The sleep disorder narcolepsy comprises four symptoms: excessive daytime sleepiness, sleep paralysis, hypnagogic hallucinations (i.e., vivid realistic imagery occurring with the onset of sleep), and cataplexy (i.e., the sudden, temporary loss of muscle tone, usually occurring in association with laughter or heightened emotions). A person does not need to have all four symptoms to be diagnosed with narcolepsy. The disorder has two major forms: narcolepsy without cataplexy and narcolepsy with cataplexy (i.e., narcolepsy-cataplexy). Cataplexy is the most debilitating symptom since the sudden loss of muscle tone can endanger a person’s life if the person is driving or performing other dangerous activities. The drug sodium oxybate effectively reduces the number of cataplexy episodes for some people with narcolepsy-cataplexy. However, because of the risk of addiction, the drug tends to be prescribed after other treatments have failed. Scientists have long known that sodium oxybate inhibits central nervous system activity and have believed that it does not depress respiratory system activity. Recent reports now indicate that sodium oxybate may induce or worsen sleep-related disordered breathing and may have contributed to deaths in some people with narcolepsy-cataplexy.

Sodium oxybate is a form of gamma-hydroxybutyrate (GHB). In the central nervous system, GHB is formed as a byproduct of the metabolism of the amino acid and neurotransmitter gamma-amino butyric acid (GABA). (In sodium oxybate, one hydrogen atom in the GHB molecule is replaced with a sodium atom). GABA and GHB are inhibitory neurotransmitters.

GHB can induce a deep sleep quickly, which initially led to its use as an anesthetic. However, it soon fell out of favor as an anesthetic since its sleep-promoting effect is short lived, lasting only two to three hours.

In 1977, Mortimer Mamelak and colleagues were investigating the sleep-promoting effects of GHB with the hope of improving sleep in people with disrupted sleep (e.g., insomnia). While using the drug, one study participant reported being paralyzed just before going to sleep (i.e., sleep paralysis). Mamelak also noted that the drug shortened the time from wake to the onset (i.e., latency) of rapid eye movement (REM) sleep. (A shortened REM sleep latency is a polysomnographic feature of narcolepsy). These phenomena stimulated scientific interest in using GHB to treat narcolepsy.

In a later study, Mamelak and his colleague Roger Broughton focused on the effect of GHB on narcolepsy symptoms. All study participants reported having improved sleep quality and fewer cataplexy episodes while using GHB.

In a 1980 study, Broughton and Mamelak continuously monitored the sleep/wake patterns of 14 narcolepsy-cataplexy patients for 48 hours before and after GHB treatment. The researchers noted that the drug increased the amount of slow-wave sleep; reduced the amount of stage N1 sleep; increased sleep efficiency (i.e., the percentage of time spent asleep during the total amount time in bed); reduced REM sleep latency; and reduced fragmentation of REM sleep. During wake, patients experienced fewer or a total loss of daytime sleep attacks (i.e., episodes of overwhelming, irresistible sleep), and cataplectic attacks. The researchers also reported that the patients did not seem to develop a tolerance to the drug, experience serious toxic side effects, or have withdrawal symptoms on discontinuing the drug.1-3

The apparent lack of addiction, lack of tolerance to the drug, and lack of withdrawal symptoms have been brought into question. Since 1990, GHB has been a problematic drug of abuse in the United States because it has a euphoric effect, and there have been reports in the medical literature of long-term GHB users who, on discontinuing the drug, suffered withdrawal symptoms (e.g., severe anxiety, insomnia, feelings of panic or terror, tremors, and diarrhea). Scientists speculate that GHB plays a role in addiction since it mediates the activity of dopaminergic nerves (i.e., nerves stimulated by or releasing dopamine [an excitatory neurotransmitter]) in brain structures that plays a role in addiction.6,7

Sodium oxybate attaches to GABA receptors on GABAergic neurons (i.e., neurons that are activated by or release GABA). Certain GABAergic neurons located in the hypothalamus play a role in promoting sleep. This action may allow the drug to improve sleep.8 How sodium oxybate reduces cataplexy remains unclear.8

Drugs that depress central nervous system activity tend to also depress respiration. Sodium oxybate is a central nervous system depressant and can induce respiratory depression. However, the risk of respiratory depression is considered low in people with narcolepsy-cataplexy.9

Drugs that depress central nervous system activity tend to also depress respiration. Sodium oxybate is a central nervous system depressant and can induce respiratory depression. However, the risk of respiratory depression is considered low in people with narcolepsy-cataplexy.9

REGINA PATRICK, RST, RPSGT

Regina Patrick, RST, RPSGT, has been in the sleep field for more than 20 years and works as a sleep technologist at the Wolverine Sleep Disorders Center in Tecumseh, Mich.
Continued from Page 13

In OSA, the muscles of the upper airway relax excessively, allowing tissues to collapse into the airway and partially or fully block (i.e., obstruct) airflow. As a result, the blood oxygen level falls. This ultimately triggers a momentary arousal during which a person takes fast, deep breaths to restore the blood oxygen level. Once restored, the person falls asleep, setting the stage for the process to recur. Central nervous system drugs, by contributing to muscle relaxation, can increase the number of OSA episodes.

