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The Effects of γ-Hydroxybutyrate on the Sleep of Narcolepsy Patients: A Double-Blind Study

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Summary: The effects of γ-hydroxybutyrate (GHB: 25 mg/kg h.s. and 3 h later) vs. placebo on objectively evaluated nighttime sleep and daytime sleepiness in narcolepsy were evaluated in a double-blind, counterbalanced crossover design. Twenty narcolepsy patients were given an overnight polysomnogram (PSG), followed by a daytime multiple sleep latency test (MSLT) at baseline and on the 1st and 29th days of GHB and placebo treatment. The overnight PSGs indicated that the narcolepsy patients had the following significant results during GHB versus placebo treatment: decreased stage 1 ($p = 0.012$), increased stage 3 ($p = 0.008$), increased delta (stage 3 and 4 combined) sleep ($p = 0.049$), fewer stage shifts ($p = 0.002$), and fewer awakenings ($p = 0.006$). Minutes of wakefulness were significantly increased only for the last 2 h of the 8 h sleep period on GHB versus placebo ($p = 0.019$), which is beyond the time of GHB's direct influence. The MSLTs indicated that the narcolepsy patients had a marginally increased sleep latency mean during GHB versus placebo treatment ($p = 0.074$) and significantly increased total stage 0 (wakefulness) on day 29 of GHB versus day 29 of placebo treatment ($p = 0.038$). Female narcolepsy patients had significantly fewer naps with REM sleep (REM naps) on day 29 of GHB vs. day 29 of placebo treatment ($p = 0.020$). The therapeutic effect of GHB in narcolepsy patients, i.e., decreases cataplexy, appears to be due to its improving nocturnal sleep quality, since its half-life is only 1.5 to 2 h. It is conjectured that GHB, an endogenous neurochemical, may be a sleep neurotransmitter or neuromodulator, since GHB rapidly induces sleep, and increases sleep continuity and delta sleep without suppressing REM sleep in both normals and narcolepsy patients. **Key Words:** Narcolepsy—Cataplexy—γ-Hydroxybutyrate—Sleep—Multiple sleep latency test.

Narcolepsy is a chronic, incurable disorder characterized by intermittent excessive daytime sleepiness and abnormal rapid-eye-movement (REM) sleep manifestations, such as sleep-onset REM periods, cataplexy, sleep paralysis, and/or hypnagogic hallucinations (1). Cataplexy is a sudden loss of muscle tone that occurs primarily during

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emotional arousal, sleep paralysis is an inability to move upon first lying down or upon waking, and hypnagogic hallucinations are dream-like hallucinations that occur at sleep onset. Most patients with narcolepsy also have disrupted nocturnal sleep (2). Narcolepsy is generally treated with a central nervous system stimulant (e.g., amphetamine, methylphenidate, or pemoline) to reduce excessive daytime sleepiness (EDS) (3), and an antidepressant (e.g., imipramine or protriptyline) to control cataplexy and other REM sleep-related symptoms (4). These drugs are only partly effective (3,5) and can have serious adverse effects on the cardiovascular, gastrointestinal, and central nervous systems (6). More recently, propranolol (80–480 mg/day) has been reported to also control cataplexy and excessive sleepiness, although it also has undesirable side effects (insomnia, low blood pressure, lethargy, gradually less effective, etc.), resulting in a high rate of treatment withdrawal (7,8).

γ-Hydroxybutyrate (GHB) is a four-carbon fatty acid that occurs naturally in the mammalian central nervous system and readily crosses the blood–brain barrier (9). GHB is found in highest concentrations in the hypothalamus and basal ganglion of the developing rat and human brain (10). Binding sites of GHB occur primarily in the limbic system, and in archicortex and cortex, with traces in the hypothalamus and thalamus, but almost none in the cerebellum, medulla, and pons (11). Recently, GHB has been reported to fulfill the criteria of a neurotransmitter (12) and to be a regulator of energy metabolism (13). GHB was reported to induce anesthesia at 60–70 mg/kg and sleep at 40–50 mg/kg (14). Although oral doses of ~25–35 mg/kg of GHB have been reported to induce rapid sleep onset and normal cycling of sleep stages at bedtime (15,16), the minimum GHB dose that will induce sleep has not been systematically determined. Unlike other hypnotics, GHB given orally rapidly induces and maintains sleep without suppressing REM or delta stages of sleep (15). It has been reported that caffeine and pyruvate counteracts the sedating effects of GHB, whereas alcohol and fasting potentiate the effects of GHB (9).

