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Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem

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SUMMARY Gaboxadol is a selective extrasynaptic $GABA_A$ receptor agonist previously in development for the treatment of insomnia. Due to its short half-life (1.5–2 h) it is expected to be free from residual effects the next morning. The present study assessed the residual effects of evening and middle-of-the-night administration of 15 mg of gaboxadol on cognitive, psychomotor and driving performance. Twenty-eight healthy volunteers entered the study with 25 (12 women; mean age 31.4 years) completing a double-blind, placebo-controlled, active-referenced five-way cross-over study. Each treatment night subjects ingested one capsule at 23:00 hours and one at 04:00 hours. Treatments were placebo at both times, 15 mg gaboxadol or 7.5 mg zopiclone followed by placebo, and placebo followed by 15 mg gaboxadol or 10 mg zolpidem. Effects on cognition and psychomotor performance were assessed between 07:30 and 08:30 hours and on driving between 09:00 and 10:00 hours. Driving, as measured by standard deviation of lateral position in an on-the-road driving test, was almost significantly ($P < 0.07$) impaired after evening administration of gaboxadol for the all-subjects-completed set ($n = 25$) but significantly ($P < 0.05$) in the full analysis set ($n = 28$). Effects of all other active treatments on driving were significant. Evening administration of gaboxadol had minor effects on divided attention only, whereas middle-of-the-night administration impaired performance significantly in all tests except memory. Zolpidem and zopiclone impaired performance significantly in every test except tracking after zopiclone; 15 mg of gaboxadol can produce minor residual effects on driving after evening administration. Administration later at night is associated with moderately impairing residual effects on driving and psychomotor performance but not on memory.

KEYWORDS gaboxadol, hypnotics, on-the-road driving, residual effects, zolpidem, zopiclone

INTRODUCTION

Residual daytime sleepiness and impairment of psychomotor and cognitive functioning the day after bedtime administration is one of the main problems associated with the use of hypnotics (Vermeeren, 2004). This poses a crucial problem for users of hypnotics who must operate vehicles. Epidemiological studies have shown that the use of benzodiazepine hypnotics, as well as zopiclone, is associated with increased risk of injurious car accidents (Barbone *et al.*, 1998). In general, risks increase with dose and elimination half-life (Neutel, 1998).

Gaboxadol [4,5,6,7-tetrahydroisoxazolo (5,4-c) pyridin-3-ol, THIP] is a selective extrasynaptic γ-aminobutyric acid

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($GABA_A$) receptor agonist previously in development for the treatment of insomnia. It has a relatively high affinity for benzodiazepine-insensitive, $\alpha_4\beta_3\delta$- and $\alpha_6\beta_3\delta$-containing $GABA_A$ receptors, which are located extrasynaptically and seems to be involved in tonic GABAergic inhibition (Ebert *et al*., 2006; Lundahl *et al*., 2006; Storustovu and Ebert, 2006). Clinical studies (Deacon *et al*., 2005, 2007; Faulhaber *et al*., 1997; Lancel *et al*., 2001; Mathias *et al*., 2001, 2005; Walsh *et al*., 2007) have shown that gaboxadol in doses of between 5 and 20 mg improves subjective and objective measures of sleep significantly and dose dependently. It was found to decrease sleep latencies and to increase total sleep time in healthy young and elderly volunteers, and in patients with insomnia. The most frequently reported adverse events after a dose of 15 mg of gaboxadol were dizziness, abdominal pain, nausea, vomiting and dysmenorrhoea.

Most important with respect to the potential of gaboxadol to produce residual effects is that pharmacokinetic studies have shown that the drug is absorbed and eliminated rapidly. Peak plasma concentrations were found approximately 30 min after oral administration (Schultz *et al*., 1981) and the average elimination half-life ranged between 1.5 and 2 h (Lund *et al*., 2005). The majority of gaboxadol is excreted unchanged and a glucuronide conjugate of gaboxadol is the only metabolite formed in significant amounts (Lund *et al*., 2006). Gaboxadol's half-life falls between those of zaleplon (1 h) and zolpidem (2.5 h), both hypnotics that have been shown to be unlikely to produce residual effects on driving the morning after bedtime administration of their recommended doses (Vermeeren, 2004; Vermeeren *et al*., 1995, 1998, 2002; Verster *et al*., 2002, 2004). It may be expected, therefore, that residual effects after an evening dose of gaboxadol are absent the following morning.

Currently, three clinical trials have been published in which the residual effects of bedtime administration of gaboxadol were assessed and that support the expectations mentioned above (Lundahl *et al*., 2006; Mathias *et al*., 2005; Walsh *et al*., 2007). None of them found significant differences from placebo on cognitive functioning the next morning. A limitation of these studies is, however, that none of them included an adequate active control drug to demonstrate the sensitivity of the procedures to detect residual effects on performance. Although 10 mg of zolpidem is adequate for comparison of efficacies, it is unlikely to produce any residual effects more than 9 h after bedtime administration (cf. Swainston Harrison and Keating, 2005; Vermeeren, 2004). In addition, the tests used were all of short duration and none of them used tests which could be extrapolated to driving performance.

