Effect of Baclofen on Sleep-Related Periodic Leg Movements

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Five patients with nocturnal myoclonus (periodic leg movements during sleep), mean age 59.6 years, were monitored polygraphically for fifteen successive nights. Using a double-blind drug study design with placebo at baseline, we investigated the effect of baclofen on these patients. All patients had the repetitive sleep-related abnormal movements during both the baseline nights and those on which baclofen had been administered. The number of movements varied during the four baseline nights, but the movements induced sleep fragmentation, i.e., very short electroencephalographic changes. Baclofen increased the number of movements but decreased their amplitude during non–rapid eye movement (REM) sleep and shortened the interval between movements. Its effect on sleep was dose related: as dosages increased, delta sleep progressively increased and REM sleep decreased. Sleep fragmentation resulting from muscle twitches decreased, as indicated by the diminution in alpha electroencephalographic arousals and K complexes. Baclofen dosages of 20 mg and 40 mg were the most efficacious.

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Nocturnal myoclonus, or periodic leg movement (PLM) [7], was first described in 1953 by Symonds [26], who distinguished it from the jerks occasionally experienced by normal individuals on falling asleep [21]. The phenomenon is a sleep-related problem involving repetitive, stereotypic discharges of variable intensity in the anterior tibialis muscles leading to extension of the big toe. The ankle, knee, and sometimes the hip may flex after the toe has been extended. The myoclonic jerks are generally bilateral but may involve either leg alone without apparent pattern. Several studies [8, 14, 17, 18] have demonstrated that there is generally an interval of 20 to 40 seconds between events. The events occur in clusters varying in length from 10 minutes to several hours, and in some patients lasting throughout nocturnal sleep. This syndrome may be isolated or associated with restless legs [17]. Although we do not know its cause, its circadian periodicity has been emphasized [6, 10, 16]. Trials with 5-hydroxytryptophan and clonazepam [13, 20] have been inconclusive or conflicting.

The goals of the present study were (1) to determine the amount of micro sleep disturbance and potential sleep fragmentation induced by nocturnal myoclonus and (2) to appreciate the effects of different dosages of (−) baclofen, a supposed gamma aminobutyric acid (GABA) II mimetic with known depressant effects on spinal excitatory transmission, on the appearance of the periodic movements.

Methods

Five patients with PLMs, two men and three women, were referred to the Stanford Sleep Disorders Clinic because of complaints of insomnia with short sleep-onset latency and disrupted nocturnal sleep. Their mean age was 59.6 years (range, 52 to 71 years). The mean length of their sleep disturbances was 14 years. Each had previously tried hypnotic medications, barbiturates, and, more recently, flurazepam, without success. None had received medications for at least six months. Their sleep complaints were confirmed by an initial polygraphic recording. One patient presented a mild restless leg syndrome [9, 17] associated with the PLMs. None of the patients had other health problems. All had normal neurological and psychiatric findings, and no abnormal movements evident during wakefulness. Nerve conduction velocities and electromyographic findings were normal.

Experimental Design

The study investigated the effect of PLMs on sleep during four baseline nights, and the effect of baclofen on nocturnal myoclonus and sleep during the next eleven nights of the study. Patients were hospitalized in the clinical research center, but were permitted to leave the hospital during the day. The study was double blind. To guard against unanticipated side effects, a physician not directly involved in the patients' daily care made the final determination in any change in the drug schedule on the basis of the patients' reactions. Sleep diaries indicating bedtime, sleep-onset time, number of awakenings after sleep onset, time of final morning awakening, time of any daytime naps, and side effects were obtained a week before and during the entire study. The drug schedule

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was identical for the five patients during the first nine days of the study. Five pills were administered at 9:45 PM (baclofen or placebo tablets of similar aspect, provided by the pharmaceutical company). Nights 1 through 4 were placebo nights. Patients received 20 mg of baclofen on nights 5 and 6, 40 mg on nights 7 and 8, and 60 mg on night 9. On nights 10 and 11, four patients received 80 mg. On night 12 the dosage was increased to 100 mg for three patients, and on night 13 to 160 mg for one patient. Patients did not receive an increased dosage if side effects were noted. Nights 14 and 15 were washout nights on which placebo was administered.

