Effects of Nocturnal Gamma-Hydroxybutyrate on Sleep/Waking Patterns in Narcolepsy-Cataplexy

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SUMMARY: *Continuous 48-hour polygraphic recordings of sleep/waking patterns were performed on 14 patients with narcolepsy-cataplexy before and after 7-10 days of treatment of their nocturnal sleep with gamma-hydroxybutyrate (GBH). GBH improved the quality of night sleep by increasing the amount of slow wave sleep, reducing stage 1, increasing sleep efficiency (percentage of time in bed spent asleep), and reducing the number of periods of short sleep under 15 minutes. Also nighttime REM sleep was reduced in latency and became less fragmented. The daytime period contained less slow wave sleep and REM sleep, and fewer episodes of prolonged sleep. Patients experienced reduction or loss of daytime attacks of irresistible sleep, cataplectic attacks, and other auxiliary symptoms. Residual daytime drowsiness subsequently improved on low doses of methylphenidate. Tolerance did not develop and there were no serious toxic side-effects. Four of the patients had been refractory to previous combinations of antidepresents and high doses of stimulants.*

RÉSUMÉ: *Quatorze malades souffrant de narcolepsie-cataplexie ont eu des enregistrements polygraphiques continus de leur éveil-sommeil avant et 7 à 10 jours après le traitement de leur sommeil nocturne avec l'hydroxybutyrate-gamma. La qualité du sommeil nocturne a été améliorée. Ceci a été expérimenté par une augmentation du sommeil avec des ondes lentes électro-encéphalographiques (les stades 3 et 4) et de l'efficacité du sommeil (le pourcentage du temps nocturne alité avec du sommeil), et par une dimunition du stade 1 (du sommeil très léger ou de la somnolence) et des périodes très brèves (moins que 15 minutes) de sommeil. La latence des périodes avec des mouvements oculaires rapides (REM) a été diminuée et le sommeil REM est devenu moins fragmenté. Le sommeil lent et le sommeil REM étaient moins fréquents pendant le sommeil diurne et les épisodes de sommeil moins prolongées. Au niveau clinique, les malades ont eu une réduction ou une disparition d'accès diurnes de sommeil, d'accès cataplectiques et d'autres symptâmes auxiliaires. Une somnolence résidualle et diurne a été améliorée avec aes dosages mineurs de méthylphenidate. Il n'y a eu ni apparition de tolérance ni effets secondaires toxiques sérieux. Quatre des malades ont été réfractaires aux combinations préalables d'antidéprimants tricycliques et de dosages élevés de produits stimulants.*

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INTRODUCTION

The pathogenesis of the excessive daytime drowsiness and sleep attacks in narcolepsy, and of the auxiliary symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis remain poorly understood. The disease appears to result from increased pressure for sleep or for sub-components of sleep at unexpected times during the sleep/waking cycle. For these reasons, central nervous system stimulants and other types of sleep suppressing medications have been used to control its manifestations (Zarcone, 1973; Dement et al., 1976). Little is known, however, about how such increased pressure develops. In recent years, investigators have paid increasing attention to the nocturnal insomnia, which so paradoxically is a common complaint in this illness (Daniels, 1934; Zarcone, 1973; Dement et al., 1976). Using modern polysomnographic techniques, it has been shown that restless night sleep, interrupted by movements and periods of wakefulness, is a typical feature of narcolepsy-cataplexy (Rechtschaffen et al., 1962; Broughton and Mamelak, 1976; Montplaisir et al., 1978). As well as being abnormally fragmented, night sleep is often reduced in total duration (Rechtschaffen et al., 1962; Montplaisir et al., 1978; Mamelak, Caruso and Stewart, in press).

Other observations made in a variety of settings, have also suggested an important role for nocturnal dyssomnia in the development of the illness. Sleep patterns similar to those characteristic of such patients have been produced by altered sleep schedules. For example, attempts have been made to establish 90 minute (Carskadon and Dement, 1975;

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Carskadon, 1976) or 3 hour (Weitzman et al., 1974) "days" in normal subjects. In the course of these experiments, which have involved the sustained fragmentation of sleep, polysomnographic patterns identical to those found in narcolepsy have rapidly emerged. Sleep onset REM periods and other manifestations of dissociated sleep, such as multiple epochs of so-called "intermediate sleep" (Barros-Ferreira and Lairy, 1976), appeared within a few hours. Although the full clinical syndrome was never elicited, it is conceivable that this might have occurred had it been possible to continue these studies for longer times. Indeed, the clinical and polysomnographic patterns of narcolepsy can develop in pathological conditions such as sleep apnea which are typified by chronic sleep fragmentation (Guilleminault et al., 1976). Narcolepsy also appears to develop preferentially in other individuals in whom sleep is chronically disrupted, for example, in shift workers or in nurses and doctors who must keep irregular hours in the course of their duties (Broughton, 1971). In 50-75% of idiopathic cases of narcolepsy-cataplexy a history of severe sleep deprivation or of irregular sleep habits preceded the onset of the disease, often by many years (Mitchell and Dement, 1968; Broughton and Ghanem, 1976). Moreover, in established narcoleptics the condition characteristically becomes unusually difficult to control when there is any disruption of the sleep/waking rhythms by shift work, jet lag, or poor sleep habits (Broughton, 1971; Zarcone, 1973; Broughton and Ghanem, 1976).

Although evidence therefore exists that preceding nocturnal sleep disturbance may have an important role in the genesis of the condition, and indeed some authors have included ordinary hypnotics as part of their treatment (Daniels, 1934; Zarcone, 1973), the major therapeutic approach has been to suppress the daytime symptoms — sleep attacks and drowsiness with stimulants; and cataplexy (and other REM-based auxiliary symptoms) with tricyclic or MAO inhibitory antidepressants.

