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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 symptômes auxiliaires. Une somnolence résiduelle et diurne a été améliorée avec des 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;

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

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

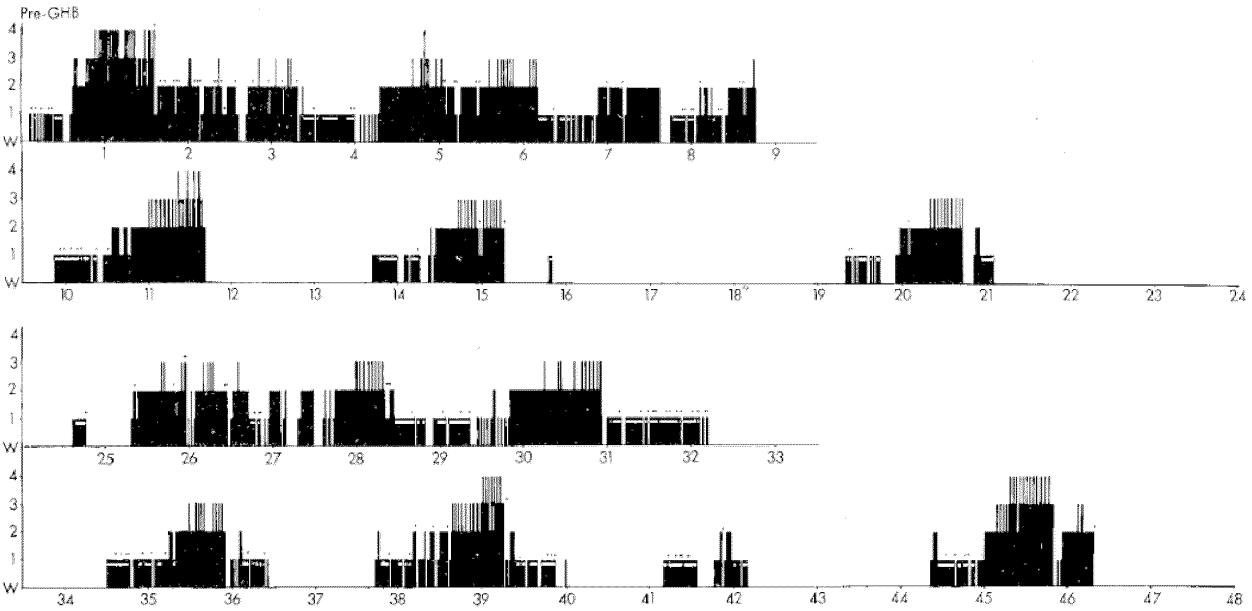

Figure 1 — A 48-hour continuous baseline recording in a typical (hospitalized) patient. It illustrates the frequent awakenings during nocturnal sleep, multiple sleep onset REM periods, fragmentation of REM sleep, and other features of sleep in narcolepsy-cataplexy (note: in Figs. 1 and 2 the vertical 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.).

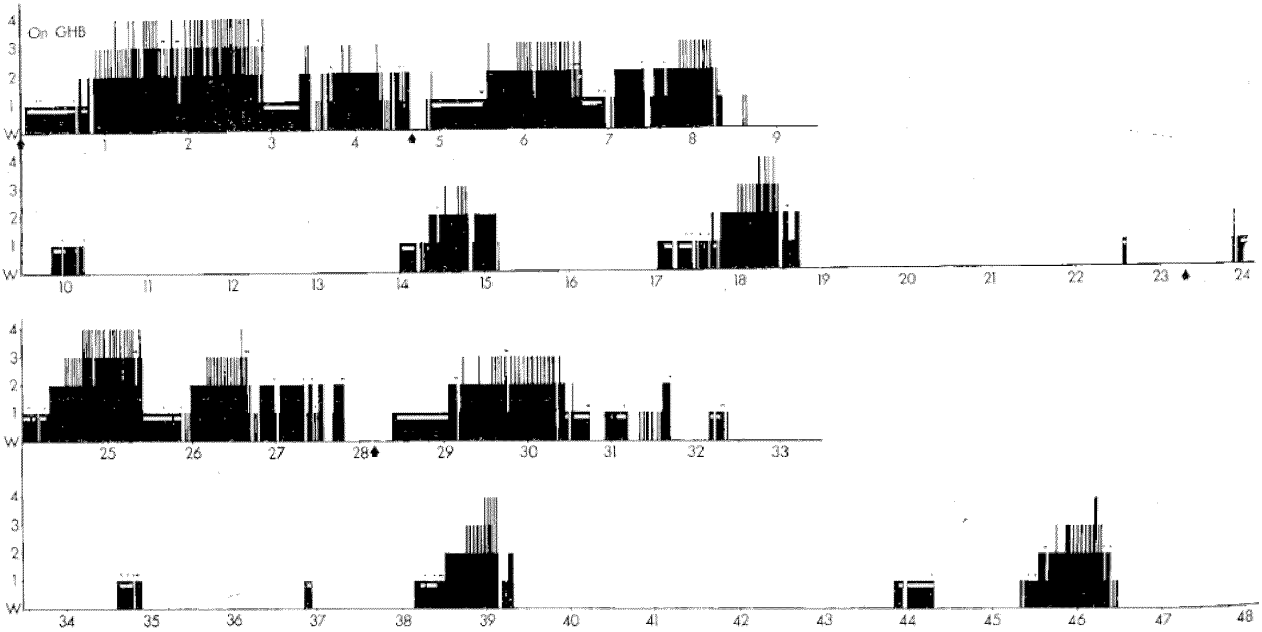

Figure 2 — A 48-hour recording of the same patient on days 9 and 10 of nocturnal GHB. Times of administration are noted by arrows below the horizontal axis. The figure illustrates the increased continuity of nocturnal REM sleep, the decrease in number of nocturnal awakenings, and the reduction of daytime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

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