Effect of Genetically Caused Excess of Brain Gamma-Hydroxybutyric Acid and GABA on Sleep

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Background: Exogenous gamma-hydroxybutyrate (GHB) increases slow-wave sleep and reduces daytime sleepiness and cataplexy in patients with primary narcolepsy.

Objective: To examine nighttime sleep and daytime sleepiness in a 13-year-old girl homozygous for succinic semialdehyde dehydrogenase (SSADH) deficiency, a rare recessive metabolic disorder that disrupts the normal degradation of 4-aminobutyric acid (GABA), and leads to an accumulation of GHB and GABA within the brain.

Methods: Sleep interview, nighttime polysomnography, Multiple Sleep Latency Tests, and continuous 24-hour in-lab recordings in the patient; overnight polysomnography in her recessive mother and in a 13-year-old female control.

Results: During quiet wakefulness, background electroencephalographic activity was slow and composed of 7-Hz activity. Sleep stage 3/4 was slightly increased (28.1% of total sleep period, norms 15%-28%), and the daytime mean sleep latency was short in the patient (3 minutes 42 seconds, norms > 8 minutes). Stage 2 spindles were infrequent in the child (0.18/minute, norms: 1.2-9.2/minute) and her mother (0.65/minute) but normal (4.6/minute) in the control. At the beginning of the second night, a tonic-clonic seizure occurred, followed by a dramatic increase in stage 3/4 sleep, that lasted 46.3% of the total sleep period, double the normal value. The mother showed a reduced total sleep time and rapid eye movement sleep percentage.

Discussion: This suggests that a chronic excess of GABA and GHB induces subtle sleep abnormalities, whereas increased slow-wave sleep evoked by a sudden event (here an epileptic seizure) may be caused by a supplementary increase in GABA and GHB.

Key Words: Slow-wave sleep, gamma-hydroxybutyrate, GHB, GABA, SSADH

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INTRODUCTION

SUCCINIC SEMIALDEHYDE DEHYDROGENASE (SSADH) DEFICIENCY IS A RARE AUTOSOMAL RECESSIVE METABOLIC DISORDER THAT DISRUPTS the normal metabolism of GABA (Figure 1), shunting it toward excessive production of gamma-hydroxybutyrate (GHB).1 SSADH deficiency is also associated with an increased level of GABA in human brain parenchyma, as demonstrated in a magnetic resonance spectroscopy study.2 Approximately 350 patients with SSADH deficiency have been described worldwide. They present a highly heterogeneous pattern with mild to very severe neurologic phenotype that includes a developmental delay, prominent language deficits, hypotonia, ataxia and, in half of the patients, seizures.3 GHB, which accumulates in the urine, serum and cerebrospinal fluid of patients (200 times the normal values), has traditionally been regarded as the neurotoxic agent leading to the clinical syndrome. The role of GHB is unclear, however, both in the pathophysiology of SSADH and as a drug.

GHB is a short-chain fatty acid, endogenously occurring in the brain4 as a metabolite (< 1% of GABA levels) of GABA. Various studies suggest that it acts as a neurotransmitter or a neuromodulator.5 Indeed, low- and high-affinity specific GHB receptors have been recently identified in discrete neurons of the mammalian brain, including hippocampus, striatum, and dopaminergic nuclei A9, A10, A12, olfactory tract, and frontal cortex.6 However, many of the pharmacologic and clinical effects observed when GHB is administrated exogenously are probably mediated via the GABA_B receptor, where GHB might act both directly as a partial weak agonist and indirectly via its conversion to GABA.5 Exogenous GHB penetrates the brain with no apparent control and, at doses that far exceed the physiologic GHB brain levels, induces various dose-dependent effects in humans. These include short-term amnesia, euphoria, and disinhibition at an oral dose of 10 mg per kg, drowsiness and sleep at 20 to 30 mg per kg, and coma, respiratory depression, and seizures at a dose of 50 to 60 mg per kg.5 In patients, GHB (sodium oxybate) was initially developed as an anesthetic and sedative agent7 and is now used to alleviate symptoms of narcolepsy-cataplexy.8,9 In addition, a misuse of GHB has recently emerged, both as a major recreational drug10 and as a means of subduing rape victims.11 The injection of low doses of GHB blocks brain dopamine and acetylcholine release in rodents,12,13 while high doses potentiate serotonin turnover.14

