Noise-induced sleep maintenance insomnia: hypnotic and residual effects of zaleplon

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Aims The primary objective of the study was to assess the residual effects of zaleplon in the morning, 4 h after a middle-of-the-night administration. The secondary objective was to investigate the effectiveness of zaleplon in promoting sleep in healthy volunteers with noise-induced sleep maintenance insomnia.

Methods Thirteen healthy male and female volunteers (aged 20–30 years) with normal hearing, who were sensitive to the sleep-disrupting effects of noise, participated in a double-blind, placebo- and active-drug controlled, four-period cross-over study. The subjects were permitted to sleep for 5 h (22.45–03.45 h) in a quiet environment before they were awoken. At 04.00 h they ingested 10 mg zaleplon, 20 mg zaleplon, 7.5 mg zopiclone (active control), or placebo before a second period of sleep (04.00–08.00 h), during which they were exposed to an 80 dB(A) 1 kHz pure tone pulse with an inter-tone interval of 1 s and a duration of 50 ms. The sound stimulus was stopped after 10 min of persistent sleep or after 2 h if the subject had not fallen asleep. Residual effects were assessed at 08.00 h (4 h after drug administration) using the digit symbol substitution test (DSST), choice reaction time (CRT), critical flicker fusion (CFF), and immediate and delayed free recall of a 20 word list. The data were analysed by analysis of variance. A Bonferroni adjustment was made for the three active treatments compared with placebo.

Results There were no residual effects of zaleplon (10 and 20 mg) compared with placebo. Zopiclone impaired memory by delaying the free recall of words ($P=0.001$) and attenuated performance on DSST ($P=0.004$) and CRT ($P=0.001$), compared with placebo. Zaleplon reduced the latency to persistent sleep (10 mg, $P=0.001$; 20 mg, $P=0.014$) and the 20 mg dose reduced stage 1 sleep ($P=0.012$) compared with placebo. Zopiclone reduced stage 1 sleep ($P=0.001$), increased stage 3 sleep ($P=0.0001$) and increased total sleep time ($P=0.003$), compared with placebo.

Conclusions Zaleplon (10 mg and 20 mg), administered in the middle of the night 4 h before arising, shortens sleep onset without impairing next-day performance.

Keywords: insomnia, noise, residual effects, sleep maintenance, zaleplon, zopiclone

Introduction

The pharmacokinetic profile of a hypnotic is a key factor in understanding its clinical usefulness. The rate of absorption determines a hypnotic's effectiveness in initiating sleep, while its duration of action depends upon the kinetics of absorption, distribution, and elimination. Indeed, the residual effects of a hypnotic upon next-day performance is an important aspect of its clinical profile, particularly in those individuals involved in skilled activity. Thus, the development of rapidly eliminated hypnotics that are free from residual effects and of accumulation upon repeated nightly ingestion is an area of continuing interest. The most rapidly eliminated hypnotic recently introduced into clinical practice is zaleplon, a pyrazolopyrimidine compound that binds selectively to the γ-aminobutyric acid $(GABA)_A$ receptor complex [1, 2]. It is rapidly absorbed, with peak plasma

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concentrations at around 1 h, and rapidly eliminated with a plasma elimination half-life of approximately 1 h [3, 4].

The pharmacokinetic properties of zaleplon indicate its potential usefulness for shortening sleep onset when there is difficulty falling asleep. Studies have shown a reduction in the latency to persistent sleep when zaleplon was given at bedtime to patients with sleep onset insomnia [5, 6] and when administered after an awakening in the middle of the night to patients with sleep maintenance insomnia [7]. The swift elimination of zaleplon means that it is unlikely to be followed by impairments in next-day performance after middle-of-the-night administration, and studies have reported freedom from residual effects when given 2 h before awakening [8]. Only one previous study has investigated both the hypnotic and residual effects of zaleplon, and so the present study was conducted to replicate these findings.

