Highway Driving in the Elderly the Morning After Bedtime Use of Hypnotics

A Comparison Between Temazepam 20 mg, Zopiclone 7.5 mg, and Placebo

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Abstract: A major problem related to hypnotic drug use is residual sedation the morning after bedtime administration. This constitutes a particular safety hazard for patients who have to drive a car the next morning. Information on the severity of residual effects is mainly derived from studies conducted with young healthy volunteers. However, most users of hypnotics are older people who may be more sensitive to drug effects.

The aim of this study was to evaluate the residual effects the morning after evening doses of temazepam 20 mg and zopiclone 7.5 mg on driving performance in healthy elderly drivers.

Eighteen healthy elderly drivers (10 females and 8 males; mean age, 64.3 years) participated in a double-blind, 3-way crossover study. Treatments were single oral doses of temazepam 20 mg, zopiclone 7.5 mg, and placebo administered at bedtime. Subjects performed a standardized highway driving test between 10 and 11 hours after hypnotic intake. Before and after the driving test, cognitive performance was assessed.

Driving performance did not differ between temazepam and placebo but was significantly impaired after zopiclone 7.5 mg ($P < 0.002$). The results of the laboratory tests were in line with the effects on driving of both hypnotics.

Temazepam 20 mg is unlikely to impair driving 10 hours or more after bedtime administration in healthy elderly aged 75 years or younger. Zopiclone 7.5 mg moderately impairs driving in the elderly at least until 11 hours after administration. The magnitude of impairing effects in the elderly was comparable with those found previously in younger volunteers.

Key Words: hypnotics, elderly, zopiclone, temazepam, highway driving performance, residual effects, cognitive and psychomotor performance

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A major problem of hypnotic drug use is residual sedation the morning after bedtime administration. It results in an impairment of a number of behavioral and mental functions, such as psychomotor performance, visual perception, attention, memory, and information processing.[1] This constitutes a particular safety hazard for patients whose activity the next morning involves skilled work and in whom impairment of performance in daily activities, such as driving a car, could be a danger to themselves or to others. Experimental studies on driving performance have shown that the duration and the severity of the residual effects differ between hypnotics, depending on the hypnotic's half-life, dose, and formulation.[1] Being aware of the differences between hypnotics should enable physicians to select the safest alternative possible for patients who have to drive a car the next morning.

The benzodiazepine temazepam and the nonbenzodiazepine zopiclone are among the most frequently prescribed hypnotic drugs.[2–4] Temazepam in its commonly prescribed dose of 20 mg is considered to be safe for patients who need to drive a car the morning after evening administration.[1,5] Zopiclone, on the other hand, in its recommended dose of 7.5 mg, has been shown to produce moderately impairing residual effects on driving performance.[6–8] Information on these effects has, however, been mainly derived from experimental studies conducted in healthy young volunteers, whereas most hypnotic users are elderly.[9,10] Drug effects may be more pronounced in elderly drivers because of age-related reductions in liver capacity and lean body mass. In addition, with age, sensitivity to the hypnotic effects may be increased.[11] It is therefore possible that hypnotic drugs like temazepam 20 mg, which have no detectable residual effects in young drivers, do have significant residual effects in older drivers. Yet, to date, the residual effects of hypnotics have never been investigated using tests of actual driving in elderly drivers.

There are studies that used laboratory tests to assess the residual effects of hypnotics in the elderly, but these may be limited with respect to assessing drug effects on driving. For example, residual effects of temazepam 20 mg and zopiclone 7.5 mg on cognitive and psychomotor functions of healthy elderly were assessed using laboratory tests, such as choice reaction time and critical flicker fusion.[12] Results showed no significant residual impairments. The lack of residual effects after zopiclone 7.5 mg suggests, however, that tests or procedures used in the study did not have sufficient sensitivity to detect effects on driving because studies using tests of actual driving have consistently shown that zopiclone 7.5 mg has moderately impairing residual effects on driving in healthy young volunteers.[6–8]

The aim of the present study was to compare the residual effects of temazepam 20 mg, zopiclone 7.5 mg, and placebo on actual driving performance in a group of 18 healthy elderly drivers using a standardized highway driving test. This test evolved from studies on driver fatigue and was standardized for assessing drug effects on actual driving performance in the early 1980s.[13,14] It has been subsequently applied in more than 75 drug studies.[1,15–17] The primary performance parameter is the standard deviation of lateral position (SDLP, in centimeters), which can be interpreted as an index of weaving or course-keeping error. The SDLP is a reliable characteristic of individual driving performance (test-retest $r = 0.7$ to 0.9)