In healthy volunteers, the administration of single low doses of GHB promote a normal sequence of non-rapid eye movement (REM) and REM sleep lasting 2 to 3 hours.15 In patients with nar-
coleptic-cataplexy, the chronic administration of oral GHB, unlike
synthesis hypnotic compounds, increases slow-wave sleep
and delta power and does not change REM sleep. In addition, GHB significantly improves daytime alertness in these patients. Although a chronic excess of GHB is expected to be associated with abnormal sleep, sleep disturbances have rarely been reported in patients with SSADH deficiency. One child (case NO) suffered from severe insomnia and nocturnal bruxism and 1 patient developed a serious sleep disorder during her third decade, while 2 adult brothers showed prolonged sleep attacks with hallucinations. While sleep recordings were not reported in these 4 cases, they have been reported in 2 other patients. Sleep spindle asymmetry was reported in one 21-year-old patient (patient 5) during a nap, and 1 newborn boy (Patient 4 in Family 2) had a lack of differentiation between REM and non-REM sleep on an electroencephalogram (EEG). In addition, daytime sleepiness has not been evaluated in patients with SSADH deficiency. We, therefore, studied sleep and vigilance in a teenager with SSADH deficiency, her mother, and a healthy age- and sex-matched control.

**Patients and Methods**

**Patient Case Report**

A 13-year-old girl (case previously reported at age 5) was born to nonconsanguineous Turkish parents without histories of genetic disease and has 2 younger healthy siblings. As an infant, according to her mother, she slept continuously until the age of 3 months and had to be awakened for feeding. She “woke up” at the age of 3 months and had thereafter a sleep duration that was normal for her age. Developmentally, her motor milestones were delayed: she sat at 9 months, stood up by herself at 18 months, walked at 30 months and had bladder and bowel control at 7 years. Menarche was at 11½ years. At the time of the study, she was a quiet smiling girl. She could follow only simple instructions but laughed in appropriate situations. Her vocabulary consisted of only a few words, and she was unable to associate 2 words. She stood with a kyphotic posture and had a dystonic posture of hands and feet (Figure 2). She measured 167 cm and weighed 50 kg, with a body mass index of 17 kg/m². She had an internal strabismus of the right eye (Figure 2), normal deep tendon reflexes and muscle strength, ligament laxity, a large tongue, hypotonia, and mild ataxia but no upper neuron syndrome, parkinsonism, or hearing or visual defect. She experienced no epileptic seizures before the sleep test.

The diagnosis of SSADH deficiency was made when she was 5 years old by screening urine organic acids using selective ion monitoring mass spectrometry that revealed a small increase of 4-hydroxybutric acid. The diagnosis was confirmed by the absence of SSADH activity in lymphocytes (Table 1).

**Sleep Recordings**

With her consent and that of her father and mother, she underwent a 48-hour recording in the sleep laboratory, including the following sequence: (1) an interview of the parents concerning her sleep habits, and determination of an Epworth Sleepiness Scale score; (2) nighttime polysomnographic recordings (Night 1) from lights off (ad lib) to 6:30 AM; (3) clinical Multiple Sleep Latency Tests (MSLT) performed at 8 AM, 10 AM, 12 AM, 2 PM, and 4 PM and allowing a 15-minute duration of sleep recordings after sleep onset during each test; (4) Night 2, from lights off (ad lib) to lights on (ad lib); and (5) continuous daytime sleep recordings, with the possibility of napping in the morning and in the afternoon, ad lib. The mother underwent a single overnight polysomnogram. The sleep of

**Table 1**—Biochemical Features of a Patient With SSADH Deficiency, Her Parents, and Controls

<table>
<thead>
<tr>
<th>Subjects</th>
<th>GHB Urine (mmol/mol creatinine)</th>
<th>SSADH Activity Lymphocytes (pmol/min per mg protein)</th>
<th>PCC Activity Lymphocytes (pmol/min per mg protein)</th>
<th>Ratio* SSADH/PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>0</td>
<td>87</td>
<td>184</td>
<td>0.47</td>
</tr>
<tr>
<td>Control 2</td>
<td>0</td>
<td>113</td>
<td>201</td>
<td>0.56</td>
</tr>
<tr>
<td>Father</td>
<td>ND</td>
<td>68</td>
<td>239</td>
<td>0.28</td>
</tr>
<tr>
<td>Mother</td>
<td>ND</td>
<td>29</td>
<td>195</td>
<td>0.15</td>
</tr>
<tr>
<td>Patient</td>
<td>258</td>
<td>0</td>
<td>161</td>
<td>0</td>
</tr>
</tbody>
</table>

