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Dose-Response Effects of Zopiclone on Night Sleep and on Nighttime and Daytime Functioning

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Summary: Six normal volunteers, aged 20 to 39 years, underwent 2 adaptation nights and three sessions of 2 consecutive experimental nights and days at 1-week intervals, according to a latin-square design. In the three sessions, subjects received either zopiclone, 3.75 mg or 7.5 mg, or placebo at 2215 h in a double-blind protocol. On nights 1 and 2 of each session, subjects were continuously monitored polygraphically, except for a 45-min provoked wake episode 135 min after sleep onset on night 2. Degree of daytime somnolence was assessed during day 1 by means of a multiple sleep latency test (MSLT) and performance evaluation was carried out during night 2 (0000 h) and day 2 (800 h and 1200 h) by means of a battery of four tests. NREM sleep stages 3 and 4 increased significantly after 3.75 mg and 7.5 mg zopiclone ($p < 0.05$). No significant differences between placebo and 3.75 mg and 7.5 mg zopiclone were found at any time in the MSLT. Two performance tests (eye-hand coordination test and choice reaction time test) showed a highly significant impairment ($p < 0.01$) at 0000 h with 7.5 mg zopiclone; one test (eye-hand coordination test) showed a significant impairment ($p < 0.05$) at 0800 h also with 7.5 mg zopiclone and none at 1200 h. From a subjective point of view, depth and quality of sleep were improved, whereas number of awakenings and feeling on awakening were not modified. Side effects (bitter taste, jitteriness, difficulty to concentrate) were reported only with 7.5 mg zopiclone. **Key Words:** Zopiclone—Sleep parameters—Daytime performance.

Zopiclone is a new hypnotic belonging to the chemical family of cyclopyrrolones. Although this compound is a nonbenzodiazepine molecule, it binds specifically to the benzodiazepine receptor complex in the brain (1). Its biological plasma half-life is 4–5 h (2).

The aim of this study was to evaluate the effects of 3.75 mg and 7.5 mg zopiclone, not only on night sleep parameters, daytime vigilance, and performances, but also on nighttime performances at a time when maximum blood level of this short plasma half-life compound could be expected.

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METHODS

This study was carried out in two male and four female healthy volunteers, aged 20 to 39 years (median age 26.5 years). Each subject was submitted to 2 adaptation nights and three sessions of 2 consecutive experimental nights and days at 1-week intervals, according to a latin-square design. The study conformed to the Declaration of Helsinki.

In the three sessions of experimental nights and days, subjects received 3.75 mg or 7.5 mg zopiclone or placebo (15 min before lights out), in a double-blind protocol.

On night 1 of each session, subjects were continuously monitored polygraphically (lights out 2230 h, lights on 0730 h). Upon awakening, subjects completed a morning questionnaire aimed at assessing the subjective quality of their sleep. Then the degree of day-time somnolence was evaluated by means of a multiple sleep latency test (MSLT) (3), performed every 2 h from 0800 h to 1800 h. The subjects were asked to lay in bed, and the recording was started. The test was stopped after 20 min if the subject did not fall asleep or after either 3 consecutive epochs of NREM sleep stage 1 or one epoch of NREM sleep stage 2.

On night 2 of each session, subjects were again continuously monitored polygraphically (lights out 2200 h, lights on 0730 h) except for a 45 min provoked wake episode during the first epoch of stage 2 occurring at least 90 min after ingestion of zopiclone or placebo. During this wake episode, a first series of performance tests was carried out, immediately followed by a 15-ml blood sampling for plasma zopiclone concentration measurement. Subjects went back to bed and sleep latency was measured. Second and third series of performance tests and blood sampling were performed at 0800 h (30 min after lights on) and at 1200 h. The battery of performance tests included an eye-hand coordination test (Purdue Pegboard), a choice reaction time test, a digit symbol substitution test (Janin's test), and a memory test (immediate recall of a list of 12 words), which were performed within ~20 min.

All night polygraphic recordings were scored visually according to Rechtschaffen and Kales (4). Statistical analysis was based on Kruskal-Wallis one-way analysis of variance by ranks.