Sleep Recordings

Sleep recordings were scored blindly and randomly, but the drug-induced polygraphic changes were so evident that nights on which medication was administered were easily identifiable. Before the study, patients were monitored during sleep for at least two nights to identify cardiorespiratory problems and to affirm PLMs. During the study, sleep monitorings were performed on each of the fifteen nights. The monitored variables included electroencephalogram (EEG) (C3/A2–C4/A1 derivations from the 10-20 international electrode placement system), electro-oculogram, chin electromyogram (EMG), and electrocardiogram, lead II. Four lower limb EMG recordings—left and right anterior tibialis and quadriceps muscles—were also monitored, using Beckman surface electrodes. The right and left anterior tibialis EMG recordings were integrated using a Grass EMG integrator. Integrated EMGs were obtained on the first four patients every other night (i.e., on odd days for patients 1 and 3 and even days for patients 2 and 4). Polygraphic monitorings were performed on a Grass model 7B polygraph at 10 mm per second. Electrodes were placed every evening at 9:00. Polygraphic monitoring started between 10:00 and 10:30. Patients were encouraged but not forced to turn their lights out before 10:30. The monitoring ended when the patients decided to arise. No daytime recordings were made, but before breakfast patients received a short neurological evaluation testing coordination, movements, muscle tone, nystagmus, and alertness.

Data Analysis

All records were scored for sleep stages in 30-second epochs using the international scoring system of Rechtschaffen and Kales [24]. Sleep disturbances and short EEG arousals were also identified and scored within each epoch, independent of the sleep stage scoring system. Simultaneously, records were scored for PLMs. On the first evening limb electrode placements were marked on the subjects' skin so that electrodes would be placed in exactly the same positions on all fifteen nights. EMG calibrations were performed on an awake, supine subject. Each patient was requested to extend both big toes from a relaxed position to a 45-degree angle. EMG discharges were recorded and gain values identified. The different gain settings on EMG channels were then kept constant during the fifteen-day protocol. The duration and amplitude of each leg EMG discharge were measured on each polygraphic recording. Amplitude gain was set at 50 μV per 10 mm. Each EMG discharge was then measured in artificial units; basic amplitude and duration units were equal to 10 mm (i.e., 50 μV and 1 second). Amplitude and duration were measured as whole "units," independent of the exact amplitude or duration. Thus, any discharge of amplitude between 76 and 99 μV (between 10 and 20 mm) was scored as 2 (i.e., 1 unit = 10 mm), and any discharge of 2 to 2.5 seconds' duration (between 20.5 and 25 mm) was scored as 5 (i.e., 1 unit = 5 mm), so that each EMG discharge was defined by two unit numbers. The same analysis was performed on the raw EMG discharge data related to the periodic movement and on the integrated EMG discharge data. Both types of data were available for a minimum of seven nights for patients 1, 2, 3, and 4 and for fifteen nights for patient 5. A statistical comparison of amplitude and duration from integrated and nonintegrated movement EMG discharges for each patient revealed no difference between the data. Accordingly, we present the results from the raw movement discharge, for which two nights' data for each baclofen dosage were available, compared with 1 night's for the integrated measurements. The EEG changes immediately following the EMG discharge were scored in four vignettes: alpha arousal, K complex, awakening, and zero (i.e., EEG findings unchanged). We used the international scoring manual's definition of awakening [24]. The first two vignettes were EEG changes of short duration. Zero was scored when the other three categories were not applicable and no change in the prior sleep stage could be identified. Each patient had one scorer, who scored no one else. Alpha arousal and K complexes were grouped together as "sleep disturbance without awakening."