* Succinic semialdehyde dehydrogenase (SSADH) activity is normalized to propionyl-coenzyme A carboxylase (PCC) activity (assayed as a control in lymphocyte extracts) to correct differences in shipment and handling. GHB refers to gamma-hydroxybutyrate; ND, not determined.
the father was not recorded. A healthy 13-year-old girl with no sleep complaint was also recorded during an unattended overnight session. Sleep recordings included 8 EEG leads (Fp1-C3, C3-O1, Fp1-T3, T3-O1, Fp2-C4, C4-O2, Fp2-T4, T4-O2), electrooculogram, chin and left and right tibialis anterior muscle, nasal flow through nasal pressure prongs, tracheal sounds through a microphone, respiratory efforts through thoracic and abdominal belts, oxygen saturation through a pulse oximeter, and numeric synchronous video through an infrared camera (Cidelec Ltd, France). Sleep stages, arousal, respiratory events, and legs movements were scored according to standard criteria.23-26 Sleep spindles were scored and counted visually by 2 experienced scorers (IA and EK) during all stage 2 periods, as 12- to 15-Hz figures lasting 0.3-1 seconds.

RESULTS

Sleep Interview

The mother reported that her daughter slept regularly and quietly 9 hours a day with a single intranight awakening, had normal vigilance during the day, and took no spontaneous naps. The patient’s Epworth Sleepiness Scale score was 4 (maximal possible score was 16 and not 24, since the questions “while driving” and “while reading” were not applicable for a disabled child).

Baseline Sleep

The background EEG of the patient during quiet wakefulness showed an abnormal diffuse, high-voltage, and low-frequency alpha rhythm, with a peak at 7 Hz, that was reactive to eye opening (Figure 3). The morphology of sleep stages 1 and 2 was normal with usual theta rhythm and K complexes but rare spindles (0.18 spindles/minute of stage 2 sleep; for norms, 1.2-9.2 spindles/minute27). Stages 3 and 4 sleep were unremarkable. REM sleep had a normal aspect, with rare muscles twitches and normal atonia except on 3 short (less than 30-seconds) episodes during the 2 first cycles of REM sleep; the child had brief stereotyped hand movements of gripping the sheets, synchronous with normal (in particular devoid of spikes or sharp waves) background EEG. The sleep structure of the patient (Figure 4A and Table 2) included a frank decrease in sleep efficiency with conversely increased wakefulness after sleep onset and a very mild decrease in stage 2 and REM sleep percentages. The percentage of stage 3/4 was at the upper limit of normal; its duration was 154 minutes in the patient versus 91 minutes in the control. There were 6 periodic leg movements per hour (never associated with arousals), 18 apneas (10 of the obstructive type, 6 of the central type), 7 hypopneas, and an apnea-hypopnea index of 2 per hour. She did not snore. Oxyhemoglobin saturation was 97% while awake, was 92% while asleep, and reached a nadir of 85% during slow-wave sleep.

The MSLTs

In daytime MSLTs, the sleep-onset latency was 2 minutes 30 seconds at 8 AM, 1 minute at 10 AM, 2 minutes at 12 AM, 4 minutes at 2 PM, and 9 minutes at 4 PM. The mean sleep latency was 3 minutes 42 seconds, a pathologic value (normal > 8 minutes).28
Daytime sleep bouts contained stage 1 and 2 (no REM sleep), and the last test at 4 PM showed stage 3 and 4 sleep.

**Night 2 Sleep and 24-Hour Recordings**

During Night 2, after 1 hour asleep and while the patient was in stage 4, the technician entered the room and awakened her briefly in order to replace an electrode. A few minutes after he left, she presented a brief isolated generalized myoclonia with diffuse bilateral trains of fast discharges or multiple spike waves on EEG. 8 episodes of myoclonia over a 5-minute period were intermingled with classic stage 4 sleep and followed by a tonic-clonic generalized seizure. After the seizure, the EEG was flattened for 20 seconds, then returned to a continuous delta wave.

**Figure 3**—Background electroencephalogram (EEG) during wakefulness with eyes closed (upward arrows) and eyes open (downward arrow), 20-second period. The alpha rhythm is abnormally slow (7 Hz). ROC refers to right outer canthus; LOC, left outer canthus; EMG, electromyogram.