The primary objective of the present study was to evaluate the residual effects of single oral doses of 15 mg of gaboxadol ingested at bedtime and in the middle of the night on driving performance the next morning, using an on-the-road driving test. Effects were to be compared with those of placebo. A secondary objective was to compare these drugs' residual effects with those of placebo on memory and psychomotor functioning, and subjective alertness. Zopiclone (7.5 mg) was selected as an active control for the bedtime dose of gaboxadol, because it was found repeatedly to have moderately impairing effects on driving the morning after bedtime administration (Vermeeren *et al*., 1998, 2002). However, Zopiclone's effects on driving the morning after a middle-of-the-night dose are known to be severe (Vermeeren *et al*., 1998). Therefore, 10 mg of zolpidem was selected as an active control for the middle-of-the-night dose of gaboxadol, because its effects on driving were previously found to be significant, but much milder than those of zopiclone after middle-of-the-night administration (Verster *et al*., 2002).

METHODS

Subjects

Twenty-eight healthy male and female volunteers (ages 22–44 years) without sleep complaints were recruited by means of advertisements in local newspapers. Volunteers were screened by a medical history questionnaire and physical examination. The latter included blood haematology and chemistry, urinalysis, drug and pregnancy tests and a 12-lead electrocardiogram. For participation, the following criteria had to be met: absence of any medical, endocrine, neurological or psychiatric condition, body mass index (BMI) between 19 and 29 kg m^{-2}, normal vision (corrected or uncorrected) possession of a valid driving licence for more than 3 years and average driving experience of at least 5000 km $year^{-1}$ and, if female, using an accepted method of contraception or surgically sterilized and not pregnant or breastfeeding.

Subjects were excluded by the following criteria: pregnant or breastfeeding, alcohol use of more than 21 or 14 alcohol-containing beverages per week for men and women, respectively, smoking more than 10 cigarettes per day, use of anxiolytics or antidepressants in the last 6 months, donation of blood or treatment with any investigational product within the last 3 months, or use of any disallowed medicines or drugs of abuse within 2 weeks prior to first dosing.

During participation in the study, use of caffeine had to be less than seven cups of coffee per day and was prohibited from 4 h prior to arrival on treatment days, until discharge the next morning. Alcohol intake was not allowed from 48 h prior to each dosing until discharge. Smoking was prohibited from arrival until discharge and eating was not permitted from arrival until breakfast. Finally, subjects were required to abstain from strenuous exercise from 24 h before dosing until discharge.

A total of 25 subjects (13 men, 12 women) completed the study. Their mean ± standard deviation (SD) age was 31.4 ± 7.5 years and their mean ± SD BMI was 23.3 ± 2.5 kg m^{-2}. Two participants were withdrawn from the study after the third treatment period, and one after the fourth treatment period, due to protocol deviations.

The study was conducted in accordance with the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and amended in Edinburgh (2000). The protocol was approved by

the Medical Ethics Committee of Maastricht University and University Hospital of Maastricht. The aims, methods and potential hazards of the study were explained to the participants, who signed a written informed consent prior to any study-related assessments.

Design

The study was conducted according to a double-blind, five-way cross-over design. Treatments were 15 mg of gaboxadol administered in the evening and middle of the night, 7.5 mg of zopiclone administered in the evening, 10 mg of zolpidem administered in the middle of the night and placebo. Evening drug administration (23:00 hours) was followed by placebo middle-of-the-night administration (04:00 hours) and vice versa or placebo at both times. Treatments were administered in identical-appearing capsules. Treatments were balanced over periods by assigning randomly five treatment sequences to the first 25 subjects.

Assessments

Residual effects were assessed using a highway driving test, a battery of laboratory tests measuring skills related to driving, memory and postural stability and subjective rating scales. All the tests have been found previously to be sensitive to the residual effects of hypnotics (Vermeeren, 2004; Vermeeren *et al*., 1995, 1998, 2002; Verster *et al*., 2002) and low doses of alcohol (Ramaekers *et al*., 1996; Vermeeren *et al*., 2002).

In the standardized highway driving test (O'Hanlon, 1984), the subject operates a specially instrumented vehicle over a 100-km (61-mile) primary highway circuit, accompanied by a licensed driving instructor having access to dual controls. The subject's task is to maintain a constant speed of 95 km h^{-1} (58 miles h^{-1}) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle speed and lateral position are recorded continuously. These signals are edited off-line to remove data recorded during overtaking manoeuvres or disturbances caused by roadway or traffic situations. The remaining data are then used to calculate mean values and standard deviation of lateral position (SDLP) and speed (SDSP). SDLP (in cm) is the primary outcome variable. SDLP is a measure of road tracking error, or 'weaving'. The test duration is approximately 1 h.

The critical tracking test (CTT) measures the ability to control an unstable error signal in a first-order compensatory tracking task (Jex *et al*., 1966). Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Subjects use a joystick to null the error by returning the cursor to the midpoint. The frequency at which the subject loses the control is the critical frequency, or lambda (λ_c), in rad s^{-1}. The final score is determined from the average of all but the lowest and highest scores in five trials.

The divided attention task measures the ability to divide attention between two simultaneously performed tasks (Moskowitz, 1973). In the primary task, the subject performs the same tracking task described above, yet at a constant level of difficulty set at 50% of his or her maximum capacity. In the secondary task, the subject monitors 24 peripheral displays in which single digits change asynchronously at 5-s intervals. Subjects are instructed to remove their foot from a pedal as rapidly as possible whenever the digit '2' appears. This signal occurs twice at every location, in random order, at intervals of 5–25 s. Tracking error (in mm) and average reaction time (in ms) are the respective performance measures.