The subjects were healthy volunteers with situational middle-of-the-night insomnia, rather than patients with sleep maintenance insomnia, as in the previous study, which can be inconsistent in an experimental context [7]. The situational insomnia induced in the present study was achieved using a sound stimulus, a method that has been used previously to investigate the hypnotic properties of benzodiazepines and the hormone melatonin [9–15]. Since the sound stimulus used in these previous studies (traffic noise or continuous white noise) disturbed sleep, but did not prolong sleep latency *per se*, a pure tone pulse was used in the present study, as this has been shown to increase sleep latency [16].

Zopiclone was used as an active control to indicate the sensitivity of the experimental procedures. It is an established hypnotic with an elimination half-life of around 5 h, and would be expected to have residual effects on performance 4 h after administration [17].

Methods

Subjects

Thirteen healthy volunteers (six females, seven males) aged 20–30 (mean 22.2, s.d. 3.1) years were enrolled in the study. Their weight (range 49.8–85.5 kg; mean 69.0 kg, s.d. 11.0) was within 20% of the normal range for their height as determined by a nomograph. The subjects were non-smokers who consumed no more than five caffeinated beverages per day. They were not taking any medication except paracetamol and oral contraceptives (females only). Prior to the study, they underwent a physical examination, a medical history was taken and clinical laboratory tests were carried out, including a urinary drug screen (for opiates, barbiturates, benzodiazepines, cannabinoids, cocaine, amphetamine), a breath ethanol test, and audiometry. The inclusion and exclusion criteria ensured that only those subjects who were in good health took part in the study. A urinary drug screen and breath ethanol test were also carried out during the study on each night the subjects slept in the laboratory, except for the adaptation night. At the end of the study, the clinical laboratory tests were repeated. The subjects gave written informed consent to take part in the study, which was approved by the local Ethics Committee.

Procedures

The subjects were instructed to retire to bed no later than 23.00 h on the night at home preceding a night in the sleep laboratory and to refrain from drinking caffeinated beverages and alcohol for 24 h prior to attendance at the laboratory. Before the double-blind phase of the study, an adaptation night (from 23.00 h–07.00 h) in a single room was undertaken to familiarize each subject with the recording procedures and to establish whether their sleep patterns were normal. Only those subjects with normal sleep patterns were included in the next phase of the screening procedure. At least 4 days after the adaptation night, these subjects reported to the laboratory on two occasions separated by at least one night to determine whether they were sensitive to the sleep-disrupting effects of noise. On both of these occasions, after a 5 h sleep period (22.45–03.45 h) in a quiet environment, the subjects got up and completed a 4 min test of performance (the digit symbol substitution task). They returned to bed at 04.00 h and, after ingestion of placebo (administered single-blind), they were asked to fall asleep. On the first single-blind placebo night, there was no sound stimulus (the mean background noise level in the bedrooms was 36.8 dB(A)), while on the second single-blind placebo night the subjects were exposed to a pure tone pulse (described below). The sound stimulus was started at 04.00 h and a recordist monitored the electroencephalogram and determined the latency to persistent sleep (10 min of stage 2, 3, 4, or rapid eye movement (REM) sleep; methods described below). The sound stimulus was stopped either after persistent sleep had been reached, or after 2 h if the subject did not fall asleep. At 08.00 h, 4 h after drug ingestion, the subjects were awoken, if necessary, and they completed a battery of performance tasks and assessments of well-being (described below).

Only those subjects who had an increase of at least 10 min in the latency to persistent sleep (LPS) from the night without noise to the night with noise were included in the double-blind phase of the study. They subsequently reported to the laboratory on four occasions separated by a period of at least 4 nights. The experimental procedure was identical to the second single-blind placebo night, except that at 04.00 h, each subject was administered placebo, zaleplon 10 mg, zaleplon 20 mg, or zopiclone

7.5 mg, double-blind, on separate occasions according to a four-period randomized cross-over design.

