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Treatment of Narcolepsy with γ-Hydroxybutyrate. A Review of Clinical and Sleep Laboratory Findings

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Summary: Previous studies on the effects of γ-hydroxybutyrate (GHB) on the sleep and clinical response of patients with narcolepsy are reviewed. New information on 48 patients treated with GHB for as long as 9 years is presented. These studies indicate that 2.25 to 3.00 g of GHB, taken in conjunction with a low dose of a stimulant during the day, rapidly alleviate the symptoms of narcolepsy in most patients. Tolerance does not develop to this treatment regimen; neither have any patients discontinued the treatment because of side effects. In poor responders, daytime drowsiness and not cataplexy has been the most common residual symptom. Sleep studies reveal that GHB induces REM followed by slow wave sleep. Although total sleep time at night may be unchanged, sleep is less fragmented. GHB appears to be effective because it can induce the symptoms of narcolepsy and contain them at night. It is noteworthy, therefore, that the central biochemical changes induced by GHB also appear comparable to those found naturally in narcolepsy. **Key Words:** Narcolepsy—Sleep—γ-Hydroxybutyrate.

γ-Hydroxybutyrate (GHB) is a naturally occurring metabolite of the human nervous system, where it is found in highest concentrations in the hypothalamus and basal ganglia (1). The recent discovery of central recognition sites with high affinity for GHB suggests that GHB functions as a neurotransmitter or neuromodulator rather than as an incidental breakdown product of γ-aminobutyric acid metabolism (2).

In healthy human volunteers, low doses (~30 mg/kg) of GHB promote a normal sequence of NREM and REM sleep lasting ~2 to 3 h (3). Slow wave activity is increased and REM sleep appears after a normal latency. Previous work in animals had also demonstrated that GHB promoted both slow wave sleep (SWS) and REM sleep (4). In addition, the animal data indicated that tolerance did not develop to the hypnotic effects of GHB (5). These properties suggested that GHB might be a useful therapeutic agent for individuals who required long-term use of a hypnotic. A clinical and sleep laboratory trial of GHB was undertaken in a group of chronic insomniacs with histories of mental depression (6). As in the healthy volunteers, GHB acted for 2 to 3 h, increased SWS, and sustained REM sleep. However, GHB shifted REM sleep to the first third of the night, significantly

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shortening the REM sleep latency and prolonging the first REM sleep period. In one subject, REM sleep occurred at sleep onset; in the morning the subject reported being unable to move for a short period before falling asleep. GHB had induced sleep paralysis. This finding led Broughton and Mamelak to examine the effects of GHB in narcoleptics (7). It was postulated that narcolepsy stemmed from a failure to consolidate sleep at night and that GHB given repeatedly during the night would help reintegrate sleep because of its unique facilitating actions on both NREM and REM sleep. It was hoped that this would alleviate the diurnal symptoms of the disease and, in the first trial of the compound, such alleviation occurred. More extensive clinical and sleep laboratory trials have since confirmed this observation.

CLINICAL AND SLEEP LABORATORY FINDINGS

This article summarizes the published clinical and sleep laboratory data on the use of GHB in narcolepsy and presents new clinical data on 48 patients who have been treated with GHB for as long as 9 years. In all the studies reviewed here, the diagnosis of narcolepsy was established on the basis of a medical history of daytime sleepiness and cataplexy and was confirmed by sleep laboratory data which demonstrated a sleep onset REM period at night or during at least one sleep latency test during the day. The patients in these studies all received ~2.25–3 g of GHB two or three times during the night. In all, they received 5–7 g of GHB every night. Broughton and Mamelak have reported two trials of GHB, the first a preliminary trial on four patients (7), and the second a more elaborate trial in which continuous 48-h recordings were made on 14 narcoleptic patients before and after 7–10 days of treatment with GHB (8,9). In these trials, patients were off all medication for at least 2 weeks before starting GHB. Scharf et al. (10) recently reported on the effects of GHB on 30 narcoleptic patients. These investigators conducted sleep laboratory studies on their patients before and after 4 weeks of treatment with this agent. During this interval the patients who were using tricyclics were withdrawn from these drugs. Overall stimulant consumption in this patient group was also reduced. Twelve of the patients were again studied in the laboratory after 6 months.

Clinical findings

All studies agree that over the first few nights of treatment, GHB virtually eliminates nightmares and hallucinations. Sleep paralysis may be intensified on the first or second night but then disappears also. Dreaming persists, but loses its frightening quality. In the morning, most patients report having slept sounder and feeling more rested. Daytime attacks of sleep and cataplexy are slower to disappear, but nevertheless are significantly reduced in number after 1 week of treatment (10). Residual attacks of cataplexy are milder, shorter in duration, and easier to control, tending to occur late in the day when the patient is tired. The most refractory symptoms are daytime drowsiness and the need for sleep. Even with stimulants, these symptoms are not fully alleviated in some cases. Nevertheless, it is important to emphasize that in spite of the sleep latency data to be reviewed below, GHB does effect an improvement in daytime alertness. For example, Montplaisir and Barbezieux (11) treated five nonapneic patients who had excessive daytime drowsiness with GHB. None of their patients were given stimulants. Within weeks, all patients reported feeling more alert during the day. However, GHB must be used in repeated doses during the night, and symptoms usually recur the following day when treatment is stopped or when only one dose is used.

