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EFFICACY AND SAFETY OF MIDAZOLAM IN THE TREATMENT OF NIGHT TERRORS IN CHILDREN

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1 Midazolam, in an oral dose of 15 mg, and placebo were administered to 15 children aged 6–15 years in treatment of night terrors.

2 After an initial adaptation night, the patients received placebo for 2 nights, followed by 15 mg midazolam for 2 nights and placebo again on the final 2 nights. Eight-hour nocturnal polygraphic recordings were made after the administration of both placebo and midazolam. The patients were continuously monitored by means of closed circuit infra-red television.

3 Ten of the patients manifested simple episodes while five had attacks associated with motor automatisms and EEG anomalies.

4 The total sleep time was lengthened by midazolam in most of the children; sleep architecture was favourably modified, mainly in terms of the amount and proportion of REM sleep (accompanied by dreams) and stage 2 sleep. Night terrors were eliminated by midazolam in all except one patient. REM sleep latency also decreased as did the number of nocturnal arousals (clinical and/or EEG). In the five cases with a background of organic cerebral disorders, the EEG anomalies and these attacks were suppressed by midazolam especially during the first sleep cycles.

5 Patients' subjective assessment of the quality of sleep was favourable. Midazolam was well tolerated with no side-effects.

Introduction

Night terrors (also referred to as *pavor nocturnus* in children and *incubus* in adults) most frequently start in early life. Episodes of *pavor nocturnus* are of sudden onset and short duration, and disturb the sleep by inducing a sensation of acute terror and panic accompanied by vocalization and intense sympathetic nervous activity (Gastaut *et al.*, 1965; Gastaut, 1973). The sufferer will usually be confused, cannot be fully wakened and will usually have no memory of the attack. Unlike nightmares (which are usually associated with REM sleep) night terrors arise mainly in the slow-wave sleep stages 3 and 4 (Broughton, 1968) during the early hours of sleep.

There is no consensus of opinion regarding treatment of *pavor nocturnus* and the problem is usually managed as the situation dictates, which essentially means that no treatment is given unless the EEG displays seizure phenomena (Kavey & Altshuler, 1979). In recent years, however, recognition of the stage 4 suppressant effect of the benzodiazepines has led to their use, with some success, in the treatment of night terrors (Fisher *et al.*, 1973; McLeod & Fisher, 1978). In view of these promising results, it was decided to investigate the usefulness in this indication of the new short-acting benzodiazepine midazolam which, in adult insomniacs, has been shown to be rapid in onset and very well tolerated (Gallais *et al.*, 1983; Vogel & Vogel, 1983).

Methods

Patients

Patients were recruited from a hospitalized population of children suffering from night terrors. Consent was obtained from the subjects' families in accordance with the provisions of the Declaration of Helsinki.

Procedure

The patients underwent the following examinations during the first 2 days: general clinical, neurological and psychiatric examination; ascertainment of the nature, intensity, timing, frequency and the content of the night terror attacks, as well as their association with other nocturnal episodic manifestations

(NEMs); standard laboratory tests, i.e. haemoglobin, erythrocytes, blood picture, blood sugar, transaminases, blood protein, creatine and creatinine, urea, bilirubin, alkaline phosphatase, and urine analysis.

After an initial adaptation night, each patient received placebo for 2 nights and, on the second placebo night, underwent 8-h polygraphical recording (from 22.00 h to 06.00 h) using a 16-channel ECEM polygraph or a Siemens-Elema Mingograph. The patients were continuously monitored by means of infra-red closed-circuit television. Sleep architecture was assessed according to the criteria of Rechtschaffen & Kales (1968) and Popoviciu (1978).

After the initial 2 placebo nights, the subjects received 15 mg midazolam on each of the following 2 nights. On the second midazolam night, polygraphic recording was repeated. Placebo was again administered on the last 2 nights.

At the conclusion of the 6 days of the study, the laboratory tests were repeated and the results were compared with baseline values.

