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Efficacy of Gamma-Hydroxybutyrate versus Placebo in Treating Narcolepsy–Cataplexy: Double-Blind Subjective Measures

Lawrence Scrima, Paul G. Hartman, Frank H. Johnson, Jr., and F. Charles Hiller

The efficacy of gamma-hydroxybutyrate (GHB) versus placebo for treating narcolepsy was evaluated in 20 patients with narcolepsy, 10 men and 10 women, using a double-blind counterbalanced crossover design. Each patient completed a daily sleep–wake log and questionnaire during a 14-day baseline, a 29-day placebo period, a 29-day GHB period (50 mg GHB/kg/night given 25 mg/kg h.s. and 25 mg/kg 3 hr later), and a 6-day washout period after each treatment. Cataplexy frequency was significantly lower during GHB treatment than during placebo treatment ($p = 0.022$). *Compared to baseline values, the number of cataplexy attacks per day declined by 52% and 69% during GHB treatment weeks 1 and 4, respectively. The number of subjective arousals from sleep was less with GHB than with placebo* ($p = 0.035$), *and the number of sleep attacks was not significantly different during GHB versus placebo treatment. GHB did not have a significant effect on subjective estimates of sleep onset latency, total sleep time, Stanford Sleepiness Scale ratings at morning wake-up, methylphenidate usage, or the number of naps per day. The results indicate that GHB is efficacious for reducing the frequency of cataplexy attacks and subjective nocturnal arousals in patients with narcolepsy within the first 4 weeks of treatment.*

Introduction

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 (Association of Sleep Disorders Centers 1979). Cataplexy is a sudden loss of muscle tone that occurs primarily during 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 (Montplaisir 1976). Narcolepsy is generally treated with a central nervous system stimulant

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(e.g., amphetamine, methylphenidate, or pemoline) to reduce excessive daytime sleepiness (EDS) (Parkes 1976) and an antidepressant (e.g., imipramine or protriptyline) to control cataplexy and other REM sleep-related symptoms (Takahashi 1976). Stimulants, however, do not fully control EDS in most narcolepsy patients (Parkes 1976) and can have undesirable side effects on the cardiovascular, gastrointestinal, and central nervous systems (Gilman et al. 1985). Treatment of cataplexy with antidepressants has been reported to be successful in most cases (Takahashi 1976; Billiard et al. 1983), but these drugs have adverse effects, including (1) prolonged cardiac conduction times that may promote dangerous ventricular arrhythmias; (2) postural hypotension; (3) anticholinergic effects, such as blurred vision, dry mouth, and impotence (Gilman et al. 1985); (4) suppression of REM sleep (Zung 1969; Cadilhac 1976); and (5) increased nocturnal myoclonus (Guilleminault et al. 1976). The anticholinergic side effects often result in patient self-withdrawal from antidepressants, which is usually followed by an increase in the frequency and severity of cataplexy events (Scrima 1981; Scharf and Fletcher 1988). Both stimulants and anticataplexy drugs may become less effective as tolerance increases (Parkes 1976; Broughton and Mamelak 1979).

Gamma-hydroxybutyrate (GHB) is a four-carbon fatty acid that occurs naturally in the mammalian central nervous system (Muyard and Laborit 1977) and has been termed a "putative neurotransmitter" (Mandel et al. 1987). GHB was reported to induce anesthesia at 60–70 mg/kg (Vickers 1969), but the report does not make it clear whether the doses were given orally or intravenously. Lower oral doses of GHB were reported to induce sleep in psychiatric patients (Mamelak et al. 1977), but the minimum GHB dose that will induce sleep has not been systematically determined. Unlike other hypnotics, GHB given orally induces and maintains sleep without suppressing REM or delta stages of sleep (Mamelak et al. 1977). It was first reported in 1976 (Broughton and Mamelak) that GHB, given orally h.s. and two to three additional times during the sleep period, improved nighttime sleep and reduced cataplexy and sleep attacks in patients with narcolepsy. Subsequent studies confirmed that most narcolepsy patients had moderate to large reductions in cataplexy frequency and daytime sleepiness, as well as reduced sleep disruption, hypnagogic hallucinations, and sleep paralysis after taking GHB in divided dose, i.e., a dose h.s. and one to two additional times during the night (Broughton and Mamelak 1979, 1980; Scharf et al. 1985). Polysomnographic recordings indicated that narcolepsy patients taking a divided dose of GHB had increased sleep continuity, decreased REM fragmentation, and increased amounts of delta sleep (Broughton and Mamelak 1980; Scharf et al. 1985). However, 1 month of oral administration of a single h.s. dose of GHB improved daytime sleepiness in only 39% of patients with narcolepsy, though cataplexy frequency was reduced in 83% of the patients (Montplaisir and Godbout 1986). Tolerance to GHB has not been found to develop, even after daily use by patients with narcolepsy for as long as 9 years (Mamelak et al. 1986). Adverse side effects have been infrequent, mild, and have occurred mainly during the first few days of treatment (Broughton and Mamelak 1979; Scharf et al. 1985; Mamelak et al. 1986).