RESULTS

First night sleep

The mean results for sleep initiation and maintenance and for sleep architecture are reported in Table 1. Stages 3 and 4 increased significantly ($p < 0.05$) on 3.75 mg and 7.5 mg zopiclone. Wake after sleep onset; number of awakenings ≥ 1 min; stage 1, REM sleep, and REM episode duration decreased slightly, although not significantly on both 3.75 mg and 7.5 mg zopiclone. Sleep latency decreased; stage 2, total sleep time, and sleep efficiency (time asleep/time in bed from lights out to lights on) increased, although not significantly, on 7.5 mg zopiclone only.

Daytime somnolence

As shown in Figure 1, the average latency to sleep onset on the MSLT, across all drug conditions, decreased regularly from 0800 h to 1600 h and increased at 1800 h. Interestingly enough, there was no significant difference between placebo and 3.75 mg and 7.5 mg zopiclone conditions in any of the tests of MSLT. In comparison, sleep latency measured after awakening for the first series of performance tests of night 2,

TABLE 1. *Sleep parameters after each treatment*

Parameter	Placebo	Zopiclone (mg)	
		3.75	7.5
Sleep latency	30.0 ± 7.0	31.5 ± 9.0	16.0 ± 3.0
Wake time after sleep onset	4.6 ± 1.9	3.3 ± 1.9	2.8 ± 1.8
Number of awakenings (≥1 min)	1.1 ± 0.6	0.8 ± 0.5	0.3 ± 0.5
Total sleep time	505.8 ± 6.0	502.6 ± 8.0	517.0 ± 4.0
Sleep efficiency	0.93 ± 0.01	0.93 ± 0.01	0.96 ± 0.01
Stage 1 (min)	34.8 ± 6.9	23.8 ± 1.8	23.1 ± 1.8
Stage 2 (min)	279.6 ± 12.8	286.5 ± 13.3	309.0 ± 10.0
Stages 3–4 (min)	81.5 ± 5.5	98.5 ± 8.0[a]	96.5 ± 7.0[a]
REM sleep (min)	105.6 ± 13.4	92.6 ± 7.6	87.1 ± 1.7
REM latency	112.3 ± 13.4	83.5 ± 8.5	108.3 ± 2.2
REM episode duration	24.0 ± 2.7	21.0 ± 1.8	19.5 ± 2.2

[a] $p < 0.05$.