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and has proven sensitive to many sedating drugs, including zopiclone 7.5 mg.[6–8,18]

METHODS

Subjects

Eighteen healthy elderly male and female drivers (age, 55–75 years) were recruited by means of advertisements in local newspapers. Subjects needed to possess a valid driving license and an average driving experience of at least 5000 km/y over the last 3 years. Volunteers were screened by a medical history questionnaire and a physical examination. The latter included a 12-lead electrocardiogram, blood chemistry and hematology, urinalysis, and tests for drug of abuse (amphetamines, benzodiazepines, cannabis, cocaine, 3,4-methylenedioxymethamphetamine, and opiates). Inclusion criteria were good health, body mass index between 19 and 29 kg/m^2, and normal vision (corrected or uncorrected). Volunteers who met any of the following exclusion criteria could not participate in the study: any history or current evidence of any clinically significant physical or mental disorders, alcoholism, or drug abuse; acute illness; use of medication known to affect driving performance; blood donation or participation in any other clinical trial within the previous 3 months; consumption of more than 6 beverages containing caffeine per day or more than 10 cigarettes per day; and drinking more than 21 alcohol-containing beverages per week.

During participation, use of caffeine was prohibited from 4 hours before arrival on treatment days until discharge the next morning. Alcohol intake was not allowed from 24 hours before each dosing until discharge. Smoking was prohibited from arrival until discharge, and eating was not permitted from arrival until breakfast.

All 18 subjects (10 females and 8 males) completed the study between November 2006 and February 2007. Their mean (SE) age was 64.3 (1.0) years, and their mean (SE) body mass index was 24.0 (0.5) kg/m^2.

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 the Maastricht University and the University Hospital of Maastricht. Subjects were explained the aims, the methods, and the potential hazards of the study, and they signed a written informed consent before any study-related assessments.

Design

The study was conducted according to a double-blind, 3-way crossover design. Treatments were temazepam 20 mg, zopiclone 7.5 mg, and placebo administered in identical looking capsules and ingested immediately before retiring to bed at 2300 hours. The order of treatment was balanced by randomly assigning 6 treatment sequences residing in 2 Latin squares to 18 subjects.

Assessments

Residual effects were assessed using a battery of laboratory tests, a highway driving test, and subjective rating scales, all of which have been previously found sensitive to the residual effects of hypnotics[6–8,19,20] and low doses of alcohol.[7,21]

In the standardized highway driving test,[14] the subject operates a specially instrumented vehicle for more than 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 95km/h (58 miles/h) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle speed and the lateral position are continuously recorded. These signals are edited off-line to remove data recorded during overtaking maneuvers or disturbances caused by roadway or traffic situations. The remaining data are then used to calculate means and standard deviations of lateral position and speed. The SDLP (in centimeters) is the primary outcome variable. The SDLP is a measure of road-tracking error or "weaving." The test duration is approximately 1 hour.

The critical tracking test (CTT) measures the ability to control an unstable error signal in a first-order compensatory tracking task.[22] 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; rad/s). The final score is determined from the average of all but the lowest and the highest scores in 5 trials.

The divided attention task measures the ability to divide attention between 2 simultaneously performed tasks.[23] 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-second 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 to 25 sec. Tracking error (in millimeters) and average reaction time (in milliseconds) are the respective performance measures.

In the stop signal task,[24] the concept of inhibitory control is defined as the ability to stop a pending thought or action and to begin another. The paradigm consists of 2 concurrent tasks, that is, a go task (primary task) and a stop task (secondary task). The go signals are the letters "X" and "O" presented one at a time in the center of a computer screen. Subjects are required to indicate as quickly as possible whether the letter presented is an "X" or an "O" by pressing 1 of 2 response buttons. The test consists of 336 trials. In 25% of the trials, the go signal is followed by a stop signal (a brief 1000-Hz tone) in which case subjects are required to withhold their response. Stop signals are presented after variable intervals dependent on the subject's go reaction time and ratio of successful and unsuccessful inhibitions. By continuously monitoring the subject's response, the stop signal reaction time (SSRT) is calculated during the task. The dependent variables are the go reaction time (in milliseconds) and the SSRT (in milliseconds).