We decided to attempt to increase the continuity and duration of nocturnal sleep and to study the effect of this on the symptoms of the condition. To achieve this we have used nocturnal doses of gamma-hydroxybutyrate (GHB), a central short chain fatty acid (Doherty et al., 1976) with hypnotic properties (Laborit, 1964). We chose GHB because it had been shown to promote both REM and slow-wave sleep (Mamelak et al., 1977) in contrast to ordinary hypnotics which often suppress these sleep states (Kales et al., 1970). GHB also possessed an additional major advantage over the usual hypnotics in that animal studies had failed to demonstrate the development of tolerance to the drug's hypnotic effects with prolonged use (Vickers, 1969).

To date, we have treated 16 narcoleptic patients with GHB. In a preliminary communication concerning 4 patients (Broughton and Mamelak, 1976) and in a companion article detailing the clinical aspects of the patients included in the present report (Broughton and Mamelak, 1979), we have shown that GHB markedly improves nocturnal sleep and that nightmares, hallucinations, and attacks of sleep paralysis vanish. During the day, pressure for sleep becomes less imperative and cataplectic attacks become milder and less frequent. In many patients virtually all symptoms of the disease disappear when small repeated daily doses of stimulants are used in combination with GHB at night. No tolerance has developed so far for this drug regimen, nor have there been any serious side effects, and patients generally find this treatment much more palatable than the usual combination of stimulants and tricyclic antidepressant drugs. In this paper, we focus on the effects of GHB upon the recorded sleep/waking patterns of our patients.

PATIENTS AND METHODS

Fourteen of the 16 patients (excluding nos. 2 and 10, for technical reasons), whose histories are summarized in the previous report (Broughton and Mamelak, 1979), have had complete studies of their 24 hour sleep/waking patterns. They consisted of seven males and seven females between the ages of 21 and 57 (mean 41.8 ± 13.6). All showed one or several sleep onset REM sleep periods during the recordings. Nine of the fourteen patients were seriously debilitated by their illness and four had not benefited much from the standard treatments combining stimulants and antidepressant medication. Before starting GHB, all previous treatment for narcolepsy was discontinued for at least two weeks. The pre-trial assessment included a history and physical examination, hematological, renal, and hepatic studies, a chest x-ray, ECG, EEG, and MMPI and a brief psychological assessment, repeated subjective assessment of sleepiness using the Stanford Sleepiness Scale (Hoddes et al., 1973), pupillometry in the Ottawa studies, and baseline polysomnographic recordings. After the investigative and purely voluntary nature of the study was explained, informed and signed consent was obtained from each patient.

The polysomnographic recordings in the Ottawa patients (N=7) were made with portable 4 channel Medilog recorders (Oxford Electrical Instrument Company). This permitted patient monitoring in their normal environment and at their usual activity levels. The derivations used were C_4-A_1, C_3-A_2, a combined horizontal-vertical oculogram and a submental EMG. Twenty-four hours of data could be recorded on one regular C120 cassette. In the Toronto studies, the patients (N=7) were hospitalized and the recordings obtained with a Grass model 78B polygraph. None of the patients had histories of excessive or intense snoring suggestive of sleep apnea, and this symptom was formally excluded in the Toronto studies in which a sufficient number of recording channels made it possible to monitor nasal and thoracic respiration. Continuous 48 hour recordings of the sleep/waking patterns were obtained in all patients in the pre-GHB baseline period and then again after 7 to 10 nights on the drug. During the 48 hour Toronto laboratory recordings, the patients were encouraged to remain in bed except for meals and bathroom breaks.

An initial 1.5 gm to 2.25 gm (10-15 ml) dose of GHB was given orally at bedtime and followed by one or two

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further 1.0 gm to 1.5 gm doses during the night with any major awakening, if more than 2.5 hours had passed from the previous dose. The patients were required to feel fully alert and clear headed before taking their next dose. The duration of GHB's hypnotic effect in man is about 2.5 hours (Mamelak et al., 1977), which corresponds closely to that of its detectable presence in the blood (Helrich et al., 1964). In most patients, two or three doses were given each night in accord with our objective of maintaining as continuous a night's sleep as possible. GHB was never given within two hours of the anticipated time of the morning awakening in order to avoid hang-over effects. The total quantity given each night ranged from 3.75 gm to 6.25 gms, corresponding to an average patient dosage of about 50 mg/kg.

The polysomnographic data were analysed according to international criteria (Rechtschaffen and Kales, 1968) and scored using 40 sec epochs as wakefulness, stages 1, 2, 3, 4 and REM sleep, plus movement time (MT, i.e., epochs obscured by movement artifacts for over 50% of their duration with previous and succeeding epochs containing sleep patterns). The night and daytime portions of the recordings were analysed separately. The former was arbitrarily defined as the time between the onset of night sleep to the time of the final awakening for breakfast. Sleep during the remainder of the 24 hours was scored as part of the daytime (Figs. 1 and 2). The time of sleep onset was taken as the beginning of the first continuous 10 min of REM or of NREM sleep, exclusive of stage 1, which corresponded to the patients's subjective appraisal of sleep onset for the night as scored on the SSS forms. Since no formal bedtime existed in the laboratory studies, nor could one be established in the portable studies, the latency from bedtime to sleep onset was not determined. For each recording period, nocturnal and diurnal, we calculated the total sleep times including and excluding stage 1 (which corresponds to drowsiness and, most authors agree, not to actual sleep). Corresponding nocturnal sleep efficiencies refer to the percentages of that portion of the recordings occupied by the relevant sleep patterns. Delta sleep latency was defined as the time from sleep onset to the first continuous 3 or more min of stage 3 or 4 sleep. REM sleep latency was defined as the time from the onset of 3 or more min in duration of stage 2 to the first continuous 3 or more min of REM sleep. If REM sleep occurred before stage 2, its latency was determined by measuring the interval between the beginning of the 3 consecutive min of REM sleep and the preceding 3 consecutive min of wakefulness. REM density refers to the percentage of 2 sec mini-epochs containing one or more rapid eye movements. The values obtained for each REM period were normalized for its duration and an average value for each of the nocturnal and diurnal recording periods was determined.