To examine the safety of using sodium oxybate in people with sleep-related disordered breathing, Canadian scientist Charles George9 and colleagues administered the drug to people with mild to moderate OSA. The study participants underwent one of four drug regimens: (1) sodium oxybate alone; (2) sodium oxybate plus modafinil (a stimulant drug that is sometimes used to reduce residual sleepiness after OSA treatment; scientists also believe that sodium oxybate enhances the wake-promoting effects of modafinil); (3) zolpidem (as a control; it is a sedative that can induce oxygen desaturation); or (4) a placebo (as a control).

George found no significant difference in the apnea-hypopnea index (AHI, the number of apneas and hypopneas per hour of sleep) before or after sodium oxybate treatment. However, the number of central apneas was significantly higher after treatment with sodium oxybate alone or sodium oxybate plus modafinil. George concluded that, in patients with mild to moderate OSA, sodium oxybate does not worsen OSA episodes (as reflected by the lack of significant change from the baseline AHI); however, he cautions that the drug may increase central apneas in some people with respiratory problems.

Series10 and colleagues investigated the impact of GHB on sleep and respiration in people with OSA. In their study, each of eight participants underwent two polysomnographic studies without the drug (i.e., the control nights) and one night with the drug. Series found no difference in the AHI between the control nights and the drug treatment night. Series further noted that most apneic events occurred during stages N1 and N2 and during REM sleep, but fewer apneas occurred during the drug treatment night; that apneas occurred during slow-wave sleep with GHB use; and that no difference existed between the drug-free and drug treatment nights in the mean apnea duration.

However, some research indicates that sodium oxybate increases the number of OSA episodes. German scientist Mareen Seeck-Hirschner11 and colleagues report two patients with mild OSA whose sleep-related disordered breathing increased after sodium oxybate treatment. The AHI in the first patient ranged from 8 to 10 events per hour during sodium oxybate treatment; this fell to 3 to 6 events per hour after the drug was discontinued. The AHI in the second patient was 24 to 45 events per hour with sodium oxybate treatment but was 5 to 11 events per hour before treatment. Based on these findings, Seeck-Hirschner concluded that sodium oxybate increases disordered breathing during sleep and suggests that narcoleptic patients with OSA who are taking sodium oxybate should be monitored polysomnographically.

A recent concern with sodium oxybate treatment is reports of deaths of patients who were prescribed the drug. For example, Brianne Akins12 and colleagues report the apparent accidental overdose death of a narcoleptic patient who had been prescribed sodium oxybate, as well as other central nervous system depressant drugs (e.g., gabapentin). Therefore, Akins speculates that the concomitant use of the drugs may have been a contributing factor to the patient’s death. Deborah Zvosec13 and colleagues report three patients whose deaths were associated with sodium oxybate treatment. The postmortem examination of one patient revealed extremely high levels of sodium oxybate in the blood, indicating abuse of the drug. The remaining two patients had therapeutic blood levels of sodium oxybate; however, other contributing factors such as the concurrent use of sedative-hypnotic drugs, OSA, and obesity may have played a role in the death. Therefore, the scientists could not definitively conclude that sodium oxybate caused their deaths.

In the United States, sodium oxybate is prescribed primarily to combat cataplexy, and to improve wakefulness in people with narcolepsy. Because of the possibility of the drug worsening or inducing disordered breathing during sleep, some scientists suggest monitoring patients polysomnographically for the development of or worsening of sleep-related disordered breathing.13,14 This monitoring may be particularly important for people diagnosed with narcolepsy and OSA. (An estimated 9 to 21 percent of people diagnosed with narcolepsy have OSA.)9 Future studies are needed to determine how the drug induces changes in respiration (e.g., in some people, sodium oxybate appears to induce Cheyne-Stokes respiration, a waxing-waning breathing pattern resulting from excessive sensitivity to small changes in oxygen and carbon dioxide levels in the blood);15 the extent that sodium oxybate worsens sleep-related disordered breathing with long-term use; clarify its effect on various central and OSA features (e.g., duration, desaturation); and how to improve the safety of using sodium oxybate in people with narcolepsy or narcolepsy and OSA if studies definitively prove that sodium oxybate worsens sleep-related disordered breathing.
REFERENCES