In narcolepsy patients, results from open trial studies found that GHB given in divided dose, i.e., a dose h.s. and one to two additional times during the night, caused moderate to large reductions in cataplexy frequency and daytime sleepiness, as well as reduced sleep disruption, hypnagogic hallucinations, and sleep paralysis (5,17,18). Our laboratory recently completed a double-blind study of GHB (25 mg/kg h.s. and 25 mg/kg 3 h later) versus placebo, which confirmed that GHB significantly decreases cataplexy, but GHB did not decrease subjective measures of daytime sleepiness (19).

Our double-blind study of GHB in narcolepsy also included objective assessment of nighttime sleep and daytime sleepiness, i.e., patients had overnight polysomnograms (PSGs) followed by multiple sleep latency tests (MSLTs) at baseline and on the first and last (29th) nights of placebo and GHB treatment. This report describes the overnight PSG and MSLT results of the first double-blind comparison of GHB versus placebo on the sleep of narcolepsy patients.

METHODS

Subjects

Ten female and ten male patients with narcolepsy, diagnosed at the accredited Sleep Disorders Center (SDC) of the University of Arkansas for Medical Sciences (UAMS), participated in this study. This research had prior approval by the Food and Drug Administration and the UAMS Human Research Advisory Committee. A written in-

formed consent was signed by all patients prior to their beginning this study. All patients were interviewed by an accredited clinical polysomnographer, given a physical examination by a physician, and had sleep disorders diagnostic test evaluations using standard procedures (20). The diagnostic tests included a PSG and an evaluation of their daytime sleepiness with an MSLT. The criteria for inclusion in this study were (a) a history of excessive daytime sleepiness and cataplexy, (b) $\geq$2 naps with REM sleep on the MSLT, (c) sleep latency mean $\leq$ 5 min on the MSLT, (d) at least 10 cataplexy attacks subjectively reported on a daily log during the 2-week baseline period, and (e) age between 16 and 65 years old. Patients were excluded if they (a) had other major health problems; (b) had other sleep disorders with the exception of those frequently associated with narcolepsy such as sleep apnea (excluded if arterial oxygen saturation $<$ 80%), and nocturnal myoclonus; (c) were fertile females who were not practicing birth control; (d) were nursing mothers; or (e) had previously taken GHB.

Table 1 lists each subject's age and weight at the time of the baseline study, as well

TABLE 1. *Patient data*

Patient sex, I.D.	Age (years)	Weight (kg)	Date* Rx stopped	Date BL log start	Date BL PSG
M01	50	87.7	3-19-86[b: 75] 1-10-86[e: 5]	3-20-86	4-3-86
M02	53	88.2	6-6-86[D]	5-22-86	6-5-86
M03	21	70.0	6-7-86[b: 0–75]	6-11-86	6-23-86
M04	64	74.5	N/A[a: 5–10]	7-9-86	8-4-86
M05	48	85.5	N/A[a: 10–30]	8-3-86	8-19-86
M06	36	87.3	N/A[a: 60–100]	10-6-86	10-21-86
M07	57	79.5	7-20-86[d: 20]	9-4-86	9-18-86
M08	51	54.1	N/A[a: 0–20]	11-6-86	11-20-86
M09	63	88.2	2-23-87[d: 50]	3-8-87	3-23-87
M10	48	90.0	4-2-87[D]	4-27-87	5-7-87
F11	44	75.9	5-2-86[e: 40]	5-26-86	6-9-86
F12	64	85.9	5-20-86[d: 75]	5-21-86	6-9-86
F13	42	89.1	8-7-86[d: 100] 8-17-86[g: 3] 8-20-86[c: 60]	9-11-86	9-25-86
F14	45	79.5	9-2-86[b: 75] 9-4-86[d: 75] 9-4-86[f: 0.375] 9-4-86[D]	10-16-86	10-30-86
F15	40	105.0	1-24-87[d: 75]	1-30-87	2-12-87
F16	34	90.0	N/A	3-9-87	3-23-87
F17	54	88.2	3-18-87[c: 25] 3-12-87[d: 150] Continued[D]	3-13-87	3-30-87
F18	16	57.3	7-86[c: 20] 3-26-87[d: 50–75]	3-28-87	4-13-87
F19	58	113.2	N/A[a: 0–5]	8-14-87	8-31-87
F20	62	68.2	8-10-87[c: 10–20] 8-10-87[D]	9-15-87	9-28-87

* Date Rx stopped—Rx code: mg/day; BL: baseline.

[a] All patients had the option of starting or reducing methylphenidate $\leq$30 mg/day allowed 8 a.m.–5 p.m., except on MSLT test days, throughout the study starting on or before the log start date. Prior to the study, all subjects used 0–30 mg of methylphenidate daily, except M06 (up to 100 mg/day reduced to 30 mg/day on BL log start date).