Two further parameters involving REM sleep were defined in order to measure the degree of REM sleep fragmentation. These were REM sleep efficiencies with and without stage 2, i.e. other patterns of definite sleep. For each REM sleep period, the number of epochs between the first and the last 40 sec REM sleep epoch of that period was determined. This was designated the "total REM sleep period duration". Because of fragmentation, it included epochs of wakefulness, stage 1, MT and, at times, stage 2. REM sleep efficiency without stage 2 refers to the percentage of the REM sleep period duration consisting of REM sleep epochs only. REM sleep efficiency including stage 2 refers to the percentage of the REM sleep period duration consisting of epochs of REM sleep or of stage 2 sleep, i.e., of definite sleep. The two REM sleep efficiency values were normalized for each REM sleep period, and an overall average mean value for each of the nocturnal and diurnal recording periods was obtained. In this study, a REM sleep epoch had to be separated from the closet preceding REM sleep epoch by at least 15 min to be scored as part of a separate REM sleep period. The number of REM sleep periods per night and their cycle duration, i.e., the time from the onset of one REM sleep period to the onset of the next period, were also calculated.

A measure for determining the degree of *overall* fragmentation of night sleep was also developed. We calculated the number of periods of sleep, be these NREM, REM, or combinations of the two, which were separated from one another by one min or more of either MT, wakefulness or stage 1. Depending upon their duration, these nocturnal sleep periods were put into five categories: 15 min or less, 16-30 min, 31-45 min, 46-60 min, and greater than 61 min. In addition, we measured the frequency of stage shifts out of stages 2, 3 and 4 collectively (i.e., out of NREM sleep) and out of REM sleep. The number of shifts out of the former was expressed per 100 min of the sum of stages 2, 3 and 4 per night, and out of the latter per 100 min of REM sleep per night.

During the daytime portions of the recordings, sleep was analysed for the duration of stages 1, 2, 3, 4, REM, and MT; and the total sleep times including and excluding stage 1 were calculated as above. The number of daytime sleep periods was also determined. A sleep period was defined as an episode of recorded sleep containing at least 3 min of stages 2, 3, 4 or REM sleep, and preceded and followed by at least 15 min of wakefulness or stage 1 (drowsiness). These sleep periods were divided into 3 groups, those of 31-45 min, of 46-60 min and of more than 61 min, corresponding to the longer measures of consolidated sleep at night.

In this paper, the 48 hours baseline polysomnographic data for each patient is compared to data after 7 to 10 nights on GHB treatment. The data of each patient for each of the two 24 hour periods before and after GHB treatment were averaged before comparison. The two tailed Student t test was applied to each variable, unless otherwise stated.

RESULTS

The data obtained using either the portable outpatient or the laboratory inpatient recording techniques were similar. The major difference was in the sleep patterns which appeared just before sleep onset at night. The inpatient recordings usually showed a period of more or less sustained wakfulness until sleep onset, which was then followed shortly by a REM

