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Effect of zolpidem on sleep and sleep EEG spectra in healthy young men

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Abstract. A single 10 mg dose of zolpidem, an imidazopyridine hypnotic, was administered to young, healthy male volunteers prior to bedtime. The drug reduced REM sleep but did not significantly affect other sleep stages and subjective sleep parameters. All-night spectral analysis of the EEG revealed that power density in nonREM sleep was reduced in the low-frequency range (1.25–2.5 Hz; 5.25–10.0 Hz) and increased in the spindle frequency range (12.25–13.0 Hz). Significant changes in the EEG spectrum were present in the first 4 h of sleep. The pattern of the spectral changes was similar to those induced by other hypnotics that bind to the $GABA_A$/benzodiazepine receptor complex. There were no residual effects of zolpidem on psychomotor performance in the morning, on the self-rated state in the morning and at noon, and on sleep and EEG parameters in the subsequent drug-free night.

Key words: Zolpidem – Hypnotic – Sleep – EEG spectra – Performance

Novel non-benzodiazepine hypnotics are currently receiving increasing attention. In contrast to the extensively investigated benzodiazepines, their effect on sleep has been documented only in a limited number of studies. While most polygraphic investigations of hypnotics were based on the scoring of the sleep stages, in some studies computer-aided methods of EEG analysis were applied to examine the effects of various benzodiazepine hypnotics (Feinberg et al. 1977; Gaillard 1977; Gaillard et al. 1973; Johnson et al. 1979, 1983; Borbély et al. 1983b, 1985b; Achermann and Borbély 1987; Dijk et al. 1989; Trachsel et al. 1990) and of zopiclone, a cyclopyrrolone hypnotic (Wright et al. 1984; Trachsel et al. 1990). These studies have shown that the analysis of the sleep EEG provides more detailed information on the effects of hypnotics on the brain than the conventional sleep scoring procedure. Furthermore, it became apparent that the spectral changes induced by these compounds were highly similar. A major aim of the present study was therefore to investigate the effect of zolpidem, a rapidly eliminated imidazopyridine hypnotic (plasma half-life approximately 2 h: Thénot et al. 1988), on sleep EEG spectra. The analysis was extended to the drug-free night following upon the drug night (post-drug night) because in previous studies persistent effects of benzodiazepine hypnotics on EEG spectra had been demonstrated (Borbély et al. 1983b, 1985b).

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Materials and methods

Subjects. The study was carried out in eight healthy, male subjects (mean age 25.4 years; range 23–30) who did not report any sleep disturbances. They were recruited among university students and paid for participating in the study. Their sleep habits and the absence of sleep disorders were established on the basis of questionnaires. Prior to the experiment, informed consent was obtained.

Protocol. The subjects were asked to refrain from alcohol and excessive caffeine consumption, and from daytime naps during the entire experiment. Moreover, they were requested to maintain their habitual bedtime on each night preceding an adaptation night. The bedtimes at home could be checked by a wrist-worn activity monitor. Sleep was recorded in the darkened, sound-attenuated bedrooms of the sleep laboratory during two blocks of 3 consecutive nights. Each block consisted of an adaptation night, a drug or placebo night, and a subsequent post-drug or post-placebo night. The initial nights of the two blocks were 1 week apart. The subjects went to bed at 23:30 hours, which corresponded closely to their habitual bedtime, and they got out of bed at 07:30 hours. A double-blind, balanced crossover schedule was used.

Drug. The 10 mg dose of zolpidem corresponds to the hypnotic dose recommended by the manufacturer. The oral administration of zolpidem or placebo occurred 15 min prior to bedtime.

Sleep recordings, EEG spectra and subjective sleep parameters. Sleep was polygraphically recorded and scored for 20 s epochs according to conventional criteria (Rechtschaffen and Kales 1968). The method of all-night spectral analysis of the EEG has been described previously (Borbély et al. 1981; Brunner et al. 1990). In brief, the EEG signal (C3/A2 or C4/A1 derivation) was low-pass filtered

Table 1. Sleep parameters after intake of 10 mg zolpidem (Zolp) or placebo (Plac), and in the post-zolpidem (Post–Z) and post-placebo (Post–P) nights. Mean values with SEM in parenthesis (N = 8) in minutes unless indicated otherwise. *F*, Friedman two-way ANOVA for repeated measures ($df = 3$) with *P*-value indicated in parenthesis. * $P < 0.05$ in comparison to Plac; $^{+}$ $P < 0.05$ in comparison to Post–P (Wilcoxon matched pairs, signed ranks test, two-sided). TIB, time in bed