The digit symbol substitution test (DSST) measures processing speed and working memory. It is a computerized version of the original paper-and-pencil test taken from the Wechsler Adult Intelligence Scale. The subject is shown briefly an encoding scheme consisting of a row of squares at the top of the screen, wherein nine digits are associated randomly with particular symbols. The same symbols are presented in a fixed sequence at the bottom of the screen as a row of separate response buttons. The encoding scheme and the response buttons remain visible while the subject is shown successive presentations of a single digit at the centre of the screen. The subject is required to match each digit with a symbol from the encoding list as rapidly as possible by clicking the corresponding response button, using the mouse. The number of digits encoded correctly within 3 min is the performance measure.

In the word learning test (Rey, 1964), measuring verbal memory, a sequence of 15 monosyllabic nouns is shown on a computer display at a rate of one per 2 s. Immediately thereafter the subject is required to recall verbally as many words as possible. The sequence is repeated in four more trials, and the highest separate trial score is the immediate recall score. After a delay of at least 30 min the subject is again required to recall as many words as possible without prompting. The total number of words correctly recalled is the delayed recall score. Finally, the subject is shown a sequence of 30 words on the computer display, including 15 words from the original set and 15 new words in random order. The subject has to indicate as quickly as possible whether or not a word originates from the original set by pressing a corresponding button. The number and speed of correct responses are recorded as the recognition score and the recognition reaction time (in ms) respectively.

Body sway was measured using the stabilometry method of the International Society of Posturography (Kapteyn *et al*., 1983). The subjects stand on a force platform for 60 s with the feet open at an angle of approximately 30°, first with their eyes open and fixed on a target 2 m away and then with their eyes closed. The system (Electropostugraph; ELP, Brussels, Belgium) calculates the momentary vector of force extending downward from the centre of gravity of the body and its movement around the vertical axis over time. Two related parameters are measured during both the eyes open and eyes closed recording epochs, i.e. the length of the vector's path (POS-L1 for eyes open and POS-L2 for eyes closed, in mm) and the area or surface circumscribed by the vector (POS-S1 for eyes open and POS-S2 for eyes closed, in mm^2).

Subjective evaluations of mood, sedation and driving quality were assessed using a series of Visual Analogue Scales (100 mm). The subjects were instructed to rate their subjective feelings using a 16-item mood scale which provides three-factor analytically defined summary scores for 'alertness', 'contentedness' and 'calmness' (Bond and Lader, 1974). The driving instructor rated each subject's driving quality and apparent sedation at the conclusion of each driving test, using two 100-mm Visual Analogue Scales.

Subjective evaluations of sleep quality and duration were assessed using the Groningen Sleep Quality Questionnaire (Mulder-Hajonides Van Der Meulen, 1981) and an estimate of total sleep time. Two questions concerning nocturnal awakenings in the Groningen Sleep Quality Questionnaire were omitted due to the forced awakening at 04:00 hours. Total scores on the sleep quality questionnaire could range between 0 (no complaints) and 12 (maximum number of complaints).

Procedure

Subjects were trained individually to perform the driving and laboratory tests. One week before the first treatment period subjects slept in the same facilities as during treatment periods, to overcome possible sleep disturbances associated with sleeping in an unfamiliar environment. On the morning following this habituation night subjects rehearsed all tests including driving.

Treatment periods started in the evening of day 1, when the subjects arrived at the site at approximately 20:00 hours, and lasted until day 2, when they were transported home after the driving test, at approximately 10:15 hours. On arrival at the sleeping facility in each treatment period, subjects' eligibility was verified. They were questioned about adverse events and use of medication since their last visit, and about recent use of coffee, alcohol and food. Vital signs were recorded, breath was assayed for alcohol using a breath analyser (Lion Alcolmeter SD-400; Lion Laboratories Limited, Vale of Glamorgan, UK) and urine was assayed for presence of drugs (Triage 8 Panel Drugs of Abuse; Biosite Diagnostics, San Diego, CA, USA). Pregnancy tests were performed for all women. Subjects ingested the first part of their medication at 23:00 hours and retired to bed. After a wake-up call, the subjects ingested the second part of their medication at 04:00 hours and were instructed to resume sleeping. They were awakened again by telephone 3 h later at 07:00 hours, and instructed to get dressed and to prepare for vital signs recording. Between 07:30 and 08:15 hours subjects performed cognitive and psychomotor tests and rated their subjective feelings and sleep. Driving performance was assessed between 09:00 and 10:00 hours, i.e. 10–11 h after ingestion of the evening dose, and between 5 and 6 h after ingestion of the middle-of-the-night dose. Upon completion of the driving test instructors rated subjects' driving quality and their appearance of being sedated.

Statistical analyses

Sample size was based on a power calculation for detecting a minimum treatment difference of 2.0 cm on SDLP with at least 90% power, using a two-sided *t*-test at a significance level of 5%, and assuming a within-subject SD of 2.1 cm, as estimated in previous studies conducted by the Maastricht University research group (Vermeeren, 2004). A treatment difference of 2.4 cm in SDLP was considered to be clinically relevant, as it corresponds to the effects found for alcohol, while mean blood alcohol concentration (BAC) was 0.5 mg mL^{-1} in a group of social drinkers using the same driving test (Louwerens *et al.*, 1987).