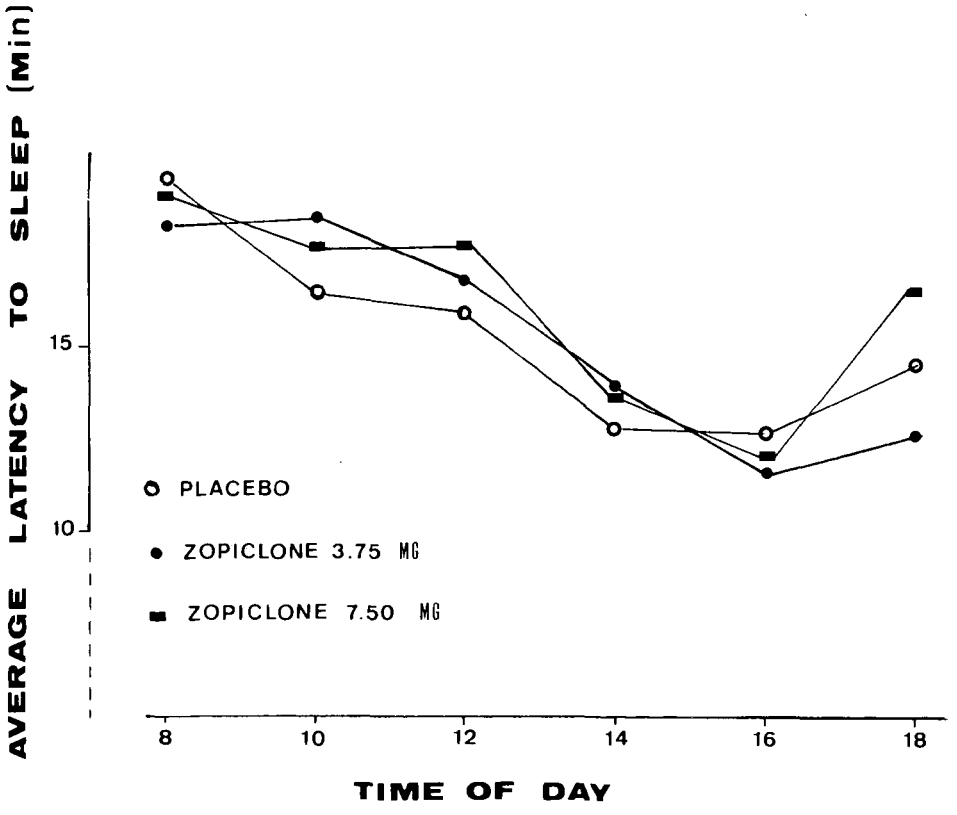

FIG. 1. Multiple sleep latency test.

~135 min after drug ingestion, was significantly shorter ($p < 0.01$) after 7.5 mg zopiclone (6.8 min) than after 3.75 mg zopiclone (14.5 min) and placebo (17.2 min).

Performance tests

Test of eye-hand coordination: Comparison of performances as a function of time (Table 2) showed that there was no significant change with placebo from 0000 h to 1200 h

TABLE 2. *Test of eye-hand coordination (Purdue Pegboard)*

Treatment	0000 h	0800 h	1200 h
Placebo	76.5 ± 4.3	79.9 ± 4.1	84.3 ± 4.1
3.75 mg zopiclone	72.0 ± 3.7[a]	80.3 ± 3.8 A	84.3 ± 1.7 B
7.5 mg zopiclone	63.6 ± 3.7[b]	76.8 ± 3.4 A[a]	85.0 ± 3.1 B C

Drug was administered at 2215 h the previous night. Letters indicate significant difference ($p < 0.05$) between 0800 h and 0000 h (A), 1200 and 0000 h (B), and 1200 and 0800 h (C).

[a] Significant difference ($p < 0.05$) with respect to placebo at time of testing.

[b] Significant difference ($p < 0.01$) with respect to placebo at time of testing.

(except for a learning effect). Conversely, there was a significant improvement from 0000 h to 0800 h on 3.75 mg and 7.5 mg zopiclone and from 0800 h to 1200 h on 7.5 mg zopiclone only, indicating a decrease of the impairment caused by the drug with time.

Comparison as a function of doses showed that at 0000 h there was a highly significant difference ($p < 0.01$) between results with 7.5 mg zopiclone versus placebo and a significant difference ($p < 0.05$) with 3.75 mg zopiclone versus placebo; at 0800 h there was still a significant difference ($p < 0.05$) between results with 7.5 mg zopiclone and placebo but not between 3.75 mg zopiclone and placebo. At 1200 h, there was no more difference between placebo and either drug dose, indicating the complete disappearance of any residual effect of the drug at that time.

Choice reaction time test: Comparison of results as a function of time of testing (Tables 3 and 4) showed that neither mean reaction time nor mean number of delayed responses improved with placebo from 0000 h to 1200 h. Conversely both test results improved significantly with 7.5 mg zopiclone from 0000 h to 0800 h, from 0000 h to 1200 h, and from 0800 h to 1200 h. With 3.75 mg zopiclone, the mean reaction time improved from 0000 h to 1200 h but the number of delayed responses did not improve.

Results as a function of doses showed a significant difference only between 7.5 mg zopiclone and placebo and only at 0000 h.

Digit symbol substitution test: A similar significant improvement was recorded from 0000 h to 0800 h, from 0000 h to 1200 h, and from 0800 h to 1200 h with placebo and both drug doses, indicating an obvious learning effect, but no difference was found between 7.5 and 3.75 mg zopiclone and placebo in any of the three tests (Table 5).

Memory test: No significant difference was observed in this test whether as a function of time of testing or as a function of the dose of zopiclone administered.

Subjective parameters (Table 6)

Subjects estimated sleep to be significantly deeper ($p < 0.01$) with either drug dose compared to placebo. In addition, they also mentioned a better quality of sleep ($p < 0.05$) with both drug doses and a shorter sleep latency ($p < 0.05$) with 7.5 mg zopiclone only. Number of night awakenings and feeling on awakening were not modified at any of the doses of zopiclone.