Condition	Plac	Post-P	Zolp	Post-Z	*F* (*P*)
Total sleep time (TST)	437.4 (10.7)	426.3 (15.8)	440.9 (5.9)	436.1 (13.7)	3.75 (0.290)
Sleep efficiency (% TST of TIB)	91.1 (2.2)	88.7 (3.3)	91.8 (1.2)	90.8 (2.9)	3.75 (0.290)
Sleep latency (to stage 2)	15.8 (8.5)	17.6 (7.1)	14.0 (4.0)	17.4 (7.9)	1.31 (0.727)
REM sleep latency (from stage 2)	76.8 (6.0)	78.9 (7.8)	85.7 (11.7)	73.0 (7.1)	6.45 (0.092)
Wakefulness after sleep onset (W)	15.3 (4.8)	24.0 (10.6)	13.1 (5.0)	15.3 (6.9)	2.68 (0.443)
Stage 1	35.0 (2.0)	30.6 (2.4)	31.1 (3.7)	31.1 (3.1)	1.95 (0.583)
Stage 2	201.1 (7.4)	212.8 (13.3)	213.1 (6.6)	201.8 (9.8)	4.95 (0.176)
Stage 3	41.3 (3.4)	37.5 (4.2)	45.3 (3.1)	46.6 (3.7)	4.65 (0.199)
Stage 4	55.8 (7.8)	42.5 (7.5)	57.6 (10.5)	45.6 (5.0)	4.95 (0.176)
Slow wave sleep (SWS; Stages 3+4)	97.1 (6.1)	80.0 (8.3)	102.9 (8.8)	92.2+ (6.3)	8.85 (0.031)
REM sleep	104.2 (5.5)	102.9 (4.9)	93.7* (5.6)	111.0 (6.4)	8.55 (0.036)
Movement time (MT)	11.6 (2.3)	12.7 (2.0)	12.1 (1.5)	11.5 (1.4)	2.52 (0.472)
MT+W+Stage 1	61.9 (3.8)	67.2 (11.1)	56.3 (5.9)	57.9 (5.6)	0.57 (0.903)

(25 Hz, 24 dB/octave), AD-converted (128 Hz), and subjected to a Fast-Fourier Transform routine. Spectra were computed for consecutive 4 s epochs and 0.25 Hz bands in the range of 0.25–25.0 Hz by applying a rectangular window. The values were then averaged for 20 s epochs and matched with the 20 s sleep scores. In addition, values of adjacent frequency bands were collapsed into 0.5 or 1.0 Hz bins.

Subjective sleep parameters were assessed 15 min after awakening by a questionnaire and by 100 mm visual analogue scales (VAS) (Table 2). VAS served also to assess the momentary state in the morning and at noon (Table 3). These methods have proved sensitive to document the hypnotic action and residual effects of various benzodiazepine hypnotics on subjective parameters (Mattmann et al. 1982; Borbély et al. 1983a, 1984, 1985a).

Performance test. A typing test of 20 min duration was administered at 09:00 hours after the drug and placebo nights, and served to evaluate psychomotor performance in the morning. The subjects were asked to copy a text on a typewriter as fast and as accurately as possible. The type-written text consisted of computer-generated nonsense words which were composed of randomly assigned letters, numbers and punctuation marks. The subjects familiarized themselves with the test on a day prior to the experiment. The number of letters typed, the number of errors and the percentage of errors were determined to assess performance. This typing test was sensitive enough to demonstrate the residual effect of triazolam (0.5 mg) 9–10 h after the intake (Borbély et al. 1983a).

Results

Sleep stages and EEG spectra

The sleep parameters for the four experimental conditions are shown in Table 1. Sleep duration, sleep efficiency, sleep latency, wakefulness after sleep onset, and the stages of nonREM sleep showed no significant differences between the conditions. The only significant effects were a reduction of REM sleep in the zolpidem night in comparison to the placebo night, and a higher level of slow wave sleep in the post-zolpidem night in comparison to the post-placebo night.