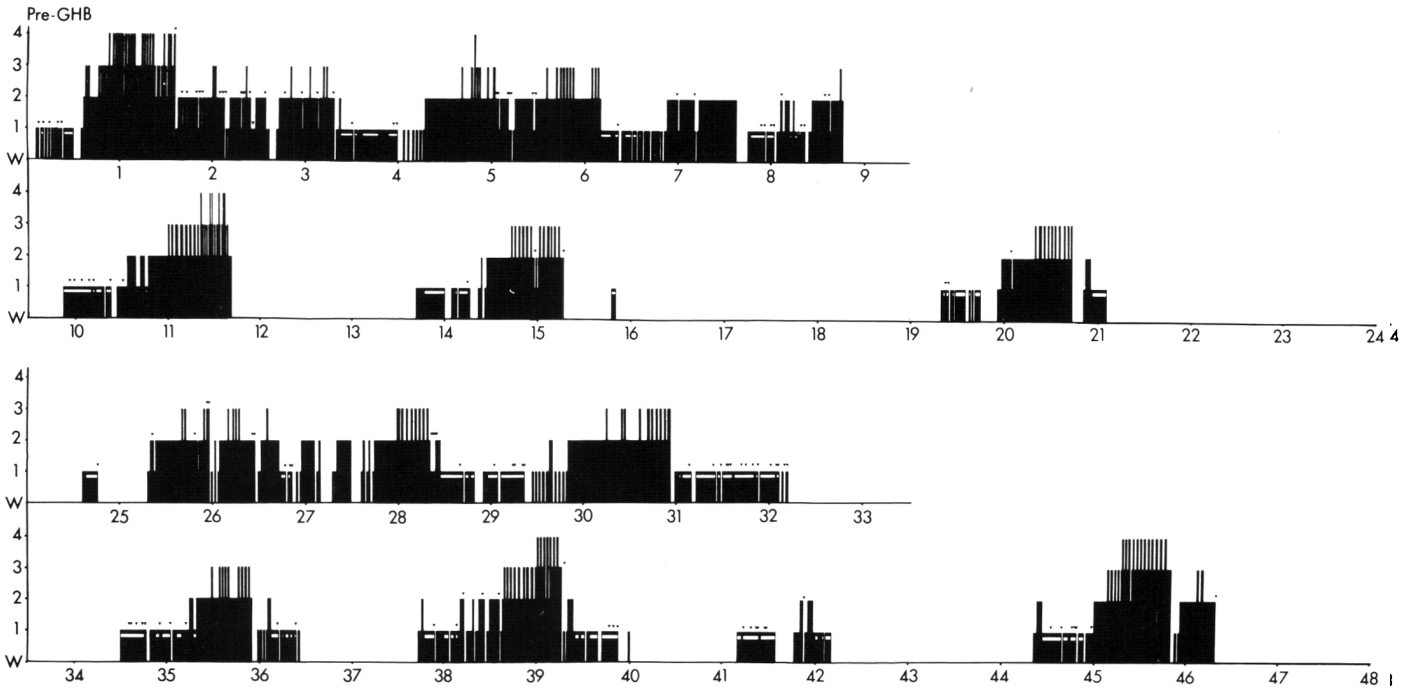

Figure 1 — A 48-hour continuous baseline recording in a typical (hospitalized) patient. It illustrates the frequent awakenings during nocturnal sleep, multiple sleep onset REM periods, fragmentation of REM sleep, and other features of sleep in narcolepsy-cataplexy (note: in Figs. 1 and 2 the vertical axis indicates sleep stages, and the horizontal axis the time in hours. REM sleep is shown as a horizontal white bar at the level of stage 1, and movement by small triangles above the sleep stage line. Time zero hours in both figures was 10:30-11:00 p.m.).

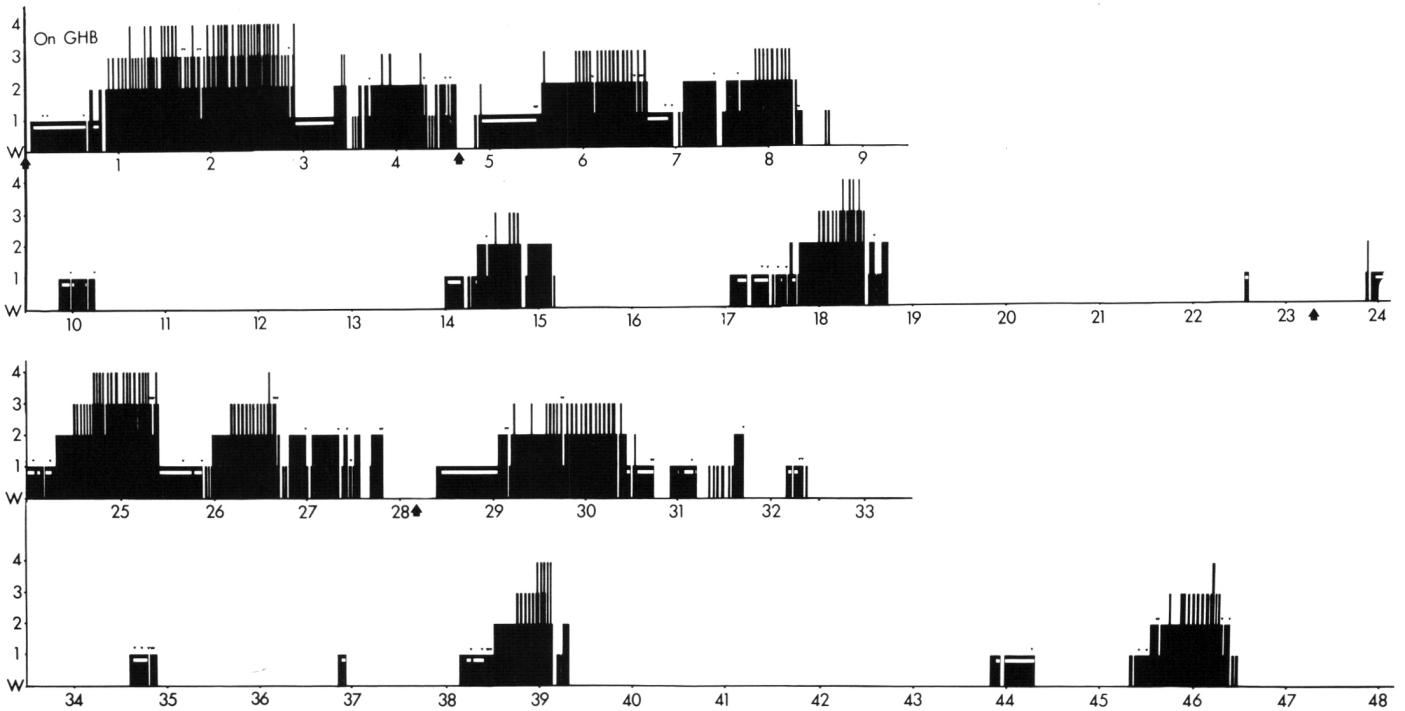

Figure 2 — A 48-hour recording of the same patient on days 9 and 10 of nocturnal GHB. Times of administration are noted by arrows below the horizontal axis. The figure illustrates the increased continuity of nocturnal REM sleep, the decrease in number of nocturnal awakenings, and the reduction of daytime sleep (despite the subjects having remained quietly in the hospital laboratory while on GHB).