**Table 2**—Sleep Measures in a Patient With SSADH Deficiency (Homozygote), Her Mother (Heterozygote), and a 13-Year-Old Sex-Matched Control

<table>
<thead>
<tr>
<th></th>
<th>Patient Night 1</th>
<th>Patient Night 2</th>
<th>Control</th>
<th>Norms* 10 Girls</th>
<th>Mother Night 1</th>
<th>Norms 11 Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13-15</td>
<td>41</td>
<td>40-49</td>
</tr>
<tr>
<td>Total sleep period, min</td>
<td>548</td>
<td>607†</td>
<td>506</td>
<td>408-563</td>
<td>466</td>
<td>386-479</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>463</td>
<td>524†</td>
<td>486</td>
<td>412-548</td>
<td>320†</td>
<td>379-471</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>88†</td>
<td>86†</td>
<td>96</td>
<td>94-98</td>
<td>68†</td>
<td>92-100</td>
</tr>
<tr>
<td>Latency, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep onset</td>
<td>30</td>
<td>49†</td>
<td>58</td>
<td>2-37</td>
<td>14</td>
<td>0-20</td>
</tr>
<tr>
<td>REM sleep onset</td>
<td>142</td>
<td>218†</td>
<td>69</td>
<td>27-187</td>
<td>71</td>
<td>15-150</td>
</tr>
<tr>
<td>Sleep stages, % of total sleep period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wakefulness</td>
<td>15.5†</td>
<td>13.6†</td>
<td>3.9</td>
<td>0-3</td>
<td>31.3§</td>
<td>0-4.1</td>
</tr>
<tr>
<td>Stage 1</td>
<td>5.3</td>
<td>1.5</td>
<td>2.2</td>
<td>0-6.3</td>
<td>6.2</td>
<td>1-7.9</td>
</tr>
<tr>
<td>Stage 2</td>
<td>34.1†</td>
<td>33.8†</td>
<td>51.2</td>
<td>36.5-60.8</td>
<td>39.3</td>
<td>37.1-70.9</td>
</tr>
<tr>
<td>Stage 3/4</td>
<td>28.1</td>
<td>46.3†</td>
<td>18.0</td>
<td>15.2-28.2</td>
<td>7.5</td>
<td>0-28</td>
</tr>
<tr>
<td>REM sleep</td>
<td>17.0†</td>
<td>4.8†</td>
<td>25.7</td>
<td>18.1-33.1</td>
<td>15.7†</td>
<td>18.7-34.7</td>
</tr>
<tr>
<td>Arousals/h</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>-</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Spindles/min</td>
<td>0.18†</td>
<td>0.17†</td>
<td>4.58</td>
<td>1.2-9.2†</td>
<td>0.65†</td>
<td>1.2-9.2†</td>
</tr>
</tbody>
</table>

*95% confidence interval (CI) calculated from age- and sex-matched normative data.28
†95% CI calculated from age-matched normative data.27
§value different (p < 0.05) from the 95% IC.
‖value different (p < 0.01) from the 99% IC.
SSADH refers to succinic semialdehyde dehydrogenase; REM, rapid eye movement sleep.
rhythm similar to her usual stage 4 sleep, followed by stage 2 sleep, awakenings, and then again stage 4 sleep (Figure 3B). The postictal sleep was characterized by a dramatic increase in stage 4 sleep, lasting 281 minutes or 46.3% of total sleep period (a value 64% higher than the upper limit of age- and sex-matched norms) and a large decrease and delay in REM sleep (Table 2). On the following day, she could not fall asleep in the morning but slept 83 minutes during an afternoon nap, with 70.1% stage 3/4 sleep. The total duration of sleep over the 24-hour period was 607 minutes, with 338 minutes (56%) of stage 3/4 sleep. With the exception of the abnormal background EEG seen during the myoclonia and the tonic-clonic seizure, there were no spike discharges or spike wave or other figures suggestive of interictal epileptic activity during Night 1, the MSLTs, Night 2, or daytime EEG recordings. After the child had the first seizure, the mother reported that the child had nocturnal seizures four times during the following 8 months.

Sleep Structure of the Mother

The mother, aged 40 years, measured 157 cm and weighed 75 kg (body mass index: 30 kg/m²). She had a normal physical and mental development. She scored 2 on the Epworth Sleepiness Scale score and reported frequent insomnias and a sensation of light sleep. Her EEG alpha rhythm was normal (10 Hz). She had normal sleep figures, except for rare spindles (0.65 spindles per minute of stage 2 sleep, when normative data are 1.2 to 9.2 spindles/minute), poor sleep efficiency and a mild decrease in REM sleep, no periodic leg movements, and 4 hypopnea but no apnea (Table 2).