The effect of zolpidem on EEG power density in nonREM sleep is shown in Fig. 1. In the upper panel, the value of the zolpidem night is expressed for each frequency bin relative to the corresponding value of the placebo night (= 100%). The relative spectrum computed for nonREM sleep (stages 2, 3 and 4) of the entire sleep episode revealed a depression of power density in the low-frequency range and an augmentation in the 12.25–13.0 Hz range. The significant reduction of the

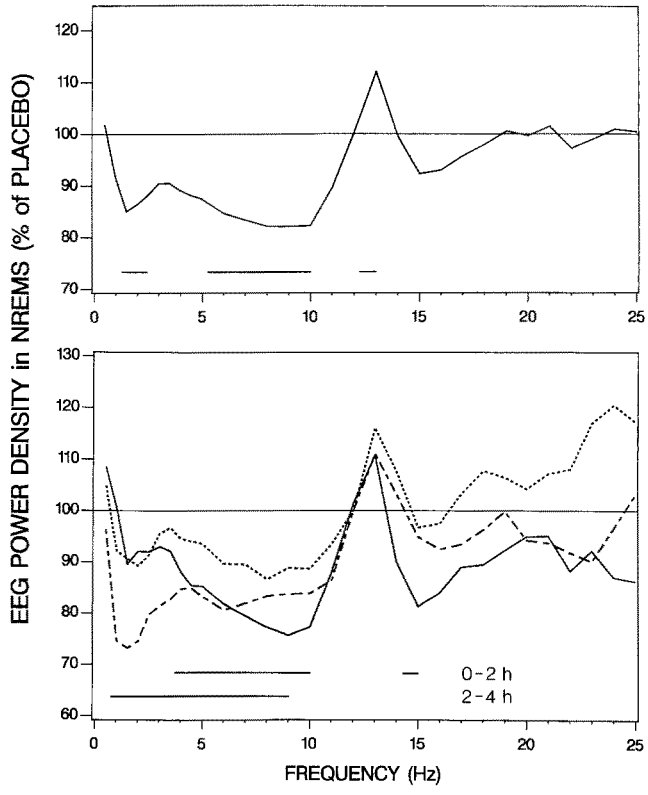

Fig. 1. Effect of zolpidem on relative EEG power density in nonREM sleep. The curves connect mean values ($N = 8$) for successive 0.5 or 1 Hz bins which are expressed as a percentage of the corresponding placebo reference value. Horizontal lines above the abscissa indicate the frequency range with significant differences from the placebo level ($P < 0.05$; paired *t*-test on log-transformed percentage values, two-sided); *t*-tests were performed only in those frequency bins in which a repeated ANOVA ($df = 3$, Huynh-Feldt corrected) over all four treatments (placebo (*P*), post-P, zolpidem (*Z*), post-Z) was significant ($P < 0.05$). *Upper panel:* Values for the entire sleep episode. *Lower panel:* Values for the first three 2 h intervals of sleep. ——— 0–2 h; – – – – 2–4 h; - - - - - 4–6 h

spectral values encompassed the 1.25–2.5 Hz band in the delta range, and the 5.25–10.0 Hz band in the theta/alpha range.

To assess the time course of the spectral changes, the data were analyzed for 2 h intervals over the first 6 h of sleep (Fig. 1, lower panel). For each interval the zolpidem values were expressed relative to the corresponding placebo values. A temporal evolution was apparent. From the first to the second 2 h interval, the range over which activity was significantly reduced shifted towards lower frequencies. Moreover, a significant decrease in the 14.25–15.0 Hz band was present only in the first 2 h. In the third 2 h interval the deviations from the placebo level had diminished and were no longer significant.

The spectral values for nonREM sleep in the post-drug night showed no significant deviations from the post-placebo reference values with the exception of one value in the 12.25–13.0 Hz bin which was reduced by 6% ($P<0.05$; statistics as in Fig. 1); however, this value did not differ significantly from the placebo level. The REM sleep spectrum of the drug night did not differ significantly from that of the placebo night. In the post-drug night, the values in frequencies higher than 12 Hz tended to be below those of the post-placebo night; however, a significant difference was present only in the 20.25–21.0 Hz bin.

Subjective sleep parameters, momentary state and performance

In accordance with the polygraphic data, the subjective estimates of sleep latency and wake time after sleep onset showed no significant effects (Table 2). After drug intake sleep was not perceived as deeper or more quiet than after placebo.

No significant differences were present in the self-rated state in the morning and at noon (Table 3). A significant difference in the mood ratings at noon was present between the drug and post-drug condition. The subjects did not report any undesired effects for the day following drug or placebo intake.

The typing test was not significantly different for the drug and placebo condition. The following results were obtained (mean ± SEM; $N=8$; placebo versus zolpidem): number of letters typed, 1285 ± 73 versus 1317 ± 85; number of errors, 15.3 ± 3.0 versus 16.5 ± 3.6; percent of errors, 1.2 ± 0.2 versus 1.3 ± 0.3.