Statistical Analysis

The data were analyzed using a one-factor (dose of baclofen: 0, 20, 40, 60, 80 mg) repeated measures analysis of variance. Because only three subjects received baclofen in 100 mg doses, the data are shown but are not included in the statistical analysis. The a posteriori comparisons among the different doses were tested using the Duncan test for multiple comparisons [27]. When the assumptions for analysis of variance were not met, we used the Friedman two-way analysis of variance to test for the main effect of a dose and the Wilcoxon matched-pairs signed rank test for differences between doses [25]. Effects were considered significant at $p < 0.05$ (two tailed).

Results

All five patients had varying numbers of PLMs every night. Despite these variations, all dosages of baclofen increased the number of movements, from a mean baseline of 80 ± 27 (mean ± SEM) to 226 ± 123 with 20 mg and 234 ± 108 with 80 mg (Friedman two-way ANOVA = 12.68; $p < 0.01$). The increase was associated with a significantly shorter periodicity of movements, particularly clear in two patients who had the largest increase in periodic movements with baclofen compared with baseline levels (mean baseline numbers were, respectively, 186 and 58, increasing to 701 and 229 with 20 mg of baclofen and 684 and 299 with 40 mg). The mean duration and amplitude of the movement EMG discharges during baseline and with each

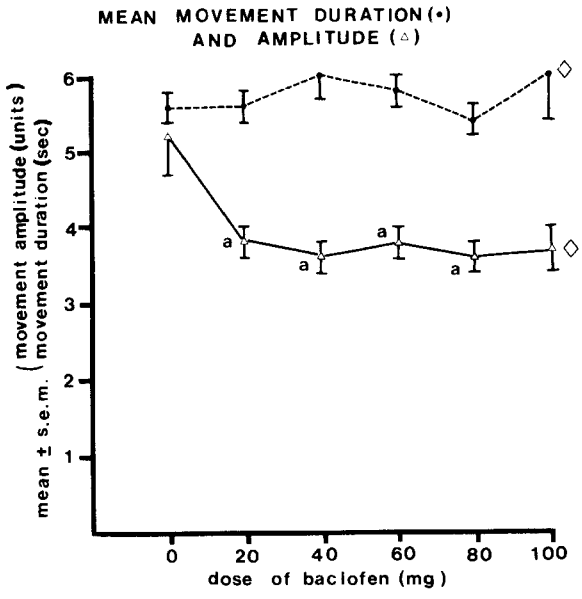

Fig 1. Evaluation of the mean electromyographic discharge obtained by monitoring the tibialis anterior muscle with surface electrodes. Duration and amplitude of the discharge have been plotted separately. A diamond indicates that no statistical analysis was performed because the number of patients (three) receiving this size dose (100 mg) was too small. Baclofen has an effect on the amplitude but not the duration of the discharge. (a = a muscle discharge with an amplitude significantly less than at baseline (0).)

drug dose are presented in Figure 1. Baclofen had no effect on the movement's duration, but all dosages (20 mg and above) decreased the movement's amplitude ($F_{4,16} = 6.57$; $p < 0.005$).

Wake after sleep onset (WASO), a cumulative measure of all awakenings as defined in the international sleep scoring manual [24], indicated that baclofen improved all patients' total sleep time (TST) from baseline measurements. Using an index correcting for each patient's TST (index = WASO/[TST + WASO] × 100 = WASO %), we found the group mean sleep disturbance index to be 0.246 during baseline and, respectively, 0.116, 0.122, 0.108, 0.18, and 0.17 after treatment with 20, 40, 60, 80, and 100 mg of baclofen.