Sleep Structure in the Control

The control teenager was a healthy 13-year-old girl, with menarche at 12 years of age. She weighed 57 kg and measured 160 cm (body mass index: 22.2 kg/m²). Her Epworth Sleepiness Scale score was 0. Her waking EEG background was normal (10 Hz), as were the sleep figures, duration, and architecture, but sleep onset was slightly delayed (Table 2). The number of sleep spindles was normal (4.6/minute of stage 2 sleep, when normative data are 1.2 to 9.2 spindles/minute). There were no apneas or hypopneas.

DISCUSSION

In a patient with SSADH deficiency, a disease caused by a mutation that leads to a dramatic increase in the production of GHB and GABA in the brain, baseline sleep was almost normal except for a mild decrease in sleep efficiency, stage 2 and REM sleep percentages, and quasi-absent spindles. Conversely, there was an abnormally short daytime sleep latency. Postictal sleep was also abnormal, as the duration of slow-wave sleep was almost doubled. Her asymptomatic recessive mother also had an almost normal sleep structure, except for a nonspecific decrease in sleep efficiency, mild decrease in REM sleep percentage, and quasi-absent spindles.

The cerebrospinal fluid levels of GHB in patients with SSADH deficiency are 200 times higher than in controls, those of GABA are 2- to 3-fold increased compared to controls. We expected that these supraphysiologic concentrations of GHB in the brain would mimic the effect of chronic GHB administration in humans, such as an increase in slow-wave sleep. However, slow-wave sleep percentage was high but within normal ranges. The patient, as a baby, slept most of the time. This suggests that constant exposure to supraphysiologic levels of GHB and GABA may down-regulate the receptor systems in the developing mammalian central nervous system, thus dose reducing the sedative properties of GHB. It might also be that excess GABA is transformed back to its precursor glutamate, an excitatory neurotransmitter that increases wakefulness, but only indirectly via the shunt in brain converting ketoglutarate to GABA at the GABA-T step, or via ketoglutarate in the Krebs cycle. This is probably not the case either, however, since mice in which the SSADH gene was inactivated accumulate 60-fold more GHB and 2- to 3-fold more GABA than wild-type littermate controls but do not accumulate more of the GABA precursor glutamate. Furthermore, magnetic resonance spectroscopy performed in a patient with SSADH deficiency showed normal brain glutamate levels. Finally, it has been argued that GHB may have no direct effect on
sleep but, rather, promotes slow-wave activity mechanisms. GHB has indeed been shown to induce slow-wave activity and a marked increase in delta power even when administered during wakefulness. Here, slow waves were not assessed using power spectrum analysis but visually. The general slowing of EEG background was obvious on EEG traces even during wakefulness, as it has been reported in 23% of a series of 35 children with SSADH. Although background EEG slowing is a nonspecific and frequent finding in children with encephalopathy, whatever the cause, it is tempting to relate it here to stimulation of the thalamocortical loop by excess endogenous GHB.

The dominant patient and her recessive mother both had mildly reduced REM sleep percentages and normal (not shortened) REM sleep latencies, while the daughter did not show any sleep onset in REM periods, either during the night or during the day in the MSLT or the daytime continuous recordings. These results contradict the REM sleep promoting or consolidating effects of GHB reported in patients with narcolepsy using low doses of GHB for a limited time and in patients with affective disorders. Two conditions independently associated with shortened REM sleep onset. It is, however, in accordance with the mild reduction in REM sleep duration and unchanged REM sleep latency recently observed in patients with narcolepsy treated long-term with high doses of oral GHB and with the unchanged REM sleep duration and latency after the administration of a single GHB dose in healthy volunteers. This suggests, in addition to our cases, that long-term exposure to high levels of GHB in the SSADH deficiency does not lead to an increase (and might even lead to a mild decrease) in REM sleep pressure.

