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Clinical Research

Gammahydroxybutyrate and Narcolepsy: A Double-Blind Placebo-Controlled Study

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Summary: We treated 24 patients with narcolepsy for 4 weeks with gammahydroxybutyrate (GHB), 60 mg/kg/night, in a randomized double-blind placebo-controlled cross-over trial. Both clinical and polysomnographic criteria were used to assess the results. Compared to placebo, GHB reduced the daily number of hypnagogic hallucinations (from 0.87 to 0.28; $p = 0.008$), daytime sleep attacks (from 2.27 to 1.40; $p = 0.001$) and the severity of subjective daytime sleepiness (from 1.57 to 1.24 on a 0–4 scale; $p = 0.028$). The number of daily cataplexy attacks was reduced from 1.26 at baseline to 0.56 after 4 weeks of GHB intake. This reduction, however, was not statistically significantly different from the difference between baseline and placebo. GHB stabilized nocturnal rapid eye movement (REM) sleep, i.e. it reduced the percentage of wakefulness during REM sleep ($p = 0.007$) and the number of awakenings out of REM sleep ($p = 0.016$), and tended to increase slow wave sleep ($p = 0.053$). Adverse events were few and mild. We conclude that GHB is an effective and well-tolerated treatment for narcolepsy. **Key Words:** Narcolepsy—Gammahydroxybutyrate—Polysomnography—Placebo-controlled clinical trial.

Narcolepsy is clinically characterized by excessive daytime sleepiness (EDS), a disturbed nocturnal sleep and the three rapid eye movement (REM) sleep-related phenomena: cataplexy, hypnagogic hallucinations and sleep paralysis (1). Polysomnographic findings of nocturnal sleep include instability of REM as well as non-rapid eye movement (NREM) sleep and shortened REM sleep latency (2–4). Standard drug treatment consists of psychostimulants for EDS and antidepressant drugs for the REM sleep-related symptoms (5).

Gammahydroxybutyrate (GHB) is a putative neurotransmitter in the human brain (6,7). After oral administration it has a hypnotic action and is considered to ameliorate (daytime) narcoleptic symptoms (8). To date, three open trials (9–11) and one double-blind placebo-controlled trial (12,13) testing this hypothesis have been published. A limitation for the interpretation of the polysomnographic effects in this last study was the previously defined duration of nocturnal sleep.

To establish the efficacy of GHB in narcolepsy, we carried out a randomized double-blind placebo-controlled cross-over trial in an unselected group of patients. Results were assessed both clinically and with polysomnographic criteria.

PATIENTS

Twenty-four patients were selected on clinical criteria. All of the patients had a history of excessive daytime sleepiness and cataplexy.

The clinical and demographic characteristics are summarized in Table 1. Medication, if any, was continued and kept unchanged for at least the 4 weeks prior to the trial.

The protocol was approved by our local ethics committee and all patients gave their written informed consent.

STUDY DESIGN

A schematic outline of the trial is shown in Fig. 1.

Following recruitment, patients were entered into a baseline observation period of 1 week. At the end of

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TABLE 1. *Demographic and clinical characteristics of the study population*

Age mean (range)	36.0 (16–65)
Sex male/female	13/11
HLA DR2/DQW6	24
Complaints (history):	
EDS/cataplexy	24
Hypnagogic hallucinations	21
Sleep paralysis	17
Co-medication[a]	
None	12
Stimulants	9
Antidepressants	7
Hypnotics	1
Other	1

[a] Five patients used more than one co-medication because of narcolepsy.

this week the first polysomnographic recording (baseline 1) was made. Immediately afterward, patients were randomly divided into two groups and treatment was started for a period of 4 weeks. On the last treatment day a second recording was made. A washout period of 3 weeks followed. This period was considered to be sufficient because GHB has a very short plasma half-life (undetectable after 3–4 hours) and because its therapeutic efficacy is of short duration (1–2 days) (7,10). At the end of the second baseline week, a third recording (baseline 2) was made and cross-over took place. A fourth polysomnogram at the end of the second treatment period completed the study.

During both baseline and treatment periods, a diary (daily questionnaire; see below) was kept, and mood ratings were scored once a week. At the end of each treatment period the global therapeutic impression was assessed by the patient.

Co-medication was continued unchanged throughout the study.

METHODS

Patients noted the following items in their diaries: number of sleep attacks, awakenings at night, cataplexy attacks, hypnagogic hallucinations, sleep paralysis, a rating of daytime sleepiness (0 = no sleepiness, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe) and a rating of the feeling of being refreshed in the morning (0 = not refreshed, 1 = slightly, 2 = moderately, 3 = sufficiently, 4 = very). The global therapeutic impression was rated on a 0–3 scale: 0 = no effect at all, 1 = possibly beneficial, 2 = beneficial, 3 = strongly beneficial. For mood rating a visual analogue mood rating scale (VAMRS) (14) was used.

Each polysomnographic recording consisted of an ambulatory 24-hour polygraphic recording [eight-channel Oxford Instruments recorder; two channels were used for electrooculography (EOG), four for electroencephalography (EEG), one for electromyography (EMG), and one channel for electrocardiography (ECG)]. A multiple sleep latency test (MSLT) was carried out during each recording at the patient's home after careful instruction of the patient and the partner, but without supervision at home.