Sleep laboratory findings

The most constant effect observed in patients after GHB is administered is an increase in SWS and a decrease in the REM sleep latency. GHB characteristically induces a sleep-onset REM period followed by a period of SWS, after which the patient often spontaneously awakes. This sequence takes ~2 to 3 h. Decreased REM latency is a persistent effect of the drug and may be observed even after 6 months of treatment (10). Total nocturnal REM sleep duration may be increased but usually is unchanged. The number of REM sleep periods is unchanged, but the REM density is decreased. Total sleep time at night may be increased or unchanged. Patients develop no tolerance to the hypnotic actions of GHB over a 6-month period. GHB improves sleep continuity at night and significantly decreases the duration of REM sleep and SWS during the day. Daytime sleep periods > 45 min in duration decrease in frequency, but drowsy stage 1 sleep may even be increased in duration (9). No change occurs in the average sleep latency during the day after 4 weeks or even after 6 months on GHB (10). REM latency during the day, however, is significantly decreased. It should be noted that the sleep and REM latency tests during the day were conducted with some patients taking stimulants. Although the average sleep latency did not change, patients required less stimulant medication when taking GHB.

LONG-TERM USE OF GHB

The cases of 48 patients who have been taking GHB for 6 months to 9 years are now being followed in Toronto. The cases of other patients who were started on this treatment in Toronto are being followed by their physicians in other parts of Canada and the United States. These patients, 21 men and 27 women, range in age from 17 to 71 years. All combine stimulants during the day with GHB at night. The commonest schedule is GHB about 30 mg/kg or 2.25–3 g twice each night and a single long-acting 15 mg dexedrine dospan in the morning. Patients are encouraged to nap late in the afternoon when the dexedrine is wearing off to produce a more alert evening, but many do not do so regularly. The use of GHB in this patient series ranges from 4.5 to 9 g/night. The use of dexedrine ranges from 10 to 30 mg daily. Some patients prefer methylphenidate, but none uses more than 30 mg daily. As part of their treatment regimen, patients are advised to refrain from heavy meals and excessive quantities of carbohydrate-rich foods. Once the treatment regimen has been adjusted to achieve optimal levels of sleep at night and wakefulness during the day, little change is required. The development of drug tolerance has not been observed.

Thirty-six patients, 13 men and 23 women, are virtually symptom-free. They are able to function satisfactorily at work or school and are not embarrassed by their illness. The remainder are symptomatic to varying degrees. As in the earlier studies, daytime drowsiness and the need for sleep are the most common residual symptoms. Cataplexy is rarely a serious concern. Poor nocturnal sleep of patients who are taking GHB appears to be one factor that predicts a poor response. Patients who relate the development of their illness to irregular work hours or to a head injury also tend to respond less well. This largely accounts for the disparity in the response observed between the men and women. Nevertheless, it should be noted that some patients who have had these predisposing factors have responded well. Cataplexy can be difficult to control in patients who have been withdrawn from high doses of tricyclics. At present only 1 patient remains on 10 mg chlorimipramine daily after nearly 3 years on GHB. Symptoms can intensify in all patients, even those who have responded well, during periods of stress. Similarly, drowsiness can prevail during long periods of monotonous activity.

Few adverse effects have been observed. All patients have been followed with serial liver, renal and blood studies, periodic chest x-rays, and electrocardiograms; no abnormalities have been noted. On the first few nights of treatment with GHB, two patients had enuresis. Scharf et al. (10) reported one such incident in their series. Patients who resist the sleep-inducing properties of the drug may become confused and emotionally labile. When treatment with GHB is first started, patients may experience sleep paralysis or discover that they are cataplectic if they try to walk after taking this agent. Price et al. (12) reported cataplexy and confusion in narcoleptic patients given GHB intravenously during the day. Nevertheless, three patients in the Toronto series have reported intermittent sleepwalking while on GHB. This is a more persistent adverse effect which may appear after a period of treatment with GHB. It has been satisfactorily controlled with 5–10 mg of methtrimeprazine at bedtime. Weight loss has been an unexpected benefit for a number of obese patients. GHB is also being used without adverse effects in one narcoleptic patient with central sleep apnea (13).

Five patients have discontinued treatment with GHB. One did so because he found the treatment regimen inconvenient. A young woman planned to become pregnant and feared the potential teratogenic effects of GHB. The other 3 patients did not feel that they were being helped.

Mechanism of action

The effectiveness of GHB can be attributed to its capacity to induce the major symptoms of narcolepsy, that is, sleep and the motor inhibitory phenomena associated with REM sleep, and to contain them at night. Thus, the reliable induction of REM and NREM sleep at night, coupled with the prevention of daytime sleep by stimulants, gradually recruits and consolidates sleep at night, and eliminates it during the day. Sleep paralysis and nocturnal hallucinations disappear with this recruitment. The treatment, however, is palliative. Short-latency nocturnal REM sleep periods and daytime REM sleep betray the persistent dissociation of sleep.