Pharmacodynamic parameters from the road tracking test and other psychomotor and cognitive tests were analysed by a mixed model analysis of variance (ANOVA) with fixed factors of treatment, sequence and period, and a random effect of subject within sequence using the SAS statistical program (version 8.2; SAS Institute Inc., Cary, NC, USA). To determine the presence of residual effects, four *a priori* drug–placebo contrasts were made using the least square means procedure.

Analyses of residual effects were performed on the full analysis set (FAS) and the all-subjects-completed set (ASCS), as described in a predefined analysis plan. The FAS consisted of 28 subjects who had received at least one dose of double-blind medication and had at least one valid postdosing assessment of the SDLP. As a total of three subjects (10.7%) were withdrawn from the FAS, the analysis was repeated using the 25 subjects who completed the study without protocol deviations (ASCS). Results of residual effects presented in this paper are based on the ASCS analyses. FAS analyses are reported only in the case of diverging results. Descriptive summary statistics presented of adverse events were calculated based on the FAS.

RESULTS

Table 1 shows mean ± standard error (SE) values for each performance parameter and subjective evaluations in each treatment condition. Table 2 presents the mean differences from placebo and 95% confidence intervals of each treatment condition for the performance parameters and subjective evaluations.

Highway driving test

Six driving tests performed by a total of four subjects (16% relative to 25 subjects comprising the ASCS) were terminated prematurely because the driving instructor judged the subject to be too drowsy to continue safely. It appeared subsequently that five of the tests were terminated following middle-of-the night administration of an active hypnotic drug (10% relative to 50 driving tests). Three subjects were stopped before scheduled completion of the test after middle-of-the-night administration of gaboxadol. After middle-of-the-night administration of zolpidem, one subject was stopped and another, whose test was also terminated prematurely after middle-of-the-night administration of gaboxadol, did not start the driving test after middle-of-the-night administration of zolpidem, due to drug-related adverse events (dizziness, nausea

Table 1 Mean (±standard error) of performance and mood parameters in each treatment condition ($n = 25$)

	Placebo	*Gaboxadol evening*	*Zopiclone evening*	*Gaboxadol night*	*Zolpidem night*
Driving test					
Prematurely terminated, *n*	0	1	0	3	2
SDLP (cm)	17.79 (0.57)	19.07 (0.78)	20.32 (0.66)	20.52 (0.93)	21.09 (0.84)
SDSP (km h^{-1})	1.66 (0.09)	1.92 (0.10)	1.91 (0.09)	1.90 (0.13)	1.91 (0.12)
Critical tracking test					
Critical frequency (rad s^{-1})	3.94 (0.14)	3.87 (0.12)	3.82 (0.14)	3.65 (0.19)	3.51 (0.14)
Divided attention test					
Average tracking error (mm)	15.87 (0.87)	17.30 (0.81)	18.37 (0.80)	19.71 (0.86)	20.03 (0.91)
Target detection reaction time (ms)	1745 (64)	1850 (73)	1869 (76)	1929 (65)	1929 (58)
Digit symbol substitution test					
Correct encodings, *n*	80.4 (2.6)	80.2 (2.2)	77.2 (2.3)	76.6 (2.4)	73.9 (2.3)
Word learning test					
Immediate recall score, *n*	13.4 (0.4)	13.5 (0.3)	13.2 (0.4)	13.2 (0.4)	12.7 (0.4)
Delayed recall score, *n*	11.0 (0.7)	11.1 (0.6)	9.7 (0.7)	10.3 (0.7)	8.7 (0.6)
Recognition score, *n*	28.6 (0.3)	28.2 (0.3)	27.0 (0.5)	27.8 (0.5)	27.4 (0.4)
Recognition reaction time (ms)	716 (20)	751 (21)	802 (27)	756 (26)	809 (25)
Body sway					
Eyes open: vector length (mm)	351 (9.7)	356 (11.7)	384 (14.4)	377 (14.3)	391 (16.6)
Eyes open: vector surface (mm^2)	104 (14.5)	111 (12.9)	144 (16.8)	145 (21.2)	182 (28.0)
Eyes closed: vector length (mm)	355 (10.7)	355 (12.3)	356 (12.8)	390 (15.5)	386 (16.3)
Eyes closed: vector surface (mm^2)	84 (7.5)	82 (7.9)	103 (10.9)	148 (18.3)	164 (36.2)
Subjective evaluation					
Alertness	69.9 (3.5)	67.0 (3.5)	66.7 (3.1)	46.6 (4.4)	53.5 (3.9)
Contentedness	75.2 (3.2)	75.2 (2.7)	76.4 (2.6)	67.9 (3.4)	69.4 (2.8)
Calmness	77.3 (3.3)	81.2 (2.6)	80.8 (2.4)	76.2 (3.3)	74.8 (2.4)
Driving quality	80.5 (1.5)	73.4 (2.0)	72.4 (2.3)	68.2 (3.4)	71.9 (2.4)
Sedation	11.1 (2.5)	21.4 (3.9)	23.1 (4.5)	34.9 (5.7)	29.1 (5.6)

SDLP, standard deviation of lateral position; SDSP, standard deviation of speed.

and vomiting). In addition, the latter subject did not complete the test following evening administration of gaboxadol. The SDLP scores were calculated from the data collected until termination of each ride. None of the subjects was stopped prematurely following placebo or zopiclone administration.

Overall analysis of SDLP showed that there were significant differences in treatment effects ($F_{4,91} = 7.55, P < 0.001$). Mean increases in SDLP compared with placebo were +1.28, +2.53, +2.73 and +3.46 cm for evening administration of gaboxadol and zopiclone and middle-of-the-night administration of gaboxadol and zolpidem respectively (Fig. 1).