Table 2. Subjective sleep parameters. Questionnaire data and self-ratings (mm) on a 100 mm visual analogue scale. Mean values with SEM in parenthesis ($N=8$). *F*, Friedman two-way ANOVA for repeated measures ($df=3$) with *P*-value indicated in parenthesis

Condition	Plac	Post-P	Zolp	Post-Z	*F* (*P*)
Sleep latency (min)	18.8 (10.3)	24.5 (13.7)	11.3 (3.3)	22.3 (14.0)	7.52 (0.057)
Number of awakenings at night	2.5 (0.7)	2.1 (0.4)	2.8 (0.5)	2.0 (0.5)	2.13 (0.546)
Duration of wake time at night (min)	21.3 (6.2)	16.6 (7.0)	24.8 (7.6)	20.1 (7.1)	2.54 (0.468)
Deep (100) vs superficial sleep (0)	47.0 (8.2)	55.6 (5.7)	50.3 (5.9)	47.8 (7.5)	3.00 (0.392)
Quiet (100) vs restless sleep (0)	40.6 (7.5)	47.4 (6.5)	44.1 (7.9)	40.6 (7.3)	1.35 (0.717)

Table 3. Self-rated state in the morning 15 min after getting out of bed and at noon. Values indicated in mm on a 100 mm visual analogue scale. Mean values with SEM in parenthesis ($N=8$). *F*, Friedman two-way ANOVA for repeated measures ($df=3$) with *P*-value indicated in parenthesis. * $P<0.05$ in comparison to Zolp (Wilcoxon matched pairs, signed ranks test, two-sided)

Condition	Plac	Post-P	Zolp	Post-Z	*F* (*P*)
Morning					
Tired (100) vs recuperated (0)	62.6 (5.2)	50.9 (5.0)	57.1 (3.7)	55.5 (6.6)	4.17 (0.244)
Good mood (100) vs bad mood (0)	51.1 (5.3)	54.0 (4.0)	51.6 (5.2)	47.9 (6.0)	1.65 (0.648)
Full of energy (100) vs lack of energy (0)	46.9 (5.8)	57.0 (4.7)	54.5 (3.8)	54.0 (4.8)	4.20 (0.241)
Relaxed (100) vs tense (0)	55.8 (5.6)	49.1 (7.7)	50.9 (4.7)	51.1 (6.0)	3.89 (0.274)
Concentrated (100) vs unconcentrated (0)	44.0 (3.8)	46.0 (3.7)	55.5 (4.8)	45.3 (5.2)	1.48 (0.687)
Noon					
Tired (100) vs recuperated (0)	39.3 (3.5)	50.1 (4.5)	48.5 (2.9)	44.5 (4.9)	3.73 (0.292)
Good (100) vs bad mood (0)	65.5 (3.8)	69.4 (3.0)	54.1 (5.2)	62.8* (5.2)	12.11 (0.007)
Full (100) vs lack of energy (0)	63.6 (3.8)	56.5 (4.0)	49.9 (5.8)	59.6 (5.9)	5.88 (0.118)
Relaxed (100) vs tense (0)	48.0 (5.7)	46.4 (5.0)	52.6 (7.4)	50.6 (4.6)	2.10 (0.551)
Concentrated (100) vs unconcentrated (0)	55.5 (4.9)	51.5 (4.0)	53.1 (4.6)	50.0 (5.8)	0.72 (0.868)

Discussion

In the healthy young subjects of the present study, the intake of a 10 mg dose of zolpidem caused no significant changes in sleep latency, sleep duration, sleep efficiency and the distribution of the substates of nonREM sleep. Moreover, in accordance with our previous results (Borbély et al. 1988), the subjective ratings of sleep parameters did not differ from the placebo condition. The present findings are in general agreement with those of Nicholson and Pascoe (1986) and Blois and Gaillard (1988), who did not observe a significant effect of zolpidem 10 mg on objective and subjective sleep parameters in young healthy subjects, apart from a reduction in the number of awakenings in the first 6 h in the former study. However, other authors reported a significant shortening of sleep latency (Lund et al. 1988; Merlotti et al. 1989). Also in the present study the mean values of the objective and estimated sleep latency were lowest in the drug night. In contrast to the consistent hypnotic effect in poor sleepers (Oswald and Adam 1988; Wheatley 1988; Monti 1989; Besset et al. 1990), a 10 mg dose exerts only a marginal effect on sleep in good sleepers.

Zolpidem induced a moderate reduction of REM sleep but did not prolong REM sleep latency. Our experimental subjects apparently were rather sensitive to the REM sleep depressing action of the drug, since in other studies a significant decrease in REM sleep (Oswald and Adam 1988; Merlotti et al. 1989; Hux et al. 1990) and a prolongation of REM sleep latency (Nicholson and Pascoe 1986; Oswald and Adam 1988) were present only after a 20 mg dose but not after a 10 mg dose.