Because WASO may not be entirely related to PLMs and may also ignore short sleep disturbances, the percentage of PLMs inducing an alpha EEG arousal, a K complex, or both was measured and analyzed for both rapid eye movement (REM) and non-REM (NREM) sleep (Table). The analysis indicated that PLMs fragment sleep. Muscle twitches varied from subject to subject, but after normalization of data for total NREM and REM sleep time differences, there were more PLMs and a greater percentage of PLMs during short arousals during NREM than during REM sleep on baseline nights. Baclofen reduced the percentage of sleep fragmentation secondary to PLM, despite the increased number of PLMs. The amount of "sleep disturbance without full awakening" and movement twitches (i.e., excluding the long awakenings) decreased at each dosage ($F_{4,16} = 41.4$; $p < 0.0001$).

Baclofen, independent of its effects on PLMs and the secondarily induced sleep fragmentation, had a significant effect on sleep and sleep structure with all dosages from 20 to 160 mg. TST increased over baseline, but, more important, sleep structure changed, with an increase in TST and slow-wave sleep (stages 3 to 4), expressed in total time in minutes or in percentage of TST, and a concurrent decrease in total time and percentage of REM sleep. Although these effects varied from patient to patient, they were seen in all of them.

Sleep time increased at 20, 40, and 80 mg baclofen dosages compared with baseline findings, with the 20 mg dose resulting in significantly longer TST than the 80 mg dose. A significant dose effect was found ($F_{4,16} = 5.00$; $p < 0.008$). WASO was not significantly different. Patients 1 and 5 experienced undesirable side effects at the 80 mg dosage, and the dosage was then reduced. With the appearance of side effects, their sleep was disrupted so that TST was reduced and WASO increased (see Fig 2). Figure 2 shows the ef-

Percentage of Periodic Leg Movements Producing an Alpha Electroencephalographic Arousal or K Complexes with Baclofen

Patient No.	NREM Sleep						REM Sleep					
	Drug Dosage (mg)											
	B	20	40	60	80	100	B	20	40	60	80	100
1	62.2	22.4	13.9	23.5	29.8	. . .	14.9	8.7	1.2	0.0	0.0	. . .
2	38.2	1.6	0.6	0.0	0.8	8.2	0.0	0.0	0.0	0.0	0.0	0.0
3	65.4	34.9	42.9	41.9	45.1	23.6	34.8	24.1	23.1	24.3	25.9	14.3
4	74	44.4	10	42.1	25.8	45	48.6	38.3	3.4	35.0	23.3	0.00
5	55	31	25	22	18	. . .	25.1	15.2	11.1	13.2	0.0	. . .
Mean	59	27	18.5	26	24	26	25	17	8	14.5	10	5

REM = rapid eye movement; NREM = non-REM; B = baseline (nights 2, 3, 4).