Drug–placebo comparisons showed that these increases were significant for all treatments ($P \leq 0.001$) except for the smallest, i.e. evening administration of gaboxadol ($P < 0.070$). The latter effect was significant, however, according to analyses of the FAS (+1.40 cm; $P = 0.0422$). For the remaining treatments, results based on the FAS were similar to those based on the ASCS.

The ability to keep a constant speed, as measured by SDSP, differed significantly between treatments ($F_{4,91} = 4.11$, $P = 0.0042$). The variability in speed was increased significantly following all hypnotics compared with placebo (all $P < 0.004$).

Critical tracking test

A significant overall treatment effect was found in tracking performance, as measured by the average critical frequency ($F_{4,92} = 6.37$, $P < 0.0001$). Drug–placebo comparisons revealed that this was due to significant impairment after middle-of-the-night administration of gaboxadol and zolpidem ($P = 0.0040$ and $P < 0.0001$ respectively).

Divided attention test

There were significant differences between treatments in both subtasks of the divided attention task (tracking: $F_{4,92} = 13.52$, $P < 0.0001$ and target detection: $F_{4,92} = 3.42$, $P = 0.0119$). Drug–placebo comparisons revealed that tracking error and target detection reaction times were increased significantly after middle-of-the-night administration of zolpidem and gaboxadol ($P < 0.0001$ for both treatments in tracking error and $P < 0.002$ for both treatments in target detection) and evening administration of zopiclone ($P = 0.0003$ and $P = 0.0351$ respectively). Following evening administration of gaboxadol, tracking performance was impaired significantly ($P = 0.0333$), but not speed of target detection ($P < 0.075$). The latter was impaired significantly, however, according to analyses of the FAS ($P = 0.0346$).

Digit symbol substitution test

The total number of correct encodings in the DSST differed significantly between treatments ($F_{4,92} = 8.62$, $P < 0.0001$).

Table 2 Mean difference and 95% confidence interval from placebo for each treatment condition ($n = 25$)

	Gaboxadol evening		*Zopiclone evening*		*Gaboxadol night*		*Zolpidem night*	
	Δ	*95% CI*	Δ	*95% CI*	Δ	*95% CI*	Δ	*95% CI*
Driving test								
SDLP (cm)	+1.28	−0.10 to 2.67	+2.53	1.14 to 3.91***	+2.73	1.34 to 4.11***	+3.46	2.06 to 4.86***
SDSP (km h^{-1})	+0.25	0.10 to 0.41**	+0.25	0.10 to 0.41**	+0.24	0.08 to 0.39**	+0.26	0.10 to 0.41**
Critical tracking test								
Critical frequency (rad s^{-1})	−0.07	−0.27 to 0.12	−0.12	−0.31 to 0.08	−0.29	−0.48 to −0.09**	−0.42	−0.31 to −0.08***
Divided attention test								
Average tracking error (mm)	+1.43	0.12 to 2.75*	+2.51	1.19 to 3.82***	+3.85	2.53 to 5.17***	+4.16	2.84 to 5.48***
Target detection reaction time (ms)	+105	−10 to 219	+123	9 to 238*	+184	69 to 299**	+184	69 to 298**
Digit symbol substitution test								
Correct encodings, *n*	−0.2	−2.8 to −2.4	−3.2	−5.8 to −0.6*	−3.8	−6.4 to −1.2**	−6.5	−9.1 to −3.9***
Word learning test								
Immediate recall score, *n*	+0.1	−0.5 to 0.8	−0.1	−0.8 to 0.5	−0.2	−0.8 to 0.5	−0.7	−1.3 to 0.0*
Delayed recall score, *n*	+0.1	−1.0 to 1.2	−1.3	−2.4 to −0.3*	−0.7	−1.8 to 0.4	−2.28	−3.4 to −1.2***
Recognition score, *n*	−0.4	−1.3 to 0.5	−1.6	−2.5 to −0.7***	−0.7	−1.6 to 0.2	−1.2	−2.1 to −0.3*
Recognition reaction time (ms)	+35	−9 to 78	+86	42 to 129***	+40	−4 to 83	+93	49 to 136***
Body sway								
Eyes open: vector length (mm)	+5	−19 to 29	+34	9 to 58*	+27	3 to 51*	+40	16 to 65**
Eyes open: vector surface (mm^2)	+7	−25 to 39	+40	8 to 71*	+41	9 to 73*	+78	46 to 110***
Eyes closed: vector length (mm)	0	−27 to 28	+1	−27 to 28	+35	8 to 63*	+32	4 to 59*
Eyes closed: vector surface (mm^2)	−3	−46 to 39	+19	−24 to 61	+63	21 to 106**	+79	37 to 122***
Subjective evaluation								
Alertness	−2.9	−11.1 to 5.3	−3.2	−11.3 to 5.0	−23.2	−31.4 to −15.1***	–	−24.5 to −8.2***
Contentedness	0.0	−5.0 to 5.0	+1.2	−3.8 to 6.2	−7.3	−12.3 to −2.3**	−5.8	−10.8 to −0.8*
Calmness	+3.9	−0.2 to 8.0	+3.5	−0.6 to 7.6	−1.1	−5.2 to 3.0	−2.6	−6.6 to 1.5
Driving quality	−7.1	−12.7 to −1.5*	−8.2	−13.8 to −2.5**	−12.4	−18.0 to −6.8***	−9.5	−15.2 to −3.8**
Sedation	+103	−0.3 to −20.8	+120	1.5 to 22.6*	+238	13.2 to 34.4***	+186	7.9 to 29.4***

Significant differences from placebo: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. SDLP, standard deviation of lateral position; SDSP, standard deviation of speed.