In the word learning test,[25] a sequence of 15 monosyllabic nouns is shown on a computer display at a rate of 1 per 2 seconds. Immediately thereafter, the subject is required to verbally recall as many words as possible. The sequence is repeated on 4 more trials, and the highest separate trial score is the immediate recall score. After a delay of at least 30 minutes, 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 a word originates from the original set or not by pressing the corresponding buttons. The number and the speed of correct responses are recorded as the recognition score and the recognition reaction time (in milliseconds), respectively.

Body sway was measured using the stabilometry method of the International Society of Posturography.[26] The subjects stand on a force platform for 60 seconds with the feet open at an angle of approximately 30°, first with the eyes open and fixed on a target 2 meters away and then with the eyes closed. The system (Electropostugraph; ELP, Brussels, Belgium) calculates the momentary vector of force extending downward from the center of gravity of the body and its movement around the vertical axis over time, as illustrated by Boyle et al.[27] Two related parameters are measured during both the eyes open and the eyes closed recording epochs, that is, the length of the vector's path (POS-L1 and POS-L2 in millimeters) and the area or surface circumscribed by the vector (POS-S1 and POS-S2, in square millimeters).

Subjective evaluations of mood, sedation, and driving quality were assessed using a series of visual analog scales (100 mm). The subject was instructed to rate their subjective feelings using a 16-item mood scale, which provides a 3-factor analytically defined summary scores for alertness, contentedness, and calmness.[28] The driving instructor rated each subject's driving quality and apparent sedation at the conclusion of each driving test, using two 100-mm visual analog scales. Subjective feelings of sleepiness were rated by means of the Stanford Sleepiness Scale.[29] The scale consists of 7 statements, describing stages of sleepiness ranging from 1 (feeling active and wide awake) to 7 (losing the struggle to remain awake and being nearly asleep). Subjective evaluation of sleep quality was assessed using the Groningen Sleep Quality Questionnaire[30] and estimates of sleep onset latency and sleep duration.

Procedure

Subjects were individually trained to perform the driving and the 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 after 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 2000 hours, and lasted until day 2, when they were transported home after the driving test, at approximately 1115 hours. On arrival at the sleeping facility in each treatment period, subjects' eligibility was verified by questioning subjects about adverse events and use of medication since their last visit and by measuring vital signs in supine position.

Subjects ingested their medication at 2300 hours and retired to bed. They were awakened by telephone at 0700 hours, that is, 8 hours after dose. At 0745 hours (ie, 845–0930 hours after dose), subjects performed the first session of laboratory tests comprising the following measures in fixed order: immediate recall of the word learning test body sway, CTT, divided attention task, and first delayed recall of the word learning test. In addition, subjects rated their sleep quality and feelings of alertness and sleepiness. From 0900 to 1000 hours, that is, 10 to 11 hours after drug intake, the highway driving test was undertaken. Upon completion of the driving test, the subjects returned to the testing facilities for a second test session, starting at approximately 1145 hours after drug intake. After rating their subjective feelings and sleepiness, the subjects performed the stop signal task, the CTT, the divided attention task, and the second delayed recall and recognition part of the word learning test.

Statistical Analyses

Sample size was based on a power calculation for detecting a clinically relevant effect of 2.4 cm in the primary measure of this study, the SDLP. This change corresponds to the effects of alcohol on SDLP, whereas blood alcohol concentrations are 0.5 g/L as measured in a previous study.[31] Given a test-retest reliability of SDLP of at least $r = 0.70$, a group of 18 subjects should permit detection of a mean change in SDLP of 2.0 cm, with a power of at least 90% and an α risk of 0.05.

The global model used in the repeated-measures analysis of variance of all cognitive and psychomotor parameters included subject, treatment, and session. In case of a significant overall effect of treatment, a subsequent analysis for comparing separate drug treatments was conducted using 3 simple contrasts. All statistical analyses were done by using the Statistical Package for the Social Sciences for Windows (version 12.0.1; SPSS Inc, Chicago, Ill).

RESULTS

A summary of the driving, the cognitive, and the psychomotor tests is shown in Table 1.

Missing Data

The divided attention task data were incomplete for 3 subjects, and the stop signal task data were incomplete for 1 subject due to technical problems. Only subjects with complete data sets entered the analysis of respective performance parameters.

Highway Driving Test

One driving test was terminated before scheduled completion because the driving instructor judged that it would be unsafe to continue. The terminated test was performed by a female subject after administration of zopiclone. The SDLP score was calculated from the data collected until termination of the ride.

