliardi of Thomas Jefferson University, Philadelphia, and his associates.

This finding is especially concerning because epidemiologic studies suggest that sleep disturbances occur in as many as 75% of patients who have frequent heartburn. If they take the sleep aid to manage their sleep disturbances, they may unwittingly worsen their heartburn.

In addition, almost 30% of patients with sleep disturbances are thought to have undiagnosed GERD, and those who use zolpidem to manage their sleep disturbances may exacerbate reflux events and induce esophageal complications, the investigators noted (Clin. Gastroenterol. Hepatol. 2009;7:948-52).

Normally, these nocturnal events trigger awakening or arousal from sleep, which leads to a swallow reflex. This initiates peristalsis and exposure of the esophageal mucosa to saliva rich in bicarbonate. The saliva neutralizes the acid content in the esophagus and the peristalsis clears the acid through to the stomach. Suppressing this protective mechanism may lead to prolonged acid exposure and mucosal injury over time.

The researchers performed a double-blind, placebo-controlled trial to examine the issue in 15 GERD patients and 8 normal control subjects. The study was supported in part by AstraZeneca Pharmaceuticals LP.

Each study subject underwent separate sleep studies at a 2-week interval after taking zolpidem (Ambien, Sanofi-Aventis) or a matching placebo. A transnasal esophageal pH catheter with a sensor placed 5 cm above the lower esophageal sphincter recorded reflux events and the acid clearance time for each event, while polysomnography recorded reflux-associated arousals and awakenings.

In both the subjects with GERD and the healthy control subjects who had taken placebo, a nocturnal acid reflux event caused arousal or awakening 89% of the time. In contrast, after they had taken zolpidem, reflux events caused arousal or awakening only 40% of the time.

Among the control subjects, the mean time until acid was cleared from the esophagus during reflux episodes was 1.15 seconds after they had taken placebo, compared with 15.67 seconds after they had taken zolpidem.

Exposure time also was dramatically increased among the GERD subjects. The mean time until acid was cleared from the esophagus was 37.8 seconds after they had taken placebo, compared with 363.3 seconds after they had taken zolpidem.

When this exposure time is multiplied by the number of reflux events over the course of the entire sleep period, it has significant ramifications for the development of erosive esophagitis, strictures, Barrett's esophagus, and esophageal cancer, the researchers noted.

Suppression of the arousal reflex was most marked early in the evening for both GERD subjects and controls, perhaps because zolpidem has a relatively short duration of action. However, reflux events are most common early in the evening.

It is possible that other CNS depressants or psychotropic medications may exert similar effects on nighttime arousals as zolpidem did in this study. The use of such sleep aids is increasing in the United States, Dr. Gagliardi and his colleagues noted. "If this effect of blunted arousals or awakenings by hypnotics is substantiated, this would suggest caution in the use of sleep aids without first considering GERD as an etiologic factor in patients with complaints of disturbed sleep," they added.

This study was limited by its small sample size, with just 23 subjects. However, the researchers attempted to counterbalance this drawback by analyzing each reflux event rather than each subject.

Dr. Gagliardi's associate, Dr. Karl Doghramji, also of Thomas Jefferson University, is a consultant for Sanofi-Aventis. No other conflicts of interest were reported. ■

Disturbances in Sleep Linked to Adverse Perinatal Outcomes

BY SUSAN LONDON

SEATTLE — Sleep disturbances during pregnancy increase the risk of adverse perinatal outcomes such as gestational diabetes and cesarean delivery, according to an overview of research presented at the annual meeting of the Associated Professional Sleep Societies.

"Sleep disturbances are common during pregnancy," said Bilgay Izci Balserak, Ph.D., of the University of Glasgow (Scotland) Sleep Centre. "The majority of pregnant women experience some level of sleep disturbance, especially in the third trimester of pregnancy."

Altered sleep during pregnancy stems from various hormonal, physiologic, and psychological factors.

DR. BALSERAK

A 2007 poll conducted by the National Sleep Foundation, Washington, found that 84% of pregnant women reported experiencing sleep problems at least a few nights per week, she noted. This compared with 67% of all women surveyed.

Altered sleep during pregnancy stems from a variety of hormonal, physiologic, and psychological factors, according to Dr. Balserak. These factors can affect sleep directly, as in the case of progesterone causing sedation, or indirectly, as in the case of heartburn or nocturia causing awakenings.

The sleep disturbances seen during pregnancy include both nocturnal perturbations (poor sleep quality, insomnia, and frequent awakenings) and daytime symptoms (fatigue and daytime sleepiness), she noted.

Pregnancy-related changes can also trigger frank sleep disorders or exacerbate preexisting ones, such as restless legs syndrome, sleep-disordered breathing, and parasomnias.

The acute sleep loss or fragmented sleep that results from sleep disturbances "can cause adverse perinatal outcomes," she said.

Retrospective and prospective studies, for example, have shown that pregnant women with sleep-disordered breathing have a two- to fivefold increased risk of developing gestational diabetes after body mass index is taken into account (Am. J. Respir. Crit. Care Med. 2007;175:A996, and Sleep 2009;32:A320-1).

Other research has linked sleep disturbances to birth outcomes. For instance, compared with women with a total sleep time of at least 7 hours in late pregnancy, women with a total sleep time of less than 6 hours or 6-6.9 hours have sharply elevated odds of cesarean delivery (odds ratios, 4.5 and 3.7, respectively) (Am. J. Obstet. Gynecol. 2004;191:2041-6). Women sleeping less than 6 hours also have longer labor, on average, than those sleeping at least 7 hours (29 vs. 18 hours).

Several studies have found correlations between unfavorable sleep parameters in late pregnancy and elevated levels of depressive symptoms, both at that time and in the early postpartum period, she noted.

In a study that was conducted among women in the third trimester of pregnancy that used the Center for Epidemiologic Studies-Depression (CES-D) scale, relative to their nondepressed counterparts (those with a CES-D score less than or equal to 15), depressed women (CES-D score of 16 or greater) had a greater frequency of sleep disturbances overall, as well as a longer latency to sleep onset, greater difficulty in maintaining sleep, poorer sleep quality, and less sleep time (J. Perinat. Neonatal Nurs. 2007;21:123-9).

"Early recognition, management, and treatment of sleep disturbances are important to prevent adverse perinatal outcomes," Dr. Balserak asserted. However, she added, there are currently no practice parameters when it comes to screening for and managing sleep disturbances during pregnancy.

"Regarding management, nonpharmacologic interventions should be considered as the first choice, including lifestyle modifications and cognitive-behavioral therapy strategies," she recommended.

Providers should encourage women to adopt healthy lifestyle behaviors, such as daily exercise, that may improve sleep, Dr. Balserak said. And they should counsel women about measures to address specific symptoms disrupting sleep, such as modifying eating habits to reduce heartburn.

"If pharmacological treatment is necessary, it should be used with caution due to potential side effects on the fetus," she concluded.

Dr. Balserak reported that she had no conflicts of interest in association with her presentation. ■

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