Results

Patients

Fifteen hospitalized children with night terrors (age range 6 to 15 years) were recruited for the study. Ten cases (Tables 1 and 2) manifested simple episodes of night terrors (psychogenic) every night but had no important abnormality in the daytime EEG recordings. All patients presented slow-diffuse hypersynchronous dysrhythmias and, sometimes, symmetrical or asymmetrical generalized slow-sharp waves and polyspikes-and-waves which occurred during the slow-wave sleep (usually during stages 3 and 4 and sometimes also during stages 1b and 2), possibly attributable to cerebral immaturity or to minor neo- and post-natal trauma (Arfel *et al.*, 1977; Samson-Dollfus *et al.*, 1977; Jiminez Espinosa *et al.*, 1977; Popoviciu, 1977, 1978, 1980).

The other five cases (Tables 1 and 2) manifested attacks of night terrors associated with other NEMs: motor automatisms, ambulatory automatisms, bruxisms, nocturnal enuresis. All these cases manifested EEG anomalies: diffuse hypersynchronous slow dysrhythmias; discharge of slow-sharp waves, polyspikes-and-waves, and even of degraded spikes-and-waves which were either generalized (on all derivations) or forming temporal foci, and which occurred mainly during stages 1a and 1b, but sometimes also during stages 2 and 3 (in one case only they also occurred during REM phases). These children had organic cerebral disorders which triggered both these NEMs and EEG anomalies (Popoviciu, 1977, 1978, 1980).

Sleep duration

Total sleep time was increased by midazolam to a mean 450.1 ± 57.6 min as compared with placebo (mean 352.3 ± 87.5 min) especially in the five cases with night terrors associated with other NEMs within the context of organic cerebral diseases (Table 1).

Sleep latency

Sleep latency was short, being reduced by midazolam from the mean placebo baseline value of 21 ± 24.5 to 2.4 ± 2.5 min (Table 1).

Sleep architecture

As shown by Table 2, under placebo the sleep of these patients was poorly organized, disturbed, with a predominance of light slow-wave sleep (LSWS) in stages 1a and 1b and a large amount of time spent awake, both before and during the sleep period. There were numerous nocturnal arousals and a greatly reduced number of REM phases, as well as a long latency to the first REM phase. Thus, stages 1a, 1b and 2 accounted for mean 4.8%, 27.2% and 34.3% of total sleep, respectively, while stages 3 and 4 (deep slow-wave sleep) together accounted for a mean 21.7%. The percentage of REM sleep was low (mean 12.5%) and the mean REM latency was 113.1 ± 33.9 min.

Under placebo administration total time awake, during the 8-h recording, was a mean 134.3 ± 81.9 min, of which 14 ± 15.8 min were due to nocturnal awakenings (Table 1).

Under midazolam treatment sleep architecture generally normalized (Table 2), and waking time

Table 1 Sleep/waking time distribution after baseline placebo and midazolam (15 mg) in 15 patients (mean ± s.d.)

	Placebo	*Midazolam*
Total sleep time (min)	352.3 ± 87.5	450.1 ± 57.6
Sleep latency (min)	21.0 ± 24.5	2.4 ± 2.5
Total waking time (min)	134.3 ± 81.9	39.2 ± 48.6
Intra-sleep awakenings (min)	14.0 ± 15.8	3.1 ± 5.6
No. episodes night terrors	1.4 ± 0.7	0.1 ± 0.5

Table 2 Sleep architecture in 15 patients with night terrors receiving placebo or midazolam (15 mg) (means ± s.d.)