[b] Pemoline, [c]dextroamphetamine, [d]impramine, [e]protriptyline, [f]triazolam, [g]lorazepam, [h]clonazepam, [i]levothyroxine.

[D] Diuretic/antihypertensive.

as their drug history prior to this study and the start of the baseline log and PSG date. The age mean ± SD (range) was 45.9 ± 14.5 (16–64) years for the female patients and 49.1 ± 12.7 (21–64) years for the males. Mean ± SD (range) weight was 85.1 ± 16.4 (57–113) kg for females and 80.4 + 11.4 (54–90) kg for males. Body mass index was 31.8 ± 7.8 (17.6–45.4) for females and 26.2 ± 2.8 (20.3–29.1) for males. All patients were off antidepressants and stimulants, other than up to 30 mg of methylphenidate, for at least 15 days prior to the baseline PSG and MSLT. One patient took propranolol for hypertension throughout the study at a dose of 40 mg/kg, which is one-half the lowest dose reported to reduce narcolepsy symptoms for some patients (7,8). This patient was included in the analysis reported here, since each patient served as their own control in a repeated-measures design and propranolol was taken throughout the study.

Procedures

A double-blind, crossover design, with order of treatment counterbalanced and randomly assigned, was utilized. Thus, each subject provided data for all phases of the study: baseline (14 days), first treatment (29 days), first washout (6 days), second treatment (29 days), and second washout (6 days). Order of treatment was randomly assigned by the UAMS pharmacy so that one-half of the males and one-half of the females received GHB in the first treatment period and placebo in the second, and the remaining subjects received placebo first and GHB second. All of the Sleep Disorders Center staff were blind to the order of treatment for subjects. On each night of the GHB treatment period, subjects took 25 mg/kg of GHB h.s. and 25 mg/kg 3 h later. During placebo treatment, subjects took a placebo (an identical-appearing quantity of sterile, distilled water and syrup of orange used to mix the GHB) h.s. and 3 h later. Subjects were instructed not to use alcohol, sleeping pills, or other central nervous system depressants during the study and to avoid drinking caffeinated beverages after 6 p.m. Each subject had an 8.0 h PSG performed on the last night of baseline and the first and last nights of both treatment periods, with an MSLT performed the day following each PSG (five PSGs and five MSLTs). The narcolepsy patients did not take methylphenidate (otherwise allowed up to 30 mg daily) after 5 p.m. on the day of PSG tests or on the following day until after the MSLT tests were completed. Each PSG included monitoring and recording standard sleep parameters (21): sleep staging from electroencephalogram (EEG), electro-oculogram (EOG), and triangularis electromyogram (chin EMG). A cardiopulmonary resuscitation (CPR)-certified licensed practical nurse (L.P.N.) technician continuously monitored patients throughout the recording. The PSG commenced at each patient's usual bedtime, immediately after ingesting the h.s. dose of GHB or the placebo. Patients were awakened exactly 3 h later by the overnight technician to take their second dose of GHB or placebo. Patients were awakened and the PSG was terminated 8 h after lights out. PSGs were scored for sleep stages in 40-s epochs according to standard scoring techniques (21), except that, rather than scoring stage 6 (movement), stage 0 was scored when movement artifact lasted ≥ 20 s. Sleep stages were scored by an accredited clinical polysomnographer (L.S.) who was blind to the order of treatment.

Data analysis

A complete crossover, repeated-measures analysis of variance was used with two between-subject factors (gender and order of treatment) and two within-subject factors [treatment (GHB vs. placebo) and day of treatment, i.e., first vs. last (29th) day of

treatment]. Sleep stages were converted to percents of total sleep time for reporting and analyses. Change scores, i.e., the difference between results on GHB or placebo minus baseline results, were used in the analysis. Placebo effects were evaluated by contrasts of the results during baseline vs. placebo day 1. The criteria for a statistically significant result was $p \leq 0.05$, and for a "marginal" result was $p \leq 0.10$.

RESULTS

Overnight PSG

Table 2 lists the means and standard deviations of the overnight PSG measures and specifies significant results. Methylphenidate usage (the number of 5 mg tablets/day) did not vary significantly during baseline (2.7 ± 0.6) or treatment intervals (placebo week 1: 3.1 ± 0.5, week 4: 2.9 ± 0.05; GHB week 1: 3.0 ± 0.6, week 4: 2.8 ± 0.06) (19).