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TABLE 1

Effects of GHB on Nocturnal Sleep/Waking Patterns

	Baseline	GHB	Sig.
Total sleep (min), incl. S1	415.3 ± 56.5	404.9 ± 77.0	—
Total sleep (min), excl. S1	341.5 ± 62.9	355.1 ± 80.5	—
Nocturnal wakefulness (min)	65.7 ± 38.4	62.4 ± 50.3	—
Stage 1 (min)	73.8 ± 32.6	47.8 ± 26.6	.005
Stage 2 (min)	187.3 ± 59.1	180.3 ± 72.9	—
Stage 3 + 4 (min)	62.8 ± 26.8	82.9 ± 26.4	.005
Stage REM (min)	91.0 ± 20.7	93.3 ± 34.5	—
Movement time (min)	19.3 ± 11.2	15.5 ± 6.8	—
Sleep effic. (%), incl. S1	76.0 ± 11.7	85.1 ± 11.4	.005
Sleep effic. (%), excl. S1	69.0 ± 11.0	75.0 ± 1.6	.01
Delta latency (min)	63.9 ± 86.6	48.0 ± 41.4	—
REM latency (min)	66.7 ± 68.4	16.9 ± 40.8	.005
REM density (min)	23.7 ± 8.9	16.7 ± 6.1	.005
No. REM periods	4.2 ± 1.2	4.1 ± 1.3	—
REM cycle duration (min)	108.2 ± 24.7	116.1 ± 33.7	—
REM sleep effic. (%), incl. S2	82.6 ± 8.6	89.0 ± 7.7	.005
REM sleep effic. (%), excl. S2	80.1 ± 9.6	84.1 ± 11.0	—
Shifts from NREM/100 min NREM	9.8 ± 4.5	9.1 ± 3.4	—
Shifts from REM/100 min REM	23.4 ± 7.5	16.0 ± 7.7	.005
Sleep fragmentation			
< 15 min (no.)	18.4 ± 9.6	11.0 ± 5.9	.025
16-30 min (no.)	3.4 ± 3.1	2.7 ± 1.3	—
31-45 min (no.)	1.3 ± 0.9	1.6 ± 1.6	—
46.60 min (no.)	1.1 ± 1.1	0.9 ± 0.8	—
> 61 min (no.)	1.3 ± 1.2	1.2 ± 1.2	—

TABLE 2

Effects of GHB on Daytime Sleep Variables

	Baseline	GHB	Sig.
Total sleep (min), incl. S1	203.7 ± 90.6	170.1 ± 100.2	—
Total sleep (min), excl. S1	168.8 ± 86.7	117.7 ± 65.7	.025
Stage 1 (min)	35.7 ± 20.9	50.2 ± 54.4	—
Stage 2 (min)	79.0 ± 54.4	69.8 ± 47.3	—
Stage 3 + 4 (min)	38.4 ± 25.1	18.9 ± 16.6	.005
Stage REM (min)	49.4 ± 32.7	28.1 ± 21.3	.01
Movement time (min)	10.1 ± 7.5	9.9 ± 11.6	—
REM density	20.2 ± 8.5	19.5 ± 5.9	—
REM sleep effic. (%), incl. S2	81.0 ± 21.0	80.7 ± 17.0	—
REM sleep effic. (%), excl. S2	80.9 ± 18.0	80.4 ± 17.1	—
Total no. "sleep periods"	4.1 ± 2.5	4.0 ± 2.6	—
No. longer "sleep periods"			
31-45 min	0.6 ± 0.5	0.8 ± 0.7	—
46.60 min	0.7 ± 0.9	0.1 ± 0.3	.025
> 61 min	0.3 ± 0.4	0.0 ± 0.0	.025

sleep period (Fig. 1). Patients recorded at home tended to drift from wakefulness in and out of brief 1-3 min periods of REM sleep or stage 1 for several minutes or even dozens of minutes, before falling into a consolidated sleep period of at least 10 min; and they usually then had much longer or even normal REM sleep latencies. The REM sleep latencies recorded in the outpatient studies were thus significantly longer than in the inpatient studies (Chi squared test, $p < 0.005$). Other REM sleep measures did not differ significantly between the two laboratories.

The nocturnal pre-GHB baseline recordings (Table 1) showed a number of features when compared to published data (Williams et al., 1974), and confirmed the findings of others for this condition (Rechtschaffen et al., 1962; Barros-Ferreira and Lairy, 1976; Montplaisir et al., 1978). These included early or direct sleep onset REM periods, frequent awakenings and periods of relatively prolonged wakefulness, low sleep efficiencies, and frequent stage shifts. In short, night sleep was characterized by marked fragmentation, which was also reflected in our measures showing frequent short (i.e., 15 min or less) periods of sleep and low REM sleep efficiencies (with and without stage 2). The daytime sleep measures before GHB are given in Table 2. Fig. 1 shows a 48-hour pre-GHB recording in a typical patient.

GHB (Table 1, Fig. 2) significantly increased the duration of nocturnal slow wave sleep at the expense of stage 1, increased the sleep efficiency measures, and decreased the number of sleep periods less than 15 min in duration. The total amount of REM sleep was unchanged, but it became less fragmented, as indicated by significantly fewer stage shifts out of REM sleep and by an increase in the REM sleep efficiency. GHB significantly decreased both the latency to REM sleep and the density of the rapid eye movements themselves. The daytime data (Table 2) indicated that nocturnal GHB resulted in a significant decrease in the duration of both diurnal slow wave sleep and REM sleep. Stage 1 patterns, however, increased (non-significantly). Because of this, although the total sleep time (including stage 1 patterns of drowsiness) during the day remained unchanged, actual sleep (excluding stage 1) was decreased and the individual daytime sleep periods became shorter. The overall major effect of the drug, then, was to improve the continuity of nocturnal sleep and to reduce long periods of daytime sleep and diurnal slow wave and REM sleep. Subjectively, the daytime sleep was perceived as being less imperative.

Finally, although there is evidence that GHB can produce EEG and behavioral manifestations similar to petit mal epilepsy in rats (Godschalk et al., 1977) and in cats (Snead et al., 1976), no potentially epileptogenic EEG discharges were present in these very prolonged recordings or in later follow-up recordings, and no clinical seizures have occurred.