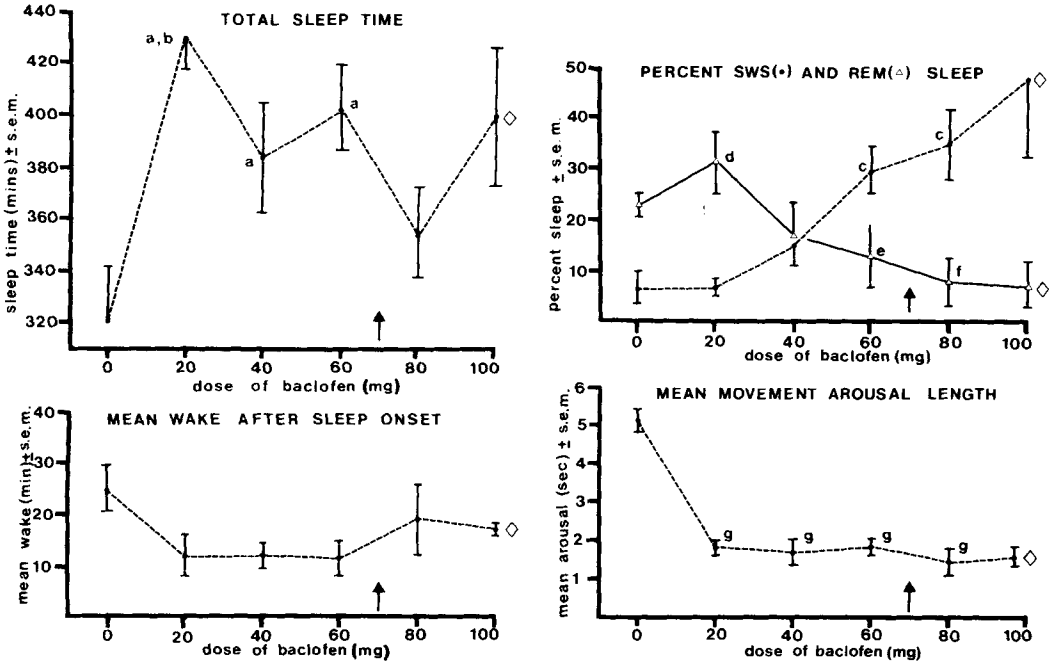

Fig 2. The effects of periodic leg movement (nocturnal myoclonus) on sleep variables at baseline (0) and with five increasing dosages of baclofen (20 to 100 mg). The diamonds indicate that only three patients received 100 mg, and no statistical analysis was performed on this small population. The arrows indicate that two patients experienced side effects, including nausea, during the night at the 80 mg dosage, which may explain the overall decrease in total sleep time (TST) at this dosage, and the moderate increase in wake after sleep onset (left side of the figure). The percentage of slow-wave (delta) sleep (SWS) *and rapid eye movement* (REM) *sleep compared with TST is not affected, however, nor is the length of movement arousal, which includes only short sleep disturbances related to the muscle discharge, i.e., alpha electroencephalographic arousal and K complexes (right side of the figure).* (a, b, c, d, e, f, *and* g *refer to statistical analyses performed using the Duncan test for multiple comparison, the Friedman two-way analysis of variance test, and the Wilcoxon matched-pairs signed rank test.* a = *a TST greater than at baseline;* b = *a sleep time greater than at baseline (0) or with 80 mg;* c = *a percentage of SWS (delta) sleep significantly greater than at baseline (0) or with 20 mg or 40 mg;* d = *a percentage of REM sleep significantly greater than at any of the other dosages, i.e., baseline (0) and 40 to 80 mg;* e = *a percentage of REM sleep significantly less than at baseline (0) or with 20 mg;* f = *a percentage of REM sleep significantly lower than at baseline (0) or with 20 or 40 mg;* g = *short arousal following leg movement (alpha EEG, K complexes) significantly less than at baseline (0).)*

fects of the drug on slow-wave (delta) sleep and on REM sleep. There was an increase in delta sleep ($F_{4,16}$ = 13.6; $p < 0.0001$) with a simultaneous decrease in REM sleep. The 20 mg dosage, however, produced different effects ($F_{4,16}$ = 15.2; $p < 0.0001$): the percentage of REM sleep was significantly greater than during baseline or at other dosages. The 60 and 80 mg doses of baclofen resulted in a significantly larger percentage of slow-wave sleep than did 0, 20, or 40 mg doses.

Discussion

The present study provides some new information on PLMs. The number of events varies daily, as can be seen from the findings on the four baseline nights. Despite this variability, each of our five patients always had clusters of PLMs that were either mild or severe. PLMs fragment or disrupt sleep, whether or not the subject awakens for several minutes. This finding is important, because sleep fragmentation not only can lead to sleep-related complaints (nocturnal sleep disruption, daytime tiredness or sleepiness), but can also affect central nervous system controls, such as control of ventilation and sleep-related responses to hypoxia and hypercapnia [23]. Our baseline data also indicate that the number of movements briefly disrupting sleep differs from NREM to REM sleep, with fewer EEG arousals in REM sleep, perhaps because muscle tone is already inhibited (see the Table).