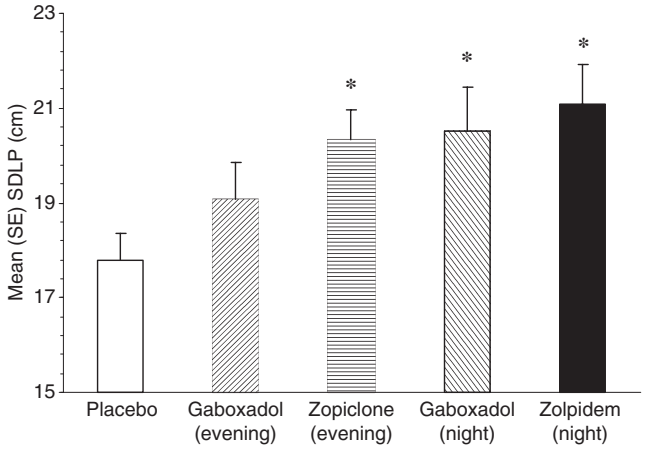

Figure 1. Mean ± standard error of the standard deviation of lateral position (SDLP) in each treatment condition. Indicated are significant drug–placebo differences ($P < 0.001$).

Compared with placebo, the number of correct encodings was decreased significantly after middle-of-the-night administration of zolpidem and gaboxadol ($P < 0.0001$ and $P = 0.0047$ respectively) and evening administration of zopiclone ($P = 0.0153$). No significant effect was found after evening administration of gaboxadol.

Word learning test

Whereas there were no significant differences between treatments in immediate recall scores ($F_{4,92} = 1.83$, $P > 0.1$), analyses revealed highly significant treatment effects in delayed recall scores ($F_{4,92} = 6.65$, $P < 0.0001$), recognition scores ($F_{4,92} = 3.89$, $P < 0.0058$) and recognition reaction times ($F_{4,92} = 6.21$, $P = 0.0002$). Both active controls, but not gaboxadol, had significant impairing effects on memory performance. Compared with placebo, evening administration of zopiclone and middle-of-the-night administration of zolpidem resulted in lower delayed recall scores ($P = 0.0163$ and $P < 0.0001$ respectively), fewer words recognized correctly ($P = 0.0007$ and $P < 0.0123$ respectively) and slower responses (both $P < 0.0002$).

Body sway

Analysis of postural stability revealed significant overall treatment effects on length and surface of the body sway vector with eyes open (POS-L1, $F_{4,92} = 4.25$, $P < 0.0033$; and POS-S1, $F_{4,92} = 7.66$, $P < 0.0001$ respectively) and eyes closed (POS-L2: $F_{4,92} = 3.40$, $P = 0.0122$; and POS-S2: $F_{4,92} = 6.16$, $P = 0.0002$ respectively).

Drug–placebo analyses showed that all active treatments, except evening administration of gaboxadol, impaired postural stability significantly. Gaboxadol affected all parameters significantly when administered in the middle of the night (POS-L1: $P = 0.0289$; POS-S1: $P = 0.0116$; POS-L2: $P = 0.0130$; POS-S2: $P = 0.0039$), whereas no effects were found after administration in the evening at bedtime. Middle-of-the-night administration of zolpidem affected all parameters significantly (POS-L1: $P = 0.0013$; POS-S1: $P < 0.0001$; POS-L2: $P = 0.0252$; and POS-S2: $P = 0.0004$). Evening administration of zopiclone had significant effects on body sway with eyes open (POS-L1: $P = 0.0071$ and POS-S1: $P = 0.0153$) but not on sway with eyes closed.

Subjective evaluations

The driving instructors' ratings of subjects' driving quality and their appearance of being sedated differed significantly between treatments ($F_{4,91} = 5.27$, $P = 0.0007$; $F_{4,91} = 5.73$, $P = 0.0004$). They rated driving quality to be significantly worse than that of placebo following all hypnotics, i.e. evening administration of gaboxadol and zopiclone ($P = 0.0135$ and $P = 0.0048$ respectively) and middle-of-the-night administration of gaboxadol and zolpidem ($P < 0.0001$ and $P < 0.0013$ respectively). In addition, instructors rated subjects to appear clearly more sedated after middle-of-the-night administration of gaboxadol and zolpidem and after evening administration of zopiclone compared with placebo ($P < 0.0001$, $P = 0.0008$ and $P = 0.0260$ respectively). The difference between evening administration of gaboxadol and placebo just failed to reach significance according to ASCS analysis ($P < 0.057$) but was significant according to FAS analysis ($P = 0.0271$).

The subjects' ratings of their feelings of alertness and contentedness were significantly different between treatments ($F_{4,92} = 12.09$, $P < 0.0001$; $F_{4,92} = 4.70$, $P = 0.0017$ respectively). They rated themselves as less alert and contented than placebo after the middle-of-the-night administrations of gaboxadol ($P < 0.0001$ and $P = 0.0046$ respectively) and zolpidem ($P = 0.0001$, and $P = 0.0237$ respectively). Evening administration of gaboxadol and zopiclone had no significant effects on subjective feelings. A significant overall treatment effect on calmness was found ($F_{4,92} = 3.8$, $P = 0.0067$), but ratings did not differ significantly between drugs and placebo.