DISCUSSION

The clinical and polysomnographic changes produced by GHB during the 7-10 day period followed a parallel course. Clinically, as previously reported (Broughton and Mamelak, 1979), there was reduction both in the duration of daytime sleep and in the incidence and intensity of cataplectic attacks; and, corresponding to this, the daytime portions of polygraphic recordings showed less actual total sleep time, and less time in slow wave sleep and in REM sleep. Subjective drowsiness, however, continued to be a problem. It was reflected in the lack of any significant change in daytime stage 1 sleep, which in fact was somewhat increased. (Drowsiness was subsequently improved with methyl-phenidate.) Night sleep was perceived as being deeper and less restless. There was loss of nightmares and hallucinations, although dreaming, in a more pleasant manner, continued. Correspondingly, the nighttime portion of the recordings showed that sleep was consolidated into longer periods, there were fewer stage shifts and sleep, particularly REM sleep, was more integrated and less fragmented. Although sleep onset REM periods still occurred, and in fact were even more frequent on GHB, these differed from their pre-treatment counterparts in that they were not frightening, they never reached hallucinatory intensity, control over mentation was lost rather than maintained, and the presence of concomitant awareness of ones' surroundings, which can occur in this condition (Hishikawa, 1976; Vogel, 1976), was no longer present.

Like other investigators such as Barros-Ferriera and Lairy (1976) and Montplaisir and colleagues (1978), we were impressed by the marked dissociation and fragmentation of nocturnal (and diurnal) sleep which we found in our patients' baseline recordings. In addition to frequent sleep onset REM sleep periods, there were numerous epochs of "intermediate sleep" (i.e., simultaneous features of stage 2 and REM sleep), multiple brief sleep fragments and prolonged periods with mixed features of sleep and wakefulness. Sleep and its subcomponents appeared to have become dispersed around the 24 hours and the barriers between sleep and wakefulness to have been breached, as exemplified both by the chronic daytime drowsiness and the wakeful awareness during polygraphically monitored REM sleep, especially at sleep onset.

GHB tended to reverse these features. It produced increased consolidation and re-integration of sleep and increasingly synchronized sleep with the nocturnal period. Each dose assured a 2 to 3 hour period of sleep at about the same time each night. In each of these periods, REM sleep usually occurred at sleep onset and was followed by a period of slow wave sleep (Fig. 2). Although the renormalization of night sleep clearly was therefore not complete, each period of drug-induced sleep consisted of sleep which was more continuous, having fewer awakenings and fewer stage shifts. The subjective assessment of patients on medication was that they were truly asleep during each two to three hour drug-induced sleep period and did not experience "twilight" states of mixed sleep and wakefulness. Although the total duration per se of nocturnal sleep was not increased by GHB, the drug's nocturnal effects did alter the duration and organization of daytime sleep. There was significant decrease in the duration of both REM sleep and slow wave

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sleep during the day and the individual sleep periods became shorter and more fragmented. This effect might have been more impressive statistically, had not half our patients (the Toronto inpatients) remained in bed during the day.

While on the drug our patients reported that, although they were still drowsy and even slept during the day, they were now better able to resist sleep and could stay awake, when this was necessary. Before starting treatment they averaged about 9 to 10 hours of sleep in a 24 hour period (of which 6 to 7 hours occurred at night). These total figures, which were not changed much by GHB treatment, are not very different from those recorded in ad lib sleep of normals, who will also sleep for about 10 to 12 hours in a 24 hour period, when freely permitted to do so (Hishikawa et al., 1976). Yet, under most circumstances, normals remain fully awake during the day with seven to eight hours of sleep at night or even less (Webb and Cartwright, 1978). What makes this pattern possible for them but not for narcoleptics? We suggest that it is because the night sleep of normals is more integrated than is the sleep of narcoleptics. That is, in normal sleep the component subsystems run their course for the most part in seven to eight consecutive hours usually synchronized with the nocturnal period. In narcoleptic sleep, on the other hand, the dissociation and temporal dispersion of the sleep sub-components prevents this and leads to daytime occurrence of sleep or of chronic drowsiness — a mixture of sleep and wakefulness. At the same time, the nighttime sleep of narcoleptics is rendered shallow and fragmented and loses its stable circadian pattern of deep NREM sleep concentrated in the first third of the night.

It is our thesis that the 6 to 7 hours of sleep facilitated by GHB has greater circadian stability and is a more fully integrated sleep, especially of the REM sleep state, than is that which occurs in narcoleptics in the absence of the drug. As evidence, we can cite the drug-induced decrease in the number of nocturnal sleep stage shifts, as well as the overall improvement in sleep efficiency at night. Nocturnal GHB appears to "glue" together the component subsystems of sleep and to impede their temporal dispersion around the 24-hours. As a result, daytime sleep becomes less consolidated, with stage 1 sleep, i.e., drowsiness, increasing at the expense of slow wave sleep and REM sleep. This accounts for the patients' subjective impression that they are better able to resist sleeping during the day on GHB. When small divided doses (5 to 10 mg t.i.d.) of methylphenidate were later added to the drug regimen during the day, diurnal sleep and drowsiness virtually disappeared in many patients (Broughton and Mamelak, 1979). It can be questioned whether methylphenidate would be necessary at all, if the duration of action of GHB could be extended to integrate sleep at night for a full seven to eight hours.