Could an abnormality in endogenous GHB metabolism be a factor in the development of narcolepsy? Early REM sleep periods occur with some consistency in two conditions, narcolepsy and depression. In both of these conditions, the early REM sleep periods are thought to reflect a metabolic shift towards increased cholinergic and decreased catecholaminergic neurotransmission (14). In narcoleptic dogs, for example, increased numbers of muscarinic cholinergic receptors have been described in the pontine region (15). Dopamine utilization is decreased in the brains of these animals, although dopamine levels are increased (16). GHB produces a comparable metabolic shift. It increases brain dopamine levels but inhibits dopamine release (17), and it enhances acetylcholine release, at least in the striatal region where this has been measured (18). GHB can induce early REM sleep periods in cats (4), but it does not do so reliably in humans except in depression and narcolepsy. The nervous system in these conditions appears particularly sensitive to the actions of GHB which, in such states, can provoke not only sleep onset REM periods, but dissociated episodes of motor inhibition in the form of sleep paralysis and cataplexy. GHB receptors are found in highest concentrations in nerve ending fractions rich in acetylcholine (2), a neurotransmitter closely implicated in the induction of REM sleep (14). It would be interesting to know if there are any changes in the sensitivity of these receptors in narcolepsy.

REFERENCES

1. Snead OC, Morley BJ. Ontogeny of gammahydroxybutyric acid. I. Regional concentration in developing rat, monkey and human brain. *Brain Res* 1981;227:579–89.

2. Maitre M, Rumigny JF, Cash C, Mandel P. Subcellular distribution of gammahydroxybutyrate binding sites in rat brain. Principal localization in the synaptosomal fraction. *Biochem Biophys Res Commun* 1983;110:262–5.
3. Yamada Y, Yamamoto J, Fujiki A, Hishikawa Y, Kanedo Z. Effect of butyrolactone and gammahydroxybutyrate on the EEG and sleep cycle in man. *Electroenceph Clin Neurophysiol* 1967;22:558–62.
4. Matsuzaki M, Takagi H, Tokizane T. Paradoxical phase of sleep: its artificial induction in the cat by sodium butyrate. *Science* 1964;146:1328–9.
5. Vickers MD. Gammahydroxybutyric acid. *Intern Anesthesiol Clin* 1969:75–89.
6. Mamelak M, Escriu JM, Stokan O. The effects of gammahydroxybutyrate on sleep. *Biol Psychiatry* 1977;12:273–88.
7. Broughton R, Mamelak M. Gammahydroxybutyrate in the treatment of compound narcolepsy: a preliminary report. In: Guilleminault A, Dement WC, Passouant P (eds). *Narcolepsy*. Spectrum, New York, 1976:659–67.
8. Broughton R, Mamelak M. The treatment of narcolepsy cataplexy with nocturnal gammahydroxybutyrate. *Can J Neurol Sci* 1979;6:1–6.
9. Broughton R, Mamelak M. Effects of nocturnal gammahydroxybutyrate on sleep waking patterns in narcolepsy–cataplexy. *Can J Neurol Sci* 1980;7:23–31.
10. Scharf MB, Brown D, Woods M, Brown L, Hirschowitz J. The effects and effectiveness of gammahydroxybutyrate in patients with narcolepsy. *J Clin Psychiatry* 1985;46:222–5.
11. Montplaisir J, Barbezieux M. Gammahydroxybutyrate de sodium (GHB) dans le traitment de l'hypersomnie essentielle. *Can J Psychiatry* 26:162–6.
12. Price PA, Schacter M, Smith SJ, Baxter CH, Parkes JD. Gammahydroxybutyrate in narcolepsy. *Ann Neurol* 1981;9:198.
13. Mamelak M, Webster P. Treatment of narcolepsy and sleep apnea with gamma-hydroxybutyrate: a clinical and polysomnographic case study. *Sleep* 1981;4:105–11.
14. Gillin JC, Sitaram N. Rapid eye movement sleep: cholinergic mechanisms. *Psychol Med* 1984;14:501–6.
15. Boehme RE, Baker TL, Mefford IM, Barchas JD, Dement WC, Ciarenella RD. Narcolepsy: cholinergic receptor changes in an animal model. *Life Sci* 1984;34:1825–8.
16. Mefford IN, Baker TL, Boehme R, et al. Narcolepsy: biogenic amine deficits in an animal model. *Science* 1983;220:629–32.
17. Roth RH, Walters JR, Aghajanian GK. Effect of impulse flow on the release and synthesis of dopamine in the rat striatum. In: Usdin E, Snyder SH (eds). *Frontiers in catecholamine research*. Pergamon Press, Oxford, 1973:567–74.
18. Stadler H, Lloyd K, Bartholine E. Dopaminergic inhibition of striatal cholinergic neurons: synergistic blocking action of gamma-butyrolactone and neuroleptic drugs. *Naunyn Schmiedebergs Arch Pharmacol* 1974;283:129–34.