Sleep was scored according to standard criteria (15) in epochs of 1 minute.

The number of sleep attacks, cataplexy attacks and hypnagogic hallucinations were considered of primary importance in the judgment of clinical efficacy.

STUDY MEDICATION

Gammahydroxybutyrate was administered orally as a 10% watery solution. To minimize differences in taste between GHB and placebo we used flavors and salt. Two daily doses of 30 mg/kg each were given; the first shortly before nocturnal sleep, the second 4 hours later.

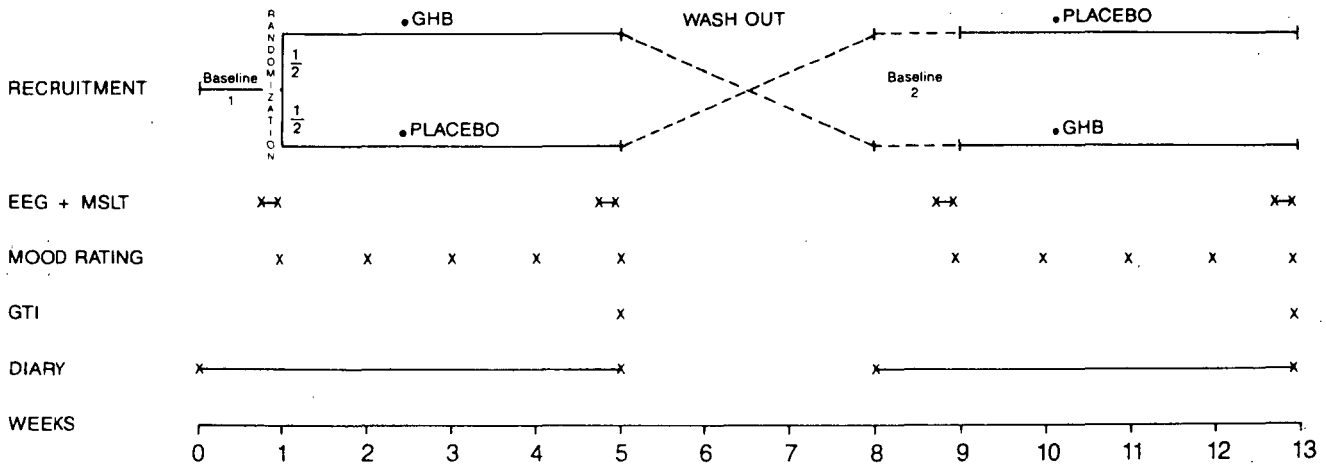

FIG. 1. Schematic outline of the protocol. GTI = Global Therapeutic Impression.

STATISTICS

To analyze treatment effects on diary variables, mean daily values during baseline were compared with the mean daily values during the fourth treatment week. The difference from baseline obtained with GHB was compared with the difference obtained with placebo. If patients did not experience a specific diary item during either baseline period, then they were excluded in the analysis for that particular item.

Intrapatient differences over time were analyzed for each group with the Wilcoxon's signed-rank test. Intergroup differences were analyzed with the Wilcoxon's two-sample test. A probability of <0.05 (two-tailed) was considered statistically significant.

RESULTS

Study population

All 24 patients completed the trial. One patient was excluded from the diary analysis because he failed to keep his diary. One patient was excluded from the polysomnographic analysis because of technical disturbances in the recordings. Seven patients properly completed all four ambulatory MSLTs.

Treatment effects

GHB reduced the daily number of hypnagogic hallucinations (n = 12) from 0.87 ± 0.58 to 0.28 ± 0.40 (placebo: 0.88 ± 0.77–0.95 ± 0.86; p = 0.008), daytime sleep attacks (n = 23) from 2.27 ± 0.93 to 1.40 ± 1.17 (placebo: 2.22 ± 1.32–2.18 ± 1.17; p = 0.001), the severity of subjective daytime sleepiness (n = 23) from 1.57 ± 0.47 to 1.24 ± 0.68 (placebo: 1.55 ± 0.60–1.59 ± 0.63; p = 0.028), the number of cataplexy attacks (n = 21) from 1.26 ± 1.76 to 0.56 ± 0.84 (placebo: 1.56 ± 1.99–1.24 ± 1.38; ns) and awakenings at night (n = 23) from 3.30 ± 1.82 to 2.45 ± 1.73 (placebo: 3.32 ± 1.82–3.49 ± 1.87; ns). The feeling of being refreshed in the morning (n = 23) increased from 1.90 ± 0.57 to 2.13 ± 0.72 (placebo: 1.83 ± 0.72–1.92 ± 0.69; ns). The effect on sleep paralysis could not be assessed because of the low incidence of this item during the baseline weeks (n = 4).

The effects on polysomnographic variables are shown in Table 2. Compared to placebo, GHB significantly reduced the number of awakenings from, and the percentage of wakefulness during, REM sleep. The increase in the amount of nocturnal slow wave sleep (SWS) during GHB treatment was considerable and nearly significant (p = 0.053). The total amount of REM sleep, nocturnal REM sleep latency and other polysomnographic parameters were not influenced by GHB.