An epileptic seizure was elicited after awakening was provoked during stage 4 sleep. Epileptic seizures have also been reported in half of the patients with SSADH deficiency. Furthermore, mice with homozygous invalidation of the SSADH gene develop lethal generalized tonic-clonic seizures that can be rescued pharmacologically with antiepileptic drugs. No previous seizures were reported in our patient before the sleep studies, but they might have occurred during the night and gone unnoticed by the parents. In contrast to baseline nighttime sleep, postictal sleep was abnormal and characterized by an increase in total sleep time and in the percentage of slow-wave sleep and a decrease in REM sleep. Increased slow-wave sleep and decreased REM sleep are classic, but poorly studied, consequences of focal and generalized seizures both in patients and in animal models of epilepsy. The diffuse slow-frequency high-amplitude EEG activity observed after the seizure is routinely frequently described immediately following a seizure in epileptic patients and could be a nonspecific marker of impaired brain functioning. However, despite the lack of normative data on postictal sleep in the literature, classic postictal EEG activity could not alone explain the doubling of slow-wave sleep, in particular, since the patient had normal intranight awakenings and normal stage 1 and 2 sleep, devoid of slow waves. In patients with seizures, epileptic activity is followed by a large (10- to 34-fold higher) release of GABA in the hippocampus. We speculate that the seizure-induced postictal release of GABA, and an associated elevation of GHB, resulted in an excess of slow-wave sleep. If this is true, any situation resulting in excessive GABA release would increase slow-wave sleep in these patients.

Finally, we observed a dramatic reduction (but not a total disappearance) in spindle activity during stage 2 sleep in both the patient and her mother. In 1 previous adult with SSADH, an asymmetry of spindles was observed during a single nap. Unfortunately, a nap is too short for reliably measuring the spindle index. Thalamocortical spindles are thought to be generated by the pacemaker properties of the GABAergic cells of the reticular thalami nucleus, resulting from mutual inhibition among the cells. Neurons, each of which are conditional oscillators, are coupled to all other reticularis neurons via fast GABA and slow GABAB synapses. Interestingly, experiences in the rat suggest that the latter, when stimulated, result in slow or desynchronized oscillatory activity. Indeed, in cat and rat brain slices, GHB hyperpolarizes the membrane of the thalamocortical neurons through GABAB receptors, leading to burst firing output that promotes slow-wave activity. Stimulation of GABAB receptors by GHB might have decreased the spindling 12- to 14-Hz properties of the thalamocortical network, to the benefit of a slower 0.5- to 2-Hz activity. In the rat, the spontaneous frontal high-voltage spindles, 6- to 9-Hz figures (different from human sleep spindles but similarly driven by thalamocortical networks), have a decreased amplitude after cortical application of GHB. This raises the idea that, in our patients, spindles could be present but masked due to a GHB-induced decreased amplitude. Deep-brain recordings during sleep in the SSADH murine model could help explain this surprising observation.

In conclusion, the evaluation of our patient indicates that a continuous excess of GHB and GABA may have demonstrable consequences on sleep and daytime vigilance. Further evaluation of sleep patterns in additional SSADH-deficient patients will expand our understanding of the link between sleep and GHB and GABA and may provide insight into potential changes in patients with narcolepsy-cataplexy undergoing chronic GHB therapy, as well as sleep disturbances in GHB addiction.

REFERENCES

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In OSAHS, PROVIGIL is indicated as an adjunct to standard treatment(s) for the underlying obstruction.

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WARNINGS: It is not known whether PROVIGIL or its metabolites are excreted in human milk. Caution should be exercised when PROVIGIL is administered to a nursing woman.

OVERDOSAGE: In an acute oral overdose study in rats, a human dose of 200 mg/day on a mg/m2 basis) had no effects on fertility.

Pregnancy Category C: PROVIGIL administered orally to pregnant rats throughout the period of organogenesis caused, in the absence of maternal toxicity, an increase in resorptions and an increased incidence of fetal losses in conjunction with a 50% reduction in fetal weight. However, in a subsequent study of pregnant rabbits, increased resorptions, and increased alterations in fetuses at a dose in the range of 100 mg/kg/day (5 times the recommended human dose of 200 mg/day on a mg/kg basis) but not at 10 mg/kg/day. However, in a subsequent study of pregnant rabbits, increased resorptions, and increased alterations in fetuses at a dose in the range of 100 mg/kg/day (5 times the recommended human dose of 200 mg/day on a mg/kg basis), had a no-effect on the postnatal development of the offspring. There is no adequate and well-controlled studies in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Leukopenia has been reported in pediatric patients taking PROVIGIL.

GERIATRIC USE: Safety and effectiveness in the elderly have not been established.

ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 3000 patients, of whom more than 2000 patients with excessive daytime somnolence associated with narcolepsy. Over 1000 patients have received PROVIGIL for more than 1 year (in 100 mg/day). Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage may be indicated when emesis is expected to yield a significant amount of material with therapeutic potential.