Sound stimulus

The sound stimulus was an 80-dB(A) 1 kHz pure tone pulse with an inter-tone interval of 1 s, rise-decay times of 2.5 ms, and a duration of 50 ms. The sound stimulus was recorded onto a computer and replayed simultaneously into each bedroom via loudspeakers positioned 1 m behind the subject's head. Before each test night, a sound level meter was positioned at the subject's pillow in each bedroom and used to ensure that intended noise levels were replayed and that noise doses did not exceed those permitted by UK Health and Safety legislation.

Psychomotor performance and memory tests

Subjects were trained to plateau performance on all tests before the study began and were observed during the tasks by means of closed circuit television. The tests were presented in the following order: digit symbol substitution, immediate word recall, critical flicker fusion, choice reaction time and delayed word recall.

Digit symbol substitution Subjects were presented with one of a series of 30 sheets with 200 randomized digits (0–9) arranged in 10 rows on each side of the sheet [18]. In the space below each digit they were required to insert the appropriate symbol indicated by a code at the top of the page. Subjects were given 90 s to complete as many substitutions as possible, and the number of correct substitutions was recorded.

Critical flicker fusion Subjects observed four red light-emitting diodes held in foveal fixation at 1 m and were required to discriminate flicker from fusion as the frequency of the flickering diodes alternately increased or decreased. Individual fusion thresholds were determined using the mean of four ascending and four descending presentations on a Leeds Psychomotor Tester [19].

Choice reaction time Subjects were required to press a key corresponding to one of six equidistant red light-emitting diodes illuminated in a random sequence of 50 presentations, from a central starting position [19]. Recognition reaction time, motor reaction time and total reaction time were recorded using a Leeds Psychomotor Tester.

Immediate and delayed memory recall Subjects were given 2 min to memorize a list of 20 nouns. The number of correct words recalled in any order during a 2 min period immediately after presentation of the list (immediate free recall) and 30 min later (delayed free recall) were recorded.

Subjective assessments

Subjects completed the Leeds Analogue Rating Scale immediately upon waking [20]. Of 11 100 mm visual analogue scales, three related to assessments of sedation and eight were dummy scales. The subjects were instructed to consider the midpoint of each scale as their normal state.

Electroencephalography

The subjects slept in single light-proofed, sound-attenuated, and air-conditioned rooms. Silver-silver chloride electrodes were used to record electroencephalograph (EEG) activity from the O_1-A_2 and C_4-A_1 positions, together with bilateral electro-oculograms (EOG) and the submental electromyogram (EMG), on a Nicolet Biomedical Ultrasom (digital EEG) system via three Nihon-Koden 4300 series EEG machines. A simulated paper speed of 10 mm s^{-1} was used and each recording from the second period of sleep (04.00–08.00 h) was scored manually upon completion of the study into 30 s epochs according to the criteria of Rechtschaffen & Kales [21]. Various measures were derived from the data for subsequent statistical analysis.

Statistical methods

Estimates of variance from a previous study with a similar experimental design [8] were used to calculate the required sample size. The power calculation indicated that 12 subjects would be required to detect a difference in the digit symbol substitution task of 6.1 symbols with 80% power at the 5% significance level.

The data from 12 subjects who completed all four treatments were analysed by an analysis of variance (ANOVA) with subjects, period, treatment, and first order carry-over as factors in the model. First order carry-over was not significant, and was therefore removed from the ANOVAs and least squares means calculated. If the overall treatment effect in the ANOVA was significant, then linear pairwise comparisons were made which included the data from a 13th subject who completed three of the four treatments (described in the results). The primary pairwise comparisons were between each of the three drug treatments and placebo. A Bonferroni adjustment was made for the three active treatments compared with placebo. The 5%, 1% and 0.1% significance levels adjusted for multiple comparisons were: $P<0.0167$ (0.05/3); $P<0.0033$ (0.01/3); and $P<0.0003$ (0.001/3), respectively. Means and s.d. of raw data are given in the tables of results, though this may occasionally lead to apparent inconsistencies with the results of the analysis, which is based on within subject comparisons.