Subjective sleep quality and estimated total sleep times differed significantly between treatments ($F_{4,92} = 4.41$ and 3.67, $P = 0.0026$ and 0.0080 respectively). The mean ± SE number of complaints decreased significantly from 4.3 ± 0.8 after placebo to 2.4 ± 0.4 and 2.0 ± 0.3 after evening administration of gaboxadol ($P = 0.011$) and zopiclone ($P = 0.002$) respectively. No significant differences were found between placebo and the two middle-of-the-night treatments. Mean ± SE estimated that total sleep time increased from 402 ± 14 min after placebo to 445 ± 8 and 454 ± 5 min after evening doses of gaboxadol ($P = 0.0008$) and zopiclone ($P < 0.0001$) and to 422 ± 12 and 435 ± 8 min after middle-of-the-night administrations of gaboxadol ($P = 0.113$) and zolpidem ($P = 0.0086$) respectively.

Safety

An overview of the incidence of reported adverse events is shown in Table 3. There were no serious adverse events.

Table 3 Incidence of reported adverse events

	All treatments (n = 28)	*Placebo (n = 28)*	*Gaboxadol evening (n = 27)*	*Zopiclone evening (n = 28)*	*Gaboxadol night (n = 26)*	*Zolpidem night (n = 26)*
Dizziness	10 (36)	0	0	1 (4)	9 (35)	4 (14)
Headache	7 (25)	1 (4)	4 (15)	3 (12)	1 (4)	1 (4)
Somnolence	6 (21)	0	3 (11)	0	3 (12)	1 (4)
Nausea	5 (18)	0	0	0	5 (19)	3 (11)
Abnormal coordination	2 (7)	0	0	0	2 (8)	0
Dysguesia	2 (7)	1 (4)	0	0	0	1 (4)
Fatigue	2 (7)	0	1 (4)	0	1 (4)	0
Mental impairment	2 (7)	0	1 (4)	0	1 (4)	0
Vomiting	2 (7)	0	1 (4)	0	1 (4)	2 (7)

Values in parentheses are percentage.

Overall, the most frequently reported adverse events in this study were dizziness, headache, somnolence and nausea. The highest number of complaints occurred after the middle-of-the-night administrations of both gaboxadol and zolpidem. After evening administration of gaboxadol the highest incidence of reported adverse events were headaches and somnolence, and after evening administration of zopiclone only headaches were reported. All adverse events were mild or moderate and resolved without treatment.

DISCUSSION

The results of this study show that 15 mg of gaboxadol administered at bedtime can have residual effects until at least 11 h after intake, as shown by significant or almost significant effects on performance in the driving test and the divided attention test. The use of 15 mg of gaboxadol in the middle of the night was associated clearly with residual effects on driving, as reflected by a significant increase in SDLP and psychomotor performance but not on memory. The middle-of-the-night dose of gaboxadol impaired performance significantly in all tests between 3.5 and 6 h after intake, except the word learning test.

Results of the driving test are most relevant with respect to traffic safety; 15 mg of gaboxadol produced a nearly significant +1.3 cm mean increase in SDLP above the placebo level, between 10 and 11 h after evening administration ($P < 0.070$), which was significant ($P < 0.042$) based upon analyses of the FAS. The severity of the effect, however, is on average of lesser magnitude than that produced by alcohol in a previous study while subjects drove with BACs of 0.5 mg mL^{-1} (+2.4 cm) (Louwerens *et al.*, 1987), which is the legal limit for driving a car in most countries. Nevertheless, analyses with the same set showed that driving instructors were capable of judging the subjects to be significantly more sedated after this dose compared with placebo. Furthermore, one subject was stopped by the driving instructor due to excessive drowsiness following the evening dose of gaboxadol, and subjects drove with significantly more variability in speed following gaboxadol compared with that of placebo (+0.25 km h^{-1}).

In addition to the effects on driving performance, the evening dose of gaboxadol was also found to have minor but significant effects on performance in the divided attention test. These effects were unexpected, as three previous studies did not find significant residual effects of gaboxadol in doses up to 20 mg administered at bedtime (Lundahl *et al.*, 2006; Mathias *et al.*, 2005; Walsh *et al.*, 2007). The discrepancy may be explained partly by the tests used. Similar to previous findings, evening doses of gaboxadol in the present study had no significant residual effects on performance in relatively short psychomotor tests (critical tracking, digit symbol substitution and body sway) and the memory test. The standardized highway driving test and the divided attention test have been found to be among the most sensitive tests to assess drug-induced sedation (e.g. Vermeeren *et al.*, 2002), probably because they are tests of longer duration and continuous high attentional demands. *Post hoc* inspection of mean SDLP scores per 15-min intervals of the test showed that performance after an evening dose of gaboxadol was similar to placebo during the first 15-min interval, but started to decline thereafter. This suggests that these effects may be counteracted by a temporary increase in effort. As effort can be increased for only a limited period of time, performance decreases thereafter (Sanders, 1983). For this reason shorter tests, as used in previous studies, may have failed to show residual effects of bedtime doses of gaboxadol. Following evening administration of zopiclone and middle-of-the-night doses of gaboxadol and zolpidem, impairment was already present during the first interval and did not increase further with time on task, suggesting that increased effort could not compensate the residual effects of these treatments.