The decrease in the frequency and intensity of cataplectic attacks is one of the earliest and most impressive clinical benefits of GHB treatment. As the duration of the direct action of GHB (Mamelak et al., 1977) and its detectable presence in the blood (Helrich et al., 1964) last only some 2.5-3.0 hours, the daytime changes must be explained mainly or only by nocturnal effects, when the substance is given. Again, it is suggested that this results from the nocturnal sleep integrating and synchronizing actions of the drug. Cataplexy has been attributed to the dissociated selective activation of the motor inhibitory component of REM sleep (Dement et al., 1976). Our data indicate that nocturnal GHB significantly decreases the total amount of REM sleep during the day: the decline in the number of diurnal cataplectic attacks may be due to this. Other studies, moreover, have shown that daytime administration of GHB in narcolepsy-cataplexy has the apparently unique effect of being able to induce sleep paralysis (Mamelak et al., 1977). This suggests that, in addition to its facilitating or activating effect on REM sleep per se, the drug can also selectively activate the motor inhibitory component of the REM sleep state in such patients. The sensitivity of this motor process to GHB was further demonstrated recently by Mamalek, Sowden and Caruso (in press) in studies on the effect of this drug on monosynaptic transmission in the spinal cord, using the H-reflex technique. Monosynaptic transmission in known to be suppressed during REM sleep (Hodes and Dement, 1964; Hishikawa and Kaneko, 1965) as part of the motor inhibitory process during this sleep state (Pompeiano, 1976). But the studies of Mamelak, Sowden, and Caruso (in press) show that with GHB monosynaptic transmission is blocked during *both* REM and slow wave states following drug administration. Since a refractory period occurs after REM sleep (Jouvet, 1962; Pompeiano, 1976), an analogous state may also prevail after the isolated activation of the motor inhibitory process. The amelioration of daytime cataplexy may be related in this way to prolonged nocturnal activation by the drug of the motor inhibitory mechanisms of REM sleep.

Why do ordinary hypnotic drugs not benefit narcoleptic patients? It should be noted first that at times they can do so. Many narcoleptic patients use such drugs at night to improve their sleep and obtain considerable relief from their diurnal symptoms (Daniels, 1934; Zarcone, 1973). Because of their long duration of action, however, these drugs may increase daytime drowsiness (Daniels, 1934); and, in addition, their consolidating effects on nighttime sleep tend to wane as tolerance develops. Moreover, ordinary hypnotic drugs often suppress both REM sleep and slow wave sleep, and can create increased pressure, at least for REM sleep, later in the night as the drugs wear off (Kales et al., 1970). GHB has none of these disadvantages. It is rapidly metabolized and is cleared from the blood stream after two to three hours (Helrich et al., 1964), tolerance fails to develop to its hypnotic effect (Vickers, 1969), and most important, it does not appear to suppress either REM sleep or slow wave sleep or sub-components of them. In fact, in direct contrast to the synthetic hypnotics, it generally increases the duration of slow wave sleep and facilitates REM sleep (Mamelak et al., 1977).

It must be emphasized, however, that the increase in delta activity produced by GHB may not represent a

true increase in physiological slow wave sleep. GHB can paradoxically induce delta activity with the subject either awake or asleep (Metcalfe et al., 1966; Yamada et al., 1967). The overall increase in delta activity recorded in our subjects may therefore represent a drug effect rather than an increase of physiological slow wave sleep. REM sleep facilitation is a more certain property of the drug. Not only were the psychological attributes of GHB-induced REM sleep similar to those of naturally occurring REM sleep, but its polysomnographic and motor characteristics are similar as well (Mamelak et al., 1977; Mamelak, Sowden, and Caruso (in press). For these reasons, it is intriguing to speculate that GHB acts mainly or perhaps specifically on REM sleep to integrate and synchronize it with the nocturnal period and that, as a result, REM sleep becomes the focus around which the other subsystems of sleep articulate and reintegrate. A corollary of this hypothesis might be that dissociation and fragmentation of nocturnal REM sleep are the primary event in the pathogenesis of narcolepsy-cataplexy.

The results also indicate that narcolepsy symptoms based on REM sleep mechanisms can be treated adequately either by suppressing REM sleep around the 24 hours (tricyclics or MAO inhibitors) or by improving the continuity of nocturnal REM sleep (GHB or similar compounds). The latter approach would appear preferable in that it is more physiological and does not have some of the unpleasant side effects of the former, in particular that of impotence in males.

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REFERENCES

BARROS-FERREIRA, M. and LAIRY, G. (1976). Ambiguous sleep in narcolepsy. In Narcolepsy, edited by C. Guilleminault, W.C. Dement and P. Passouant, pp. 57-75. Spectrum: New York.

BROUGHTON, R. (1971). Neurology and sleep research. Can. Psychiatr. Assoc. J., 16, 283-292.

BROUGHTON, R. and GHANEM, Q. (1976). A study of the impact of compound narcolepsy on the life of the patient. In Narcolepsy, edited by C. Guilleminault, W.C. Dement and P. Passouant, pp. 201-220. Spectrum: New York.

BROUGHTON, R. and MAMELAK, M. (1976). Gamma-hydroxybutyrate in the treatment of compound narcolepsy: A preliminary report. In Narcolepsy, edited by C. Guilleminault, W.C. Dement and P. Passouant, pp. 659-667. Spectrum, New York.

BROUGHTON, R. and MAMELAK, M. (1979). The treatment of narcolepsy-cataplexy with nocturnal gamma-hydroxybutyrate. Can. J. Neurol. Sci., 6, 1-6.

CARSKADON, M. (1976). The role of sleep onset REM periods in narcolepsy. In Narcolepsy, edited by C. Guilleminault, W.C. Dement and P. Passoutant, pp. 499-519. Spectrum: New York.

CARSKADON, M. and DEMENT, W. (1975). Sleep studies on a 90-minute day. Electroencephalogr. Clin. Neurophysiol., 39, 145-155.

DANIELS, L. (1934). Narcolepsy. Medicine (Baltimore), 13, 1-22.

DEMENT, W.C., CARSKADON, M.A., GUILLEMINAULT, C. and ZARCONE, V.P. (1976). Narcolepsy: diagnosis and treatment. Primary Care, 3, 609-623.

DOHERTY, J., HATTOX, S., ANDO, N., SNEAD, O., and ROTH, R. (1976). Identification of gammahydroxybutyric acid as an endogenous metabolite in monkey and human brain. Fed. Proc., 35, 270.