Results

Twelve of the 13 subjects enrolled in the study completed all four treatments. One subject was withdrawn from the study after the third drug treatment because drug treatments two and three had been administered in reverse order and therefore the order of treatment did not meet that specified by the randomization.

At 08.00 h, 4 h after drug ingestion, 11 of the 13 subjects required awakening after all treatments. One subject required awakening following all treatments except 10 mg zaleplon, while another subject was awoken on one occasion only, after 7.5 mg zopiclone.

No residual effects of zaleplon (10 and 20 mg) were found on psychomotor performance, memory, or subjectively assessed sedation. The active control, zopiclone (7.5 mg), impaired performance 4 h after ingestion on the digit symbol substitution task ($P=0.004$) and choice reaction time task ($P=0.001$), and reduced the number of words recalled on the delayed memory recall task ($P=0.001$), compared with placebo (Table 1). However, the subjects as a group did not report any change in sedation 4 h after zopiclone ingestion, compared with placebo.

The latency to persistent sleep was reduced by both doses of zaleplon (10 mg, $P=0.001$; 20 mg, $P=0.014$) and the duration of stage 1 (drowsy) sleep was reduced by the 20 mg dose ($P=0.012$), compared with placebo (Table 2). Zopiclone reduced stage 1 sleep ($P=0.001$), increased stage 3 sleep ($P=0.0001$) and increased total sleep time ($P=0.003$), compared with placebo.

No serious adverse events or discontinuations due to adverse events were reported during the study. The only treatment-emergent adverse event that was reported by more than one subject was a bitter after-taste with zopiclone ($n=5$ subjects, 38%).

Discussion

This study has confirmed previous findings that the therapeutic dose of zaleplon (10 mg), taken in the middle of the night, does not impair psychomotor performance the following day [7, 8]. Although one study has reported an impairment of memory (delayed free recall) following administration of zaleplon 3 h before awakening [22], the present study found no residual effects of zaleplon on memory 4 h after ingestion. Other investigators have reported that zaleplon is free from adverse effects on memory 2, 3, 4, and 5 h after nocturnal administration [8]. In the present study, the test measures were sufficiently sensitive to detect residual effects of the active control, zopiclone, upon psychomotor performance and memory, although the subjects as a group did not report sedation with zopiclone.

Table 1 Residual effects of zaleplon and zopiclone (4 h after ingestion) on performance, memory, and subjective sedation (means ± s.d.).

		Zopiclone	*Zaleplon*	
	Placebo	*7.5 mg*	*10 mg*	*20 mg*
Measure	*(n = 13)*	*(n = 13)*	*(n = 13)*	*(n = 12)*
Digit symbol substitution (Number of substitutions)	59.3 (8.9)	52.8 ± 9.8[a]	58.3 ± 12.0	55.6 ± 12.5
95% CI		−10.5, −2.1	−4.9, 3.5	−7.7, 0.9
Choice reaction time (ms)				
Recognition reaction time	344.3 ± 38.6	375.0 ± 47.3[b]	339.6 ± 35.2	347.8 ± 41.2
95% CI		11.9, 48.2	−22.6, 13.7	−20.0, 17.1
Motor reaction time	260.3 ± 64.3	292.8 ± 87.3[a]	257.0 ± 74.8	268.6 ± 77.1
95% CI		10.1, 51.0	−24.9, 16	−7.1, 34.8
Total reaction time	604.6 ± 68.9	667.8 ± 86.7[b]	596.6 ± 78.7	616.6 ± 98.0
95% CI		29.9, 91.3	−39.5, 21.8	−19.1, 43.8
Immediate word recall (Number correctly recalled)	14.8 ± 4.1	11.9 ± 4.2	13.3 ± 4.1	13.4 ± 4.5
95% CI		−5.0, −0.7	−3.6, 0.7	−4.1, 0.4
Delayed word recall (Number correctly recalled)	13.2 ± 4.8	7.9 ± 4.6[b]	11.0 ± 4.8	10.6 ± 5.6
95% CI		−7.6, −2.5	−4.5, 0.6	−5.5, −0.3
Critical flicker fusion (Hz)	29.9 ± 2.9	28.7 ± 2.0	30.0 ± 2.7	29.9 ± 3.3
95% CI		−2.2, −0.1	−0.9, 1.1	−1.1, 1.1
Subjective assessment of sedation (LARS[+])	61.9 ± 11.6	62.8 ± 12.0	64.4 ± 12.9	63.0 ± 15.0
95% CI		−6.1, 7.9	−4.3, 9.7	−6.0, 8.4