Middle-of-the-night administration of 15 mg of gaboxadol produced a significant +2.7 cm mean increase in SDLP above the placebo level, between 5 and 6 h after administration. This effect is of greater magnitude than that produced by alcohol while subjects drove with BACs of 0.5 mg mL^{-1} (Louwerens *et al.*, 1987). In addition, the driving instructor terminated three tests prematurely due to excessive drowsiness of the subjects.

Middle-of-the-night dose of 10 mg of zolpidem impaired performance significantly in all tests the following morning. One subject did not start the driving test due to dizziness and nausea, and another was stopped prematurely by the driving instructor due to excessive drowsiness following this dose. The mean increase in SDLP between 5 and 6 h after administration was +3.5 cm. This corresponds closely to the increase in SDLP of +3.8 cm found between 4 and 5 h after the middle-of-the-night administration of the same dose in a study with 30 healthy volunteers by (Verster *et al*., 2002). These investigators did not find significant effects of 10 mg of zolpidem on word learning, critical tracking, divided attention and DSST performance, however, due probably to the later time of testing. Laboratory testing in their study started at 6 h after administration, whereas it started at 4.5 h after administration in the present study. The results of the present study confirm the importance of instructing patients to ingest 10 mg of zolpidem only prior to a full 8 h of uninterrupted sleep and not in the middle of the night (cf. Verster *et al*., 2007).

The evening dose of 7.5 mg of zopiclone had significant residual effects on driving, body sway, word learning, DSST and divided attention, but not on tracking performance. The average increase in SDLP (+2.53) found in the present study confirms our previous conclusions that 7.5 mg of zopiclone can produce residual effects on driving comparable with those found for alcohol when BAC 0.5 mg mL^{-1} or more, and that patients should be warned accordingly (Vermeeren *et al*., 1998, 2002). The latter is particularly important because results from the subjective rating scales showed that subjects themselves were not aware of any residual effects of the evening dose of zopiclone. Although they felt less alert and contented on mornings following middle-of-the-night administration of gaboxadol and zolpidem, they failed to notice their reduced alertness following zopiclone.

A limitation of the present study may be that the subjects were medication-naive healthy volunteers. The results may overestimate the impairing effects on driving performance compared with those in insomniacs using hypnotics. First, it is sometimes argued that hypnotics may improve daytime cognitive performance in insomniacs as a result of improving sleep. Although subjects in the present study were healthy young volunteers without complaints of insomnia, they rated the quality of their sleep to be better and their sleep duration to be longer after the evening administration of gaboxadol and zopiclone compared with that of placebo. However, no improvement in performance was detected after the use of these drugs in any of the tasks. By contrast, following zopiclone administration most performance scores showed impairment. This indicates that potentially positive effects of sleep improvement could not compensate the residual sedative effects of the drugs on performance in our subjects, at least not completely.

Second, a majority of insomniacs use hypnotics for prolonged periods (Curran *et al*., 2003) which, consequently, may result in the development of tolerance to the impairing effects of hypnotics. Experimental studies investigating the effects of hypnotics on actual driving performance in chronic users, however, do not exist. Epidemiological studies have shown that there is still a significantly increased risk of crash involvement after 1 month of treatment, suggesting that tolerance was not complete (Neutel, 1998). It remains to be determined, therefore, whether the results of hypnotics' effects on sleep, their residual sedation and tolerance is the same in insomniac patients using hypnotics frequently as in healthy volunteers.

A remarkable finding was the lack of effects of gaboxadol on memory. In contrast to the effects of zolpidem and zopiclone, no significant effects were found on any of the four performance parameters in the word learning test after gaboxadol, irrespective of the time of administration. This cannot be explained by the pharmacokinetic factors, because the middle-of-the-night dose of gaboxadol impaired performance significantly on all other tests, indicating that it was clearly central nervous system (CNS) active at the time of testing. An explanation is therefore related most probably to its receptor-binding profile. Gaboxadol is primarily an agonist at extrasynaptic α_4- and α_6-containing $GABA_A$ receptors, whereas the amnestic effects of benzodiazepines and zolpidem seem to be mediated by their affinity for α_1 and α_5 subunits (Savic *et al*., 2005). According to a recent review by Savic *et al*. (2005), the α_5 subunits, expressed mainly in the hippocampus, modulate the effects of benzodiazepines on explicit memory, while α_1 subunits are also involved substantially in procedural memory. Because gaboxadol has a relatively low affinity for these receptor subunits, it may produce less memory disturbances than other GABAergic hypnotics.

In conclusion, the results of this study indicate that 15 mg of gaboxadol can produce minor residual effects on driving between 10 and 11 h after evening administration. Administration later at night is associated with moderately impairing residual effects on driving and psychomotor performance until 6 h after intake but not on memory. Results also show that 10 mg of zolpidem taken at night has moderately severe impairing effects on driving the next morning, at least until 6 h after intake. This confirms the importance of instructing patients to ingest 10 mg of zolpidem only prior to a full 8 h of uninterrupted sleep. Finally, this study shows that 7.5 mg of zopiclone taken at bedtime consistently impairs driving the next morning at least until 11 h after intake, while subjects seem unaware of this effect. This stresses the importance of warning patients concerning residual effects of hypnotics by their physicians or pharmacists.

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