Sleep stage	*Placebo*		*Midazolam*	
	min	*(%)*	*min*	*(%)*
Stage 1a	13.7 ± 20.4	(4.8)	7.0 ± 11.1	(4.4)
1b	95.5 ± 49.1	(27.2)	44.8 ± 34.3	(9.8)
2	121.9± 55.9	(34.3)	222.9 ± 84.5	(49.9)
3–4	76.1 ± 53.1	(21.7)	99.6 ± 58.2	(23.2)
REM total	45.1 ± 31.6	(12.5)	71.8 ± 26.4	(15.7)
REM latency	113.1 ± 33.9	—	59.8 ± 37.0	—

decreased (Table 1) to a mean 39.2 ± 48.6 min of which only 3.1 ± 5.6 min were within the sleep. Sleep stages 1a (mean 4.4%) and 1b mean (9.8%) were both shortened (Table 2). There was a lengthening of stage 2 (from 34.3% under placebo to 49.9% under midazolam) and of stages 3 and 4 (from 21.7% under placebo to 23.2% under midazolam). Midazolam increased the amount of REM sleep to 15.7% as against 12.5% under placebo, and shortened REM latency from mean 113 ± 33.9 min under placebo to 59.8 ± 37 min, in addition to bringing about a normal or almost normal distribution of the REM phases during the night (Figures 1–4).

Effect on night terror episodes

The baseline placebo polygraphic recordings revealed a total of 21 night terror episodes (between one and three attacks per subject). Television monitoring and polygraphy demonstrated that the temporal distribution pattern of these episodes differed. For the first 10 children (with simple night terrors) most of the attacks occurred during the first hours of the night, in stages 3 to 4, and only twice in the transition from stage 3 to stage 2. All these episodes were followed by a change in the electrical phase (to a more superficial sleep stage) or even by an awakening of a few minutes or more (Figures 1 and 2).

In five children with night terrors associated with motor and ambulatory automatisms, the episodes occurred mostly in LSWS stages (1a and 1b, and only once in a stage 3). One case (S.D.) had three episodes associated with motor automatisms and attempted sleepwalking: at 00.42 h in stage 2 sleep, at 02.20 h in a REM phase (this one associated with bruxisms), and at 02.40 h in a transitional phase from REM into

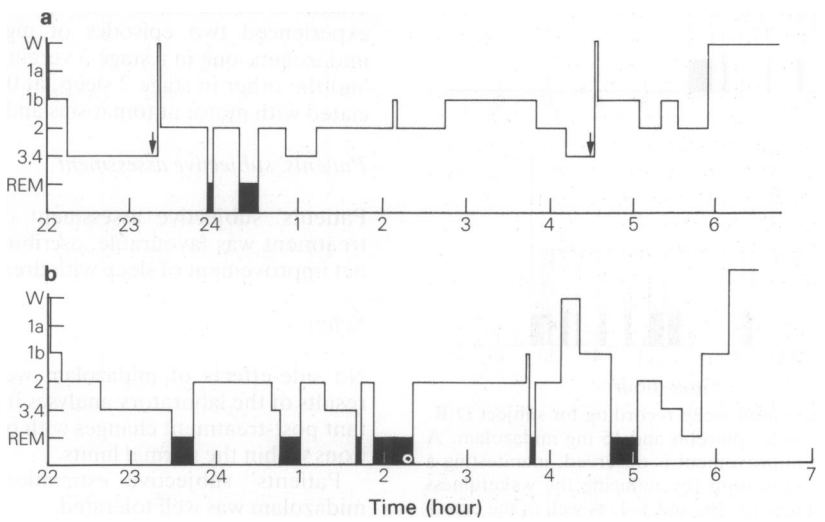

Figure 1 Eight-hour sleep recordings for subject M.F. (12 years old) under placebo and 15 mg midazolam. A slight extension of the total sleep duration is observed but sleep was better organized showing a reduction of the duration of stages 1a and 1b and an increase in stages 3 and 4, as well as the recurrence of 6 REM sleep periods; REM sleep percentages increased from 3.87%, under placebo (arrowed), to 19.18% under midazolam. The child manifested two night terror attacks during some sleep stages 3 and 4 but these did not occur during the midazolam treatment. (**a**) placebo: wake time (W), 6 min; light slow-wave sleep (LSWS), 127 min; deep slow-wave sleep (DSWS), 331 min; REM sleep (REMS), 16 min; paradoxical sleep total sleep (PS TS), 3.87%. (**b**) midazolam: W, 22 min; LSWS, 57 min; DSWS, 332 min; REMS, 90 min; PS TS, 19.18%.