Baclofen increases the total number of PLMs; it shortens the mean interevent duration but decreases the amplitude of the EMG discharge without changing its duration significantly. The increase in the number of PLMs varied from patient to patient, but an increase was noted in all five cases. It occurred with the lowest dosage administered (20 mg) but did not seem to increase with higher dosages. Despite this rise in frequency, however, baclofen appears to reduce the number of EEG disruptions following PLM, i.e., to reduce brief sleep disruptions and fragmentation. Decrease in amplitude of the EMG discharges both during baseline REM sleep and during TST following baclofen admin-

istration seems to correlate with the decrease in the number of brief EEG arousals. With baclofen there was a sharper decrease in brief EEG sleep disruptions during NREM sleep than during REM sleep, perhaps because during REM sleep the percentage of PLM-induced short arousals and the amplitude of the movement-related EMG discharge is already reduced, as seen from baseline REM sleep data, and baclofen cannot decrease it further.

The effect of REM sleep on spinal cord motor neurons is well known. The discharge of extensor and flexor motor neurons is normally inhibited during REM sleep through activation of the medullary inhibitory reticular formation, whose signals impinge on the motor neurons via the reticulospinal pathway and induce a local membrane hyperpolarization [4, 5, 12]. The action of baclofen at the spinal level appears to be selective for primary afferents [3, 11, 15, 19, 22]. It causes a reduction in excitatory transmitter release from nerve terminals by an action on a novel bicuculline- and picrotoxin-insensitive GABA receptor (GABA II) [2]. The receptor inhibits both monosynaptic and polysynaptic reflexes by hyperpolarizing the afferent terminals. Thus, hyperpolarization of the afferent terminals (by baclofen), or hyperpolarization of the membrane of motor neurons (in REM sleep), does not interrupt the periodic appearance of the discharge but leads to a discharge of smaller amplitude with fewer brief sleep EEG disturbances. Baclofen, at the same time, allows the number of periodic EMG discharges to increase drastically, as if it were interacting with a "gating system," letting a supraspinal pulsing signal impinge more frequently on the lower motor neurons. This gating system is not sleep-state dependent, and its "opening" may be benign if it does not induce an arousal response.

One may question whether baclofen's beneficial effects are related only to hyperpolarization of primary afferents and not at least partially to a hypnotic effect. This compound undoubtedly has a major effect on sleep and sleep stages, independent of its effects on PLM. Baclofen 20 mg given at bedtime increased TST, slightly increased total REM sleep time, and increased slow-wave sleep (stages 3 to 4, delta sleep). Increasing dosages from 20 to 100 mg caused a dose-related increase in delta activity and a simultaneous decrease in REM sleep. The crossing of the REM sleep time and delta sleep time curves occurs with 40 mg taken at bedtime, indicating that sleep changes detectably at a fairly low dosage. The increase in delta sleep may signify that baclofen modifies the arousal threshold, a change that may be related to the decrease in movement-induced sleep disruption.

As a therapeutic agent, baclofen at dosages of 20 to 40 mg taken at bedtime appears to be of possible value in nocturnal myoclonus, because it decreases WASO and the movement-induced sleep fragmentation. Because of the increased frequency of EMG discharges, however, the drug is not the definitive answer to the problem.

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Erratum

An error in reference citation appears in "Lack of Clinical Efficacy of Chronic Oral Physostigmine in Alzheimer's Disease," by Seymour Jotkowitz, MD, published in the December 1983 issue (Ann Neurol 14:690–691, 1983). The last sentence reads: "This result would be analogous to the relative lack of efficacy of anticholinergic medication in the treatment of Eaton-Lambert syndrome, in which impaired release of acetylcholine by the presynaptic terminal has been demonstrated." The proper citation for this passage is Elmquist D, Lambert EH: Detailed analysis of neuromuscular transmission in a patient with the myasthenic syndrome sometimes associated with bronchogenic carcinoma. Mayo Clin Proc 43:689–713, 1968.