Figure 1 presents the mean (SE) SDLP values recorded after every treatment. There was a significant overall treatment effect ($F_{2,16} = 12.51$, $P < 0.001$). Zopiclone significantly increased SDLP as compared with placebo (+2.0 cm, $P < 0.002$) and temazepam ($P < 0.001$). Effects of temazepam on SDLP were not significantly different from placebo.

Mean speed variability, reflected by the standard deviation of speed (SDSP), differed significantly between treatments ($F_{2,16} = 4.71$, $P = 0.025$). The SDSP was significantly increased after zopiclone as compared with temazepam ($P = 0.011$). There were no significant differences between the hypnotics and the placebo.

Critical Tracking Test

No overall treatment effect was found in tracking performance on either time of measurement.

Divided Attention Task

A significant overall treatment effect was found in tracking performance in the divided attention task on the first test session ($F_{2,13} = 4.08$, $P = 0.042$) but not on the second test session. At 0845 hours after administration, tracking after zopiclone was significantly worse than after temazepam ($P = 0.010$). There were no significant differences between drugs and placebo. No overall treatment effects were found on the target detection subtask.

Stop Signal Task

The ability to inhibit an ongoing action, as reflected by the SSRT, was significantly different between treatments ($F_{2,15} = 6.09$, $P = 0.012$), whereas no significant differences between treatments were found in the go reaction time. The SSRT was significantly increased after administration of zopiclone, as

compared with placebo ($P = 0.008$). Inhibitory control after temazepam administration did not differ from placebo or zopiclone.

Word Learning Test

No overall treatment differences were found for the immediate recall of verbally learned words.

For the delayed recall of the words, a significant treatment effect was revealed for both test sessions (0845 hours after dose, $F_{2,16} = 8.58$, $P = 0.003$; 1145 hours after dose, $F_{2,16} = 6.75$, $P = 0.007$). Delayed recall was significantly worse after zopiclone at both times of testing as compared with placebo ($P = 0.008$ and 0.002, respectively) and as compared with temazepam ($P = 0.001$ and 0.017, respectively). Temazepam had no significant effects on delayed recall.

There was a highly significant treatment effect on the number of correctly recognized words ($F_{2,16} = 12.89$, $P < 0.001$), which was due to a significantly lower recognition score after administration of zopiclone as compared with placebo ($P < 0.001$). No differences were found between temazepam and placebo and between the 2 treatment conditions. Reaction times to correctly recognized words also differed significantly between treatments ($F_{2,16} = 9.74$, $P = 0.002$). Compared with placebo, the subjects responded significantly slower after administration of both hypnotics (temazepam, $P = 0.003$; zopiclone, $P = 0.002$).

Body Sway

There was a significant treatment effect on body sway measured by vector surface with eyes open ($F_{2,16} = 4.19$,

TABLE 1. Mean (SE), Overall Treatment Effects, and Contrast Analyses of Driving and Cognitive Performance Tests for Each Treatment