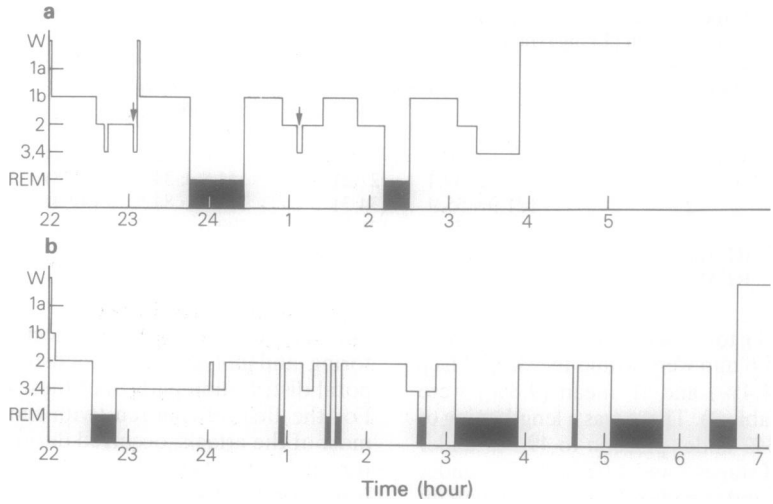

Figure 2 Eight-hour sleep recordings in subject B.S. (9 years old) under placebo and 15 mg midazolam. Midazolam markedly extended the total sleep time, the sleep being relatively well organized with a reduction in stages 1a and 1b and an increase in stage 2 and REM phases with a rebound towards morning. Under placebo the child manifested 2 episodes of night terrors in the first part of the night (arrowed), in two 3–4 sleep stages. During midazolam treatment he had no episodes of night terrors. (**a**) placebo: W, 0 min; LSWS, 140 min; DSWS, 126 min; REMS, 88 min, PS/TS, 24.85%. (**b**) midazolam: W, 1 min; LSWS, 4 min; DSWS, 375 min; REMS, 133 min; PS/TS, 25.97%.

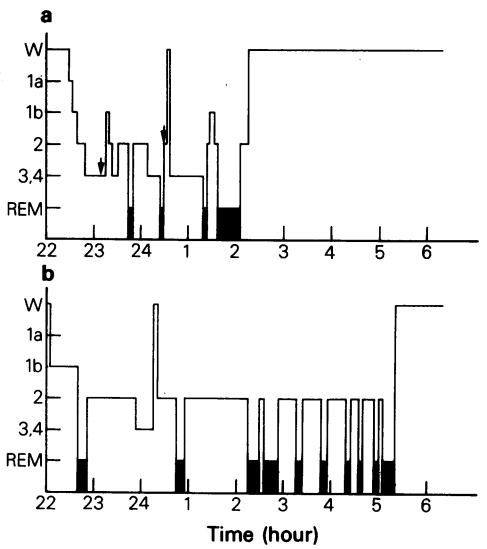

Figure 3 Eight-hour sleep recording for subject D.R. (8 years old) under placebo and 15 mg midazolam. A marked sleep improvement is observed, manifesting a good sleep organization (by reducing the wakefulness periods and stages 1a, 1b, and 3–4, as well as the extension of stages 2 and the increase and normal distribution of the REM phases with a percentage of 18.35%). Under placebo the child presented 2 night terror attacks (arrowed) which did not occur under the treatment with midazolam. (**a**) placebo: W, 257 min; LSWS, 20 min; DSWS, 170 min; REMS, 33 min; PS/TS, 14.79%. (**b**) midazolam: W, 66 min; LSWS, 38 min; DSWS, 300 min; REMS, 76 min; PS/TS, 18.35%.

stage 3 and then towards stage 2) requiring a cut-off in the recording, with decoupling and remounting of the electrodes (Figure 4). Midazolam suppressed the attacks in all the children except in patient S.D. who experienced two episodes of night terrors under midazolam: one in a stage 3 verging on 2, at 00.20 h, and the other in stage 2 sleep, at 01.15 h, both associated with motor automatisms and sleepwalking.