TABLE 2. *Polysomnographic data for nocturnal sleep (n = 23)*

	GHB		Placebo		Effect
Sleep structure (EEG)	Mean	SD	Mean	SD	p[a]
Sleep architecture					
Stage 1 (%)					
Before	18.8	11.7	17.7	9.3	
After	14.0	9.4	16.7	7.6	ns
Stage 2 (%)					
Before	40.2	8.7	40.5	10.4	
After	43.6	10.6	43.9	10.9	ns
Stage 3 + 4 (%)					
Before	24.9	9.0	25.5	9.4	
After	29.0	12.5	24.0	10.5	0.053
Stage REM (%)					
Before	16.1	4.7	16.3	6.6	
After	13.4	6.8	15.5	5.9	ns
Sleep stage shifts (total)					
Before	53.0	14.1	52.3	13.1	
After	42.5	13.8	50.8	14.2	ns
REM sleep variables					
Awakenings (no.)[b]					
Before	2.6	3.0	2.6	2.5	
After	1.9	2.4	3.8	3.4	0.016
Percentage wake[b]					
Before	19.6	39.6	11.4	19.7	
After	10.9	23.0	17.1	14.5	0.007
Sleep stage shifts[c]					
Before	6.5	2.1	8.0	4.1	
After	4.4	1.9	7.3	3.4	ns

[a] Wilcoxon's signed-rank test; ns = not significant.
[b] Awakenings/hour REM sleep and percentage of wake during REM sleep.
[c] Number of sleep stage shifts towards REM sleep/hour REM sleep.

In the seven patients who had correctly performed all four multiple sleep latency tests, GHB did not alter the mean sleep latency of the MSLT [GHB: 5.79 ± 5.03–3.67 ± 2.41 minutes; placebo: 5.22 ± 4.07–3.24 ± 1.73 minutes; p = 0.58 (ns)].

Mood ratings underwent no change [GHB: 204 ± 55–211 ± 63; placebo: 196 ± 51–205 ± 59; p = 0.67 (ns); n = 17].

The global therapeutic impression as rated by the patients was significantly more often in favor of GHB ("beneficial effect": 15 patients during GHB treatment versus 2 during placebo; "no beneficial effect": 9 during GHB versus 22 during placebo; $p < 0.001$).

Carry-over and period effects

Diary and polysomnographic baseline data did not differ significantly between the GHB and placebo groups, nor between the baseline periods 1 and 2 (= washout). Treatment responses showed no significant period effects.

Tolerability

One patient reported a single period of protracted sleep paralysis in combination with a hypnagogic hallucination in the first week of treatment with GHB. Another patient reported loss of weight in the first 2 weeks of treatment with GHB. One patient reported stranguria during placebo treatment.

DISCUSSION

Gammahydroxybutyrate significantly reduced all narcoleptic symptoms compared to baseline, whereas placebo slightly reduced only the number of cataplectic attacks without influencing any of the other items. The placebo effect on the number of cataplectic attacks was short lasting and may have been related to the disproportionately high baseline frequency in the placebo group.

The clinical effects of GHB in our study are consistent with those observed in earlier open studies (9–11,16). Compared to the only other controlled clinical trial (12), we found milder baseline complaints and a more marked reduction of excessive daytime sleepiness. This may have been because in that particular study patients were selected on the frequency of cataplectic attacks, all anti-cataplectic medication was stopped prior to the study and virtually all patients also used stimulants during the trial.

Gammahydroxybutyrate stabilized nocturnal REM sleep and tended to increase nocturnal SWS. In this respect it seems to (partially) restore the presumed disturbed-state boundary control in narcolepsy (17). The reduction of cataplexy and hypnagogic hallucinations may be a reflection of the stabilization of nocturnal REM sleep, as has been suggested before (18). Compared to the earlier open trials (10,11), the polysomnographic effects in our study are more specific, especially on REM sleep variables.

In the only other double-blind study (13), REM sleep analysis was limited and the variables we found to have changed significantly were not measured. The reported pattern of changes in nocturnal sleep included an increased amount of SWS, a decreased amount of stage 1 sleep and fewer stage shifts and awakenings (13). We found a similar trend, although it was not statistically significant (Table 2).

Our observation that GHB, in contrast to stimulants (19), did not change the mood rating supports the hypothesis that GHB has a selective effect on nocturnal sleep.

Theoretically, the mechanism of action of GHB might have been a purely potentiating effect on co-medication, which was taken by half the study population. However, this possibility is unlikely because patients both with and without co-medication showed similar improvement.

Because the ambulatory MSLT at home was unsupervised, we were not able to reliably assess the effects of GHB on the sleep latency of the MSLT.

In summary, GHB is an effective and well-tolerated treatment for narcolepsy with a pronounced effect on (nocturnal) REM sleep. Although GHB produces hypnotic effects, it does not cause a hangover the next morning. Its clinical use is currently being limited because its short duration of action makes a second dose at night necessary, and because its long-term safety has not been determined (16).

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