[a]$P<0.0167$, [b]$P<0.0033$ (the 5% and 1% significance levels, respectively, adjusted for multiple comparisons) compared with placebo.
[+]LARS: Leeds Analogue Rating Scale.
95% CI: Confidence interval of individual differences between placebo and each drug treatment.

Zaleplon (10 and 20 mg) was effective in reducing the latency to persistent sleep using a model of sleep maintenance insomnia in healthy volunteers. This model would appear to be a useful method of assessing the sleep-promoting properties of hypnotics following an early morning awakening. Although the model required the selection of noise-sensitive subjects, which increased the overall pre-study screening failure rate to approximately 50%, the use of a sound stimulus appears to be a more consistent method of delaying sleep onset than using patients with sleep maintenance insomnia [7]. The sleep-promoting properties of zaleplon were similar to those reported previously in patients with insomnia [5–7]. The present study found no change in the various stages of sleep with zaleplon, except for a reduction in drowsy (stage 1) sleep with the 20 mg dose, a finding that accords with the limited published data on effects of zaleplon on sleep architecture [6]. Zopiclone also reduced stage 1 sleep, in addition to increasing slow wave sleep (stage 3), an effect which has been reported previously in healthy subjects [23–25]. An increase in slow wave sleep has also been observed with zolpidem [25–27], which has a selectivity similar to zaleplon for the benzodiazepine type 1 receptor on the $GABA_A$ receptor complex [2, 28]. Whether the reported differential effect of zaleplon and zolpidem on slow wave sleep is related to a greater intrinsic activity of zolpidem is unknown. Further studies, which include a delta frequency analysis of the EEG, would be required to confirm any difference.

Zaleplon appears to be a useful hypnotic for individuals who experience difficulty in falling asleep either at bedtime or in the middle of the night, as it is free from

Table 2 Effect of zaleplon and zopiclone (ingested at 04.00 h) on various measures of sleep during exposure to a sound stimulus from the start of a second period (04.00 h–08.00 h) of nocturnal sleep (means ± s.d.).