GODSCHALK, M., DZOLJIC, M.R. and BONTA, I.L. (1977). Slow wave sleep and a state resembling absence epilepsy induced in the rat by gamma-hydroxybutyrate. Eur. J. Pharmacol., 44, 105-111.

GUILLEMINAULT, C., TILKIAN, A. and DEMENT, W. (1976). The sleep apnea syndromes. Annu. Rev. Med., 27, 465-484.

HELRICH, M., McASLAN, T.C., SKOLNIK, S. and BESSMAN, S.P. (1964). Correlations of blood levels of 4-hydroxybutyrate with state of consciousness. Anaesthesiology, 25, 771-775.

HISHIKAWA, Y. (1976). Sleep paralysis. In Narcolepsy, edited by C. Guilleminault, W.C. Dement and P. Passouant, pp. 97-123. Spectrum: New York.

HISHIKAWA, Y. and KANEKO, Z. (1965). Electroencephalographic study on narcolepsy. Electroencephalogr. Clin. Neurophysiol., 18, 249-295.

HISHIKAWA, Y., WAKAMATSU, H., FURUYA, E., SUGITA, Y., MASAOKA, S., KANEDA, H., SATO, M., NAN'NO, H. and KANEKO, Z. (1976). Sleep satiation in narcolepsy patients. Electroencephalogr. Clin. Neurophysiol., 41, 1-18.

HODDES, E., ZARCONE, V., SMYTHE, H., PHILLIP, S. and DEMENT, W. (1973). Quantification of sleepiness: A new approach. Psychophysiology, 10, 431-436.

HODES, R. and DEMENT, W. (1964). Depression of electrically induced reflexes (H-reflexes) in man during low voltage EEG "sleep". Electroencephalogr. Clin. Neurophysiol., 17, 617-629.

JOUVET, M. (1962). Recherches sur les structures nerveuses et les mechanisms responsables des differentes phases du sommeil. Arch. Ital. Biol., 100, 125-206.

JOUVET, M. (1967). Neurophysiology of the states of sleep. Physiol. Rev., 47, 117-177.

KALES, A., PRESTON, T., TAN, T. and ALLEN, C. (1970). Hypnotics and altered dream sleep patterns. Arch. Gen. Psychiat., 23, 211-218.

LABORIT, H. (1964). Sodium-4-hydroxybutyrate. Int. J. Neuropharmacol., 3, 422-451.

MAMELAK, M., CARUSO, V. and STEWART, K. (1979). Narcolepsy — a family study. Biol. Psychiatry (in press).

MAMELAK, M., ESCRIU, J.M. and STOKAN, O. (1977). The effects of gamma-hydroxybutyrate on sleep. Biol. Psychiatry, 12, 273-288.

METCALFE, D., EMDE, R. and STRIPE, J. (1966). An EEG-behavioral study of gammahydroxybutyrate in humans. Electroenceph. Clin. Neurophysiol., 20, 506-512.

MITCHELL, S.A. and DEMENT, W.C. (1968). Narcolepsy symptoms: antecedent, contiguous and concomitant nocturnal sleep disordering and deprivation. Psychophysiology, 4, 398.

MONTPLAISIR, J.Y., BILLARD, M., TAKAHASHI, S., BELL, I., GUILLEMINAULT, C. and DEMENT, W.C. (1978) Twenty-four hour recording in REM narcoleptics with special reference to nocturnal sleep disruption. Biol. Psychiatry, 13, 73-89.

POMPEIANO, O. (1976). Mechanisms responsible for spinal inhibition during desynchronized sleep: experimental study. In Narcolepsy, edited by C. Guilleminault, W.C. Dement and P. Passouant, pp. 411-449. Spectrum: New York.

RECHTSCHAFFEN, A., WOLPERT, E., DEMENT, W., MITCHELL, S. and FISHER, C. (1962). Nocturnal sleep of narcoleptics. Electroencephalogr. Clin. Neurophysiol., 15, 599-609.

RECHSCHAFFEN, A. and KALES, A. (1968). A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. U.S. Department of Health, Education and Welfare Publication No. 204, U.S. Government Printing Office, Washington, D.C.

SNEAD, O.C., YU, R.K. and HUTTENLOCKER, P.R. (1976). Gamma hydroxybutyrate: Correlation of serum and cerebrospinal fluid levels with electroencephalographic and behavioral levels. Neurology (Minneap.), 26, 51-56.

VICKERS, M.D. (1969). Gamma-hydroxybutyrate. Int. Aneasthesiol. Clin., 7, 75-89.

VOGEL, G. (1976). Mentation reported from naps of narcoleptics. In Narcolepsy, edited by C. Guilleminault, W.C. Dement and P. Passouant, pp. 161-168. Spectrum: New York.

WEBB, W. and CARTWRIGHT, R. (1978). Sleep and dreams. Annu. Rev. Psychol., 29, 223-252.

WEITZMAN, E., NOEGEIRE, C., PERLOW, M., FUHUSHUNIA, D., SASSIN, J., McGREGOR, P., GALLAGLER, T. and WELLMAN, L. (1974). Effects of a prolonged 3-hour sleep-waking cycle on sleep stages, plasma cortisol growth hormone and body temperature in man. J. Clin. Endocrinol. Metab., 38, 1018-1030.

WILLIAMS, R.L., KARACAN, I., and HIRSCH, C.J. (1974). EEG of human sleep: clinical applications. Wiley: New York.

YAMADA, Y., YAMAMOTO, J.,FUJIKI, A., HISHIKAWA, Y. and KANEKO, Z. (1967). Effects of butyrolactone and gamma-hydroxybutyrate on the EEG and sleep cycle in man. Electroencephalogr. Clin. Neurophysiol., 22, 538-562.

ZARCONE, V. (1973). Narcolepsy. N. Engl. J. Med. 288, 1156-1166.

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