							Simple Contrast Analysis		
		Mean (SE)			Overall Treatment Effect		Placebo Versus Temazepam	Placebo Versus Zopiclone	Temazepam Versus Zopiclone
Test	Time After Intake (h:min)	Placebo	Temazepam	Zopiclone	*F*	*P*	*P*	*P*	*P*
Highway driving test									
SDLP (cm)	+10:0	17.8 (0.8)	17.8 (0.7)	19.8 (1.0)	12.51	<0.001	NS	<0.002	<0.001
SDSP (km/h)	+10:0	2.3 (0.2)	2.2 (0.3)	2.5 (0.4)	4.71	0.025	NS	NS	0.011
Critical tracking task									
Lambda (rad/s)	+8:45	3.60 (0.10)	3.62 (0.11)	3.40 (0.14)	NS		–	–	–
	+11:45	3.51 (0.13)	3.58 (0.11)	3.29 (0.15)	NS		–	–	–
Divided attention task									
Average error (mm)	+8:45	17.42 (1.54)	16.86 (1.32)	18.62 (1.12)	4.08	0.042	NS	NS	0.010
	+11:45	18.96 (1.20)	18.05 (1.44)	19.44 (1.01)	NS		–	–	–
Reaction time (ms)	+8:45	1905 (79)	2005 (71)	2024 (93)	NS		–	–	–
	+11:45	2067 (64)	1979 (73)	2048 (72)	NS		–	–	–
Stop signal task									
Go reaction time (ms)	+11:45	537 (25)	546 (27)	537 (26)	NS		–	–	–
SSRT (ms)	+11:45	192 (8)	203 (11)	205 (10)	6.09	0.012	NS	0.008	NS
Word learning test									
Maximum immediate recall	+8:45	13.2 (0.6)	12.8 (0.5)	12.3 (0.6)	NS		–	–	–
Delayed recall	+8:45	10.9 (0.9)	10.6 (0.7)	8.8 (0.8)	8.58	0.003	NS	0.008	0.001
Delayed recall	+11:45	9.6 (0.9)	8.8 (0.8)	6.8 (0.9)	6.75	0.007	NS	0.002	0.017
Recognition score	+11:45	26.8 (0.7)	26.0 (0.7)	24.6 (0.6)	12.89	<0.001	NS	<0.001	NS
Recognition reaction time (ms)	+11:45	842 (25)	906 (31)	928 (33)	9.74	0.002	0.003	0.002	NS
Body sway									
POS-L1 (mm)	+8:45	357 (12)	360 (11)	366 (12)	NS		–	–	–
POS-S1 (mm^2)	+8:45	74 (7)	107 (13)	102 (11)	4.19	0.034	0.013	0.015	NS
POS-L2 (mm)	+8:45	349 (8)	348 (12)	360 (12)	NS		–	–	–
POS-S2 (mm^2)	+8:45	76 (6)	84 (10)	109 (19)	NS		–	–	–
Subjective evaluations									
Driving quality	+10:0	69 (2)	68 (3)	64 (4)	NS		–	–	–
Sedation	+10:0	10 (2)	15 (3)	21 (4)	3.62	0.050	NS	0.013	NS
Alertness	+8:45	66 (5)	72 (4)	65 (5)	NS		–	–	–
	+11:45	72 (5)	72 (5)	68 (4)	NS		–	–	–
Contentedness	+8:45	70 (5)	75 (5)	73 (4)	NS		–	–	–
	+11:45	74 (6)	75 (6)	74 (4)	NS		–	–	–
Calmness	+8:45	71 (5)	75 (4)	72 (4)	NS		–	–	–
	+11:45	69 (5)	71 (6)	72 (4)	NS		–	–	–
Sleepiness	+8:45	2.0 (0.3)	1.9 (0.2)	2.4 (0.2)	4.47	0.029	NS	NS	0.008
	+11:45	1.6 (0.2)	1.8 (0.2)	2.4 (0.3)	NS		–	–	–

POS-L1 indicates postural sway–vector length–eyes open; POS-S1, postural sway–vector surface–eyes open; POS-L2, postural sway–vector length–eyes closed; POS-S2, postural sway–vector surface–eyes closed; NS, not significant.

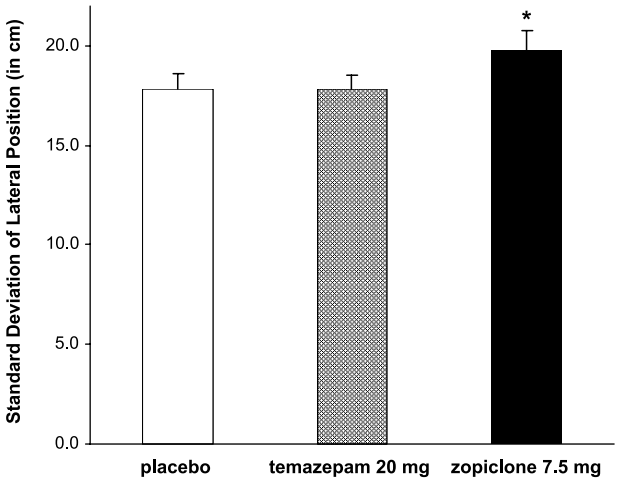

FIGURE 1. Mean (SE) SDLP in each drug condition. *Significantly different from placebo ($P < 0.001$).

$P = 0.034$) but not measured with eyes closed or vector length. Sway surface, with eyes open, was significantly increased by temazepam ($P = 0.013$) and zopiclone ($P = 0.015$) as compared with placebo.

Subjective Evaluations

Subjects' ratings of sleepiness as measured by the Stanford Sleepiness Scale differed significantly between treatments during the first test session ($F_{2,16} = 4.47$, $P = 0.029$). Subjects felt more sleepy after administration of zopiclone than after administration of temazepam ($P = 0.008$). This difference had disappeared on the second test session, that is, 1145 hours after dose. The effects of the drugs did not differ from placebo. There were no significant differences between treatments in alertness, calmness, and contentedness as measured by Bond and Lader