		Zopiclone	*Zaleplon*	
	Placebo	*7.5 mg*	*10 mg*	*20 mg*
Measure	*(n = 13)*	*(n = 13)*	*(n = 13)*	*(n = 12)*
Latency to persistent sleep (min)	42.4 ± 21.1	33.5 ± 8.5	28.6 ± 13.2[b]	33.0 ± 12.8[a]
95% CI		−16.1, −1.3	−21.2, −6.4	−17.2, −2.1
Latency to REM[+] (min)	39.6 ± 11.3	52.8 ± 16.9	44.5 ± 13.7	46.6 ± 18.0
95% CI		0.1, 26.9	−8.2, 18.5	−5.9, 21.6
Total sleep time	189.2 ± 31.7	204.9 ± 8.6[b]	199.2 ± 14.9	200.2 ± 14.7
95% CI		5.6, 24.7	0.3, 19.4	1.6, 21.2
Number of awakenings	7.0 ± 3.0	5.0 ± 3.0	7.0 ± 4.0	7.0 ± 3.0
95% CI		−3.7, 0.1	−1.6, 2.2	−1.6, 2.2
Awake (min)	8.7 ± 9.4	4.0 ± 4.1	6.3 ± 5.2	6.0 ± 5.6
95% CI		−8.1, −1.1	−5.8, 1.2	−6.4, 0.8
Stage 1 (min)	20.8 ± 8.5	13.4 ± 6.1[b]	16.5 ± 6.4	16.5 ± 6.6[a]
95% CI		−10.8, −3.8	−7.8, −0.8	−8.3, −1.1
Stage 2 (min)	98.8 ± 20.7	110.5 ± 19.3	100.4 ± 20.8	97.5 ± 14.6
95% CI		−1.6, 24.3	−11.2, 14.6	−13.9, 12.6
Stage 3 (min)	7.8 ± 7.1	22.1 ± 13.6[b]	13.6 ± 8.7	17.5 ± 8.4
95% CI		6.6, 21.9	−1.9, 13.3	1.6, 17.2
Stage 4 (min)	0.4 ± 1.4	4.5 ± 8.1	5.5 ± 10.1	7.3 ± 7.6
95% CI		−1.9, 9.8	−1.1, 10.6	1.5, 13.5
REM[+] (min)	62.4 ± 18.6	54.4 ± 16.0	64.3 ± 14.7	61.5 ± 12.3
95% CI		−18.6, 2.3	−8.5, 12.3	−11.9, 9.5
Stage 1 (%)	11.0 ± 5.0	6.0 ± 3.0	8.0 ± 3.0	8.0 ± 3.0
95% CI		−6.2, −2.2	−4.6, −0.6	−4.8, −0.7
Stage 2 (%)	49.0 ± 7.0	53.0 ± 8.0	49.0 ± 9.0	47.0 ± 6.0
95% CI		−2.3, 9	−6.4, 4.9	−7.9, 3.8
Stage 3 (%)	4.0 ± 4.0	11.0 ± 7.0	7.0 ± 4.0	9.0 ± 4.0
95% CI		2.6, 10.3	−1.4, 6.3	0.3, 8.1
Stage 4 (%)	0.0 ± 1.0	2.0 ± 4.0	3.0 ± 5.0	4.0 ± 4.0
95% CI		−0.8, 4.9	−0.4, 5.3	0.8, 6.7
REM[+] (%)	31.0 ± 8.0	26.0 ± 8.0	31.0 ± 7.0	30.0 ± 5.0
95% CI		−9.7, 0.3	−4.6, 5.4	−6.4, 3.9

[a]$P < 0.0167$, [b]$P < 0.0033$ (the 5% and 1% significance levels, respectively, adjusted for multiple comparisons) compared with placebo.
[+]REM: Rapid eye movement sleep.

residual effects 4 h after ingestion. Such sleep problems may be common as a sleep survey in the United States found that 56% of respondents reported difficulty in falling asleep and 67% reported awakening in the middle of the night [29]. Many currently available hypnotics will sustain sleep and reduce the incidence of early morning awakenings if taken at bedtime. Given that the severity of an individual's sleep problem is likely to vary from night to night, a potential benefit of zaleplon may be a reduction in the requirement for nightly prophylactic use of hypnotic medication. This may avoid the phenomenon of rebound insomnia after cessation of prolonged treatment. Clearly, assessment of the nature of the insomnia would be essential and patients would need to be given guidelines on the use of such a short-acting hypnotic in order to avoid ingestion of unnecessarily large prophylactic doses in an attempt to sustain sleep.

Little information is currently available on the effectiveness of zaleplon in healthy volunteers with transient insomnia arising from transmeridian travel or shiftwork. The present study suggests that the drug is likely to be useful following a westward time zone change when individuals may experience an early morning awakening and are unable to return to sleep. Zaleplon may also be effective if used occasionally to promote sleep in those who have to rest at unusual times of the day, for example, in the early evening before a night shift. However, further work would be required to establish whether zaleplon is useful in the management of this type of transient insomnia in healthy individuals involved in skilled activity when residual effects are to be avoided.

In conclusion, the present study has shown that zaleplon (10 mg and 20 mg) is free from residual effects 4 h after ingestion in the middle of the night, and possesses hypnotic properties in a noise-induced sleep maintenance insomnia model in healthy subjects.

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