Treatment main effects. During GHB (day 1 and 29) versus placebo (day 1 and 29) treatment, the narcolepsy patients had the following significant PSG results: decreased percent stage 1 sleep ($p = 0.012$), increased stage 3 sleep ($p = 0.008$), increased delta (stages 3 and 4) sleep ($p = 0.049$), longer sleep latency ($p = 0.029$), and fewer sleep stage shifts ($p = 0.002$). They also had significantly fewer awakenings ($p = 0.006$), but significantly increased minutes of stage 0 (wakefulness) ($p = 0.040$) and significantly

TABLE 2. *Overnight sleep in narcolepsy patients during GHB vs. placebo treatment: Means ± SD for 10 males and 10 females*

		Placebo		GHB	
	Baseline	Day 1	Day 29	Day 1	Day 29
Sleep measures					
PSG time (min)	475.9 ± 13.5	472.6 ± 29.4	473.9 ± 26.2	474.7 ± 19.3	480.8 ± 3.5
Total sleep (min)	397.4 ± 46.7	413.6 ± 46.5	416.5 ± 41.3	397.2 ± 59.1	409.1 ± 41.7
Stage 0 (min)[a]	78.5 ± 45.5*	58.9 ± 39.2*	57.4 ± 38.6	77.5 ± 50.5	71.6 ± 40.7
No. of wakes[b]	27.2 ± 9.6	25.4 ± 10.2	29.4 ± 11.7	20.6 ± 6.4	23.0 ± 6.2
Sleep efficiency	83.5 ± 9.5*	87.5 ± 8.1*	88.0 ± 7.9	83.5 ± 11.1	85.1 ± 8.5
Sleep stages (%)					
Stage 1[a]	28.8 ± 11.0	26.8 ± 8.7	29.3 ± 10.8	22.4 ± 11.6	24.1 ± 8.4
Stage 2	40.6 ± 8.5*	44.6 ± 8.8*	44.0 ± 10.8	46.4 ± 10.7	44.6 ± 6.3
Stage 3[b]	3.4 ± 3.4	3.1 ± 3.6	2.3 ± 2.6	4.0 ± 4.2	5.8 ± 5.3
Stage 4	4.2 ± 6.6	3.5 ± 6.2	4.4 ± 5.8	5.3 ± 6.7	4.6 ± 4.8
Non-REM	77.0 ± 4.6	77.9 ± 5.1	80.1 ± 5.5	78.1 ± 5.7	79.1 ± 5.3
Delta[a]	7.6 ± 9.5	6.6 ± 9.4	6.8 ± 7.2	9.3 ± 9.3	10.4 ± 9.1
REM sleep	23.0 ± 4.6	22.1 ± 5.1	19.9 ± 5.5	21.9 ± 5.7	20.9 ± 5.3
No. of REM epochs	14.2 ± 6.4	13.6 ± 4.6	12.0 ± 4.7	12.1 ± 5.4	10.8 ± 4.5
Stage shifts[b]	123.4 ± 23.8	127.0 ± 25.6	132.2 ± 32.2	101.9 ± 24.8	114.8 ± 29.2
Latency to					
Sleep[a]	4.2 ± 4.6†	2.4 ± 1.6†	2.4 ± 2.1	3.5 ± 2.9	3.2 ± 2.5
Stage 2	11.0 ± 12.2	10.8 ± 12.4	8.1 ± 12.5	18.0 ± 21.3	11.4 ± 14.1
Delta sleep	39.0 ± 22.3	36.6 ± 17.2	37.7 ± 18.0	67.8 ± 67.4	47.4 ± 52.2
REM sleep	48.5 ± 78.2	31.6 ± 31.1	46.1 ± 47.4	29.8 ± 49.1	23.7 ± 27.5
First 6 h					
Stage 0 (min)	60.0 ± 41.8	44.5 ± 30.9	37.6 ± 25.2	48.0 ± 40.2	42.3 ± 23.5
Sleep efficiency	83.3 ± 11.6	87.6 ± 8.6	89.6 ± 7.0	86.7 ± 11.2	88.3 ± 6.5
Last 2 h					
Stage 0 (min)[a]	18.5 ± 12.7	15.2 ± 12.4	19.9 ± 18.2	29.4 ± 22.0	29.3 ± 23.7
Sleep efficiency	84.1 ± 10.3	87.3 ± 10.2	81.5 ± 15.5	71.7 ± 24.4	75.4 ± 20.4

Repeated-measures ANOVA of treatment differences from baseline: GHB (day 1 and 29) vs. placebo (day 1 and 29): [a]$p < 0.05$, [b]$p < 0.01$.

Baseline vs. placebo day 1: *paired-*t*: $p < 0.05$, †paired-*t*: $p < 0.10$.

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