Patients' subjective assessment

Patients' subjective assessment of the midazolam treatment was favourable, ascribing to midazolam a net improvement of sleep with dreaming.

Safety

No side-effects of midazolam were reported. The results of the laboratory analyses indicated no important post-treatment changes with only minimal variations within the normal limits.

Patients' subjective estimations indicated that midazolam was well tolerated.

Discussion

Our present data support earlier clinical polygraphical observations (Popoviciu & Szabó, 1975; Popoviciu, 1977, 1978, 1980) demonstrating disorganized

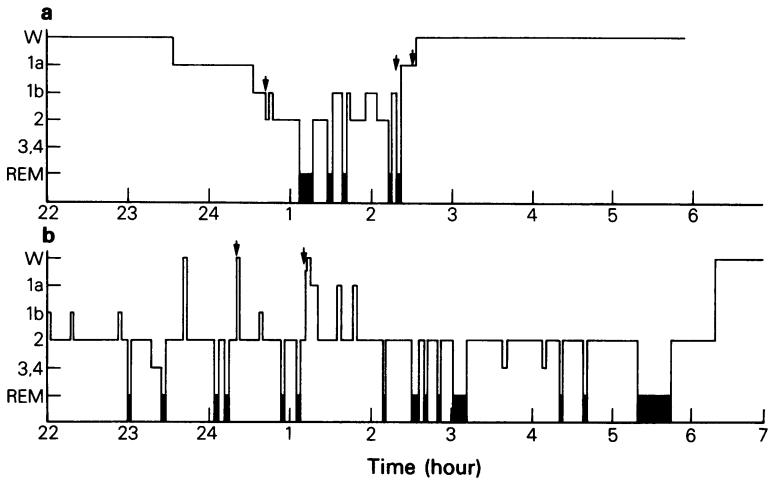

Figure 4 Eight-hour sleep recordings for subject S.D. (15 years old) under placebo and 15 mg midazolam. Diagnosis: night terror attacks, ambulatory automatisms and bruxisms. A clear extension and improvement of sleep is observed with the decrease of the wakefulness periods and of stages 1a and 1b, as well as an increase of stages 2 and of the REM phases. Under placebo, the child manifested 3 night terror episodes (arrowed) which were very short and attempted sleepwalking: at 00.42 h in a stage 2, at 02.20 h in a stage 1a. Under midazolam he also presented 2 night terror attacks (arrowed) which were very short and accompanied by motor automatisms: one in a stage 2 at 00.20 h and the other in a transitional state from a stage 2 to 1a, at 01.15 h. (**a**) placebo: W, 280 min; LSWS, 120 min; DSWS, 64 min; REMS, 16 min; PS·TS, 8%. (**b**) midazolam: W, 6 min; LSWS, 16 min; DSWS, 428 min; REMS, 54 min, PS·TS, 10.84%.

sleep architecture in children with night terrors and other NEM.

Midazolam would appear to be effective in the treatment of both night terrors and associated NEMs. Our present experience compared with previous work (Popoviciu, 1978) seems to indicate that this compound is more effective than other benzodiazepines used so far in this indication.

The efficacy of midazolam in this context is due to its rapid action in inducing sleep that has a normal or almost normal architecture. The compound induces sleep, suppresses nocturnal arousals, lengthens the total sleep time, reorganizes sleep stages, increases and redistributes REM sleep and stage 2 sleep, and reduces stage 1a and 1b (especially) of the LSWS. Since it reorganizes sleep architecture, midazolam reduces the likelihood of night terrors at those times at which they most frequently occur (in the first part of the night, at midnight and towards morning). In this study, midazolam was most effective in the treatment of episodes associated with other NEMs (motor automatisms, ambulatory automatisms, bruxisms, nocturnal enuresis) which develop in the setting of organic cerebral disease with EEG anomalies.

Midazolam regularizes and balances the sleep stages and, being very well tolerated, it can be used in the treatment of night terrors in children of all ages.

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