In view of the short half-life of zolpidem and the recommended dose administered, no residual effects were expected after awakening in the morning. In fact, neither the performance test in the morning nor the subjective ratings of the state in the morning and at noon revealed significant differences from placebo. One may argue that possible residual effects may have not been detected because of the small sample size ($N=8$). However, the fact that the mean values of the self-ratings in the morning were situated with one exception between the mean placebo and post-placebo values (Table 3), makes it appear unlikely that a genuine residual effect was not recognized. In a previous study, there was no significant effect even after a 20 mg dose (Borbély et al. 1988). Also, in confirmation of our previous results obtained for doses of 10 mg and 20 mg zolpidem, no impairment of psychomotor performance was observed in the morning. Although the performance test has been sensitive enough to detect the residual effect of a short-acting benzodiazepine hypnotic (Borbély et al. 1983a), we are hesitant to draw any general conclusion from the results of a single test. Yet since larger test batteries also failed to reveal an impairment of performance in the morning in healthy volunteers (10–30 mg; Nicholson and Pascoe 1986) and in insomniac patients (10 mg; Monti 1989), it is unlikely that major performance deficits are induced by the recommended hypnotic dose. In the present study, there were neither indications for delayed effects of zolpidem on subjective sleep parameters in the post-drug night nor on subjective state parameters in the subsequent morning.

One of the main objectives of our study was to assess the effect of zolpidem on the power spectra of the sleep EEG. The drug reduced the power density of the nonREM sleep EEG in the low-frequency range (up to 9–10 Hz), and enhanced EEG activity in the frequency range of sleep spindles. The former effect was significant in the first two 2 h intervals of sleep. In hours 4–6 the spectrum no longer deviated significantly from the placebo level, although the mean curve still exhibited the typical pattern. The results show that a 10 mg dose of zolpidem modifies the nonREM sleep EEG, although it does not significantly affect the sleep stages of nonREM sleep. We have repeatedly demonstrated (Borbély et al. 1983b, 1985b; Dijk et al. 1989; Trachsel et al. 1990) that the distribution of the sleep stages based on the conventional scoring criteria reflects inadequately the effects of hypnotics on sleep. The present study provides further evidence that a computer-aided analysis of the EEG signal is mandatory in pharmacological sleep studies.

The modifications of the EEG spectrum by zolpidem were strikingly similar to those induced by various benzodiazepine hypnotics [flunitrazepam, flurazepam, triazolam (Borbély et al. 1983b, 1985b); temazepam (Dijk et al. 1989), and midazolam (Trachsel et al. 1990)], and by zopiclone, a cyclopyrrolone hypnotic (Trachsel et al. 1990). All compounds reduced the EEG activity in the low-frequency range and enhanced the activity in the range of spindle frequencies. Also, the time course of the changes was similar. Thus in the initial period after drug administration the reduction was most prominent in the theta/alpha range, whereas subsequently the reduction was most prominent in the low delta range (Borbély et al. 1985b; Trachsel et al. 1990). However, there were also differences between the various hypnotics. The deviations of the spectra from the placebo reference level were smaller for zolpidem than for the other hypnotics that had been examined by spectral analysis. Moreover, zolpidem was the only compound that did not induce significant changes in the EEG spectra of REM sleep. Whether these differences reflect merely dose-response relations or reflect a pharmacodynamic specificity, remains to be examined.

A common property of the benzodiazepine and nonbenzodiazepine hypnotics which we have so far been analyzed by all-night spectral analysis, is the specific binding to the $GABA_A$/benzodiazepine receptor complex. Even though their precise binding sites on the complex, and their affinity to receptor subtypes may differ (Snyder 1987; Benavides et al. 1990; Pritchett and Seeburg 1990), it is tempting to assume that the analogous modification of the sleep EEG by all these hypnotics may represent a "spectral GABA-benzodiazepine signature".

Interpreting the effect of hypnotics on the sleep EEG is difficult. One of the main questions is whether the drugs affect the sleep process per se or whether they act merely on the EEG generating mechanisms. There are indications that the homeostatic and ultradian sleep regulating processes are not disrupted by benzodiazepine hypnotics (Achermann and Borbély 1987; Borbély and Achermann 1991). As the present results show, a modification of the EEG may occur in the absence of a significant sleep-promoting action. Further electrophysiological studies are required to obtain a deeper insight into the neurophysiological mechanisms.

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