Side effects

The only records of side effects were mentioned with 7.5 mg zopiclone. Jitteriness, difficulty to concentrate, and bitter taste were each reported by three subjects. Fa-

TABLE 3. *Choice reaction time test*

Treatment	0000 h	0800 h	1200 h
Placebo	61.30 ± 3.2	59.15 ± 3.3	57.26 ± 2.74
3.75 mg zopiclone	62.23 ± 3.4	58.73 ± 2.3	56.39 ± 2.3 B
7.5 mg zopiclone	69.85 ± 3.8[a]	60.48 ± 2.9 A	56.83 ± 2.3 B C

Drug was administered at 2215 h the previous night. Letters indicate significant difference ($p < 0.05$) between 0800 and 0000 h (A), 1200 and 0000 h (B), and 1200 and 0800 h (C).

[a] Significant difference ($p < 0.01$) with respect to placebo at time of testing.

TABLE 4. *Choice reaction time test: Mean number of delayed responses*

Treatment	0000 h	0800 h	1200 h
Placebo	10.8 ± 3.6	9.33 ± 4.12	5.33 ± 2.55
3.75 mg zopiclone	13.1 ± 3.6	6.16 ± 2	3.33 ± 1.30
7.5 mg zopiclone	18.71 ± 4.3[a]	8.5 ± 2.69 A	5.50 ± 1.78 B C

Drug was administered at 2215 h the previous night. Letters indicate significant difference ($p < 0.05$) between 0800 and 0000 h (A), 1200 and 0000 h (B), and 1200 and 0800 h (C).

[a] Significant difference ($p < 0.05$) with respect to placebo at time of testing.

TABLE 5. *Digit symbol substitution test*

Treatment	0000 h	0800 h	1200 h
Placebo	124.50 ± 7.8	148 ± 5.52	159 ± 7.5 B C
3.75 mg zopiclone	120.8 ± 6.6	138.9 ± 12.1	150.1 ± 9.6 B C
7.5 mg zopiclone	113.6 ± 10.3	145.1 ± 8.7	154.5 ± 9.7 B C

Drug was administered at 2215 h the previous night. Letters indicate significant difference ($p < 0.05$) between 0800 and 0000 h (A), 1200 and 0000 h (B), and 1200 and 0800 h (C).

tigue, evening sleepiness, or a mild degree of ataxia were each mentioned by two subjects. Disturbance of accommodation and bursts of worries were each indicated by one subject.

Plasma concentration of zopiclone

Plasma concentrations of zopiclone measured at 0000, 0800, and 1200 h in each drug dose are shown in Table 7. The plasma half-life of zopiclone was estimated to be ~5 h with each drug dose according to a semi-logarithmic representation of the three values obtained at 0000, 0800, and 1200 h. Overall, these results indicate a normal drug elimination in the six subjects of the present study.

TABLE 6. *Dose-related effects of zopiclone on subjective parameters*

Parameter	Placebo	Zopiclone (mg) 3.75	7.5
Min to fall asleep	43	39	18[a]
Quality of sleep (1, worst; 5, best)	3	4.1[a]	4.8[a]
Quality compared to usual (+1, better; −1, worse)	−0.8	0	+0.3
Depth of sleep (0, very light; 12, very deep)	7.7	9.2[b]	10.1[b]
Night awakenings (0, none; −2, several)	−1.3	−0.8	−0.5
Feeling on awakening (4, very alert; 1, very sleepy)	2.1	2	2.4

[a] $p < 0.05$ with respect to placebo.
[b] $p < 0.01$ with respect to placebo.

TABLE 7. *Mean plasma zopiclone concentration*

Time	Zopiclone (mg) 3.75	7.5
0000 h	20.1 ± 0.4 ng/L	38.0 ± 3.5 ng/L
0800 h	6.2 ± 0.1 ng/L	14.1 ± 1.4 ng/L
1200 h	5.0 ± 0.9 ng/L	7.2 ± 0.7 ng/L

DISCUSSION

The present results show a significant increase of stages 3 and 4 in accordance with previous results (5). A significant increase of stage 4 has been found in insomniac subjects (6) and a nonsignificant increase of stages 3 and 4 has been reported in women over 40 years of age with subjective sleep disorders (7). On the other hand, a significant decrease of stage 3 and 4 was also shown in chronic insomniacs (8). Despite consistent trends, other parameters did not differ significantly with either 7.5 or 3.75 mg of zopiclone.