This report describes the results of the first double-blind study of the effects of GHB on subjective symptoms of narcolepsy as compared to those of a placebo.

Methods

Subjects

Ten women and 10 men with narcolepsy, diagnosed at the accredited Sleep Disorders Center (SDC) of the University of Arkansas for Medical Sciences (UAMS), participated

in the study. All patients were interviewed by an accredited clinical polysomnographer, were given a physical examination by a physician, and had sleep disorders diagnostic tests (Guilleminault 1982). The diagnostic tests included an overnight polysomnogram (PSG) and an evaluation of their daytime sleepiness with the multiple sleep latency test (MSLT). The criteria for inclusion in this study were: (1) a history of excessive daytime sleepiness and cataplexy, (2) ≥2 REM onsets on the MSLT, (3) a sleepiness index of ≥75 on the MSLT, (4) at least 10 cataplexy attacks subjectively reported on a daily log during a 2-week baseline period, and (5) age between 16 and 65 years. Patients were excluded if they had other major health problems; were fertile women who were not practicing birth control; were nursing mothers; or had previously taken GHB or had other sleep disorders, with the exception of those commonly associated with narcolepsy, such as sleep paralysis, mild to moderate sleep apnea (arterial oxygen saturation ≥80%), and nocturnal myoclonus.

The age mean ± standard error was 45.9 ± 4.6 years (range 16–64) for the women and 49.1 ± 4.0 (21–64) for the men. Weight (kg) mean ± SE was 85.1 ± 5.2 (range 57–113) for women and 80.4 ± 3.6 (54–90) for men. Body mass index was 31.8 ± 2.5 (17.6–45.4) for women and 26.2 ± 0.9 (20.3–29.1) for men. Prior to the study, 7 patients were on stimulants alone (methylphenidate, pemoline, or dextroamphetamine), 11 were on a combination of stimulants and anticataplexy medications (imipramine or protriptyline), and 2 patients were not taking stimulants or anticataplexy medications. Patients who were taking stimulants other than methylphenidate switched to methylphenidate (≤30 mg/day) for the duration of the study. Seven patients were withdrawn from anticataplexy medications at least 2 weeks before the baseline period, and the remaining 4 patients on anticataplexy medications were withdrawn from imipramine 6, 6, 5, and 3 days prior to baseline, respectively. Only the patient who stopped imipramine 5 days prior to baseline appeared to have elevated amounts of cataplexy events during the first 2 days of the baseline (18 and 12 events, respectively; mean and SD for the rest of the baseline period: 5.7 ± 3.5 events); these 2 days were excluded from the analysis. One patient continued taking propranolol to control hypertension throughout the study at a dose (40 mg/day) that was half the lowest dose of propranolol (80–480 mg/day) reported to reduce narcolepsy symptoms for some patients (Kales et al. 1979; Meier-Ewert et al. 1985). This patient was included in the analysis of results, but analysis of the data with this patient excluded yielded the same pattern of statistically significant results.

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 half of the men and half of the women received GHB in the first treatment period and placebo in the second, whereas the remaining subjects received placebo first and GHB second. All SDC staff were blind to the order of treatment for subjects. During GHB treatment, subjects received 58 bottles prepared by the pharmacy, each containing 25 mg GHB/kg body weight, mixed with distilled water and syrup of orange. During the placebo treatment, subjects received 58 identical bottles with an equivalent amount of fluid, consisting of syrup of orange in distilled water. During each treatment period, subjects were instructed orally and in writing to (1) refrigerate, but not

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