Until now, there had not been any evaluation of sleep tendency after zopiclone measured by the MSLT. The results are interesting in that they show no increased daytime sleepiness from 0800 to 1800 h with 3.75 mg or 7.5 mg zopiclone compared with placebo. This is clearly related with the short half-life of the drug since during night 2, sleep latency measured 135 min after drug ingestion, at a time corresponding to the reported peak concentration of the drug, was significantly shorter ($p < 0.01$) after 7.5 mg than after 3.75 mg zopiclone and placebo.

Results from the different performance tests are also particularly interesting in that they show very limited impairment at 0800 and nonimpairment at 1200 h. Indeed, a significant decrease in performance is only found in a single test at 0800 h, namely in the eye-hand coordination test after 7.5 mg zopiclone, whereas no significant impairment of other performance tests (choice reaction time, digit symbol substitution, memory) is evidenced.

In agreement with these results, no significant modification of the performance was

found in a digit symbol substitution test after morning awakening (9). On the other hand, a residual effect was found 9 h after 7.5 mg zopiclone or 10 mg zopiclone in a digit symbol substitution test (10).

In comparison, a highly significant impairment ($p < 0.01$) is present at 0000 h with 7.5 mg zopiclone in the tests of eye-hand coordination and choice reaction time (mean reaction time); this expected result is likely to be the main and unavoidable draw-back of a short half-life hypnotic.

The significant subjective improvement of the depth and quality of sleep might be related to the increase of stages 3 and 4. On the other hand, subjects did not mention any modification of the feeling on awakening. However, this result might be at variance in insomniac subjects when sleep onset is no longer delayed and/or sleep not interrupted by intervening wakefulness.

Among side effects, bitter taste (11), jitteriness, and difficulty to concentrate were the most frequently mentioned. On the other hand, a single subject reported bursts of worries and no subject reported a rebound insomnia previously described with short-acting hypnotics (12,13).

RÉSUMÉ

Six volontaires sains âgés de 20 à 39 ans ont été soumis à 2 nuits d'adaptation et à 3 sessions expérimentales de 2 nuits et 2 jours consécutifs à une semaine d'intervalle, selon un protocole en carré latin. Au cours des 3 sessions, les sujets ont reçu en double aveugle, soit 3.75 mg soit 7.5 mg de zopiclone, ou un placebo, à 22 h 15. Durant les nuits 1 et 2 de chaque session, les sujets étaient soumis à un enregistrement polygraphique continu sauf pendant un éveil provoqué de 45 minutes, 135 minutes après l'endormissement, la seconde nuit. Le degré de somnolence diurne était évalué pendant le jour 1 au moyen de mesures répétées de la latence de sommeil et les performances au cours de la 2ème nuit (à 0 h) et du jour 2 (à 8 h et 12 h), au moyen d'une batterie de 4 tests. Les stades 3 et 4 du sommeil lent ont augmenté de façon significative après 3.75 et 7.5 mg de zopiclone ($p < 0.05$). Aucune différence entre produit aetif placebo et n'a été trouvée à aucun des temps de mesure de la latence de sommeil. Deux tests psychomoteurs (coordination et temps de réaction de choix) ont révélé une altération très significative ($p < 0.01$) à 0 h à la dose de 7.5 mg et un test (coordination) a montré une altération significative ($p < 0.05$) à 8 h à la dose de 7.5 mg, mais aucun changement n'a été observé à 12 h. D'un point de vue subjectif, la profondeur et la qualité du sommeil ont été améliorées, alors que le nombre de réveils nocturnes et l'impression au réveil n'ont pas été modifiés. Les effets secondaires (goût amer, agitation, difficulté de concentration) ont été notés seulement à la dose de 7.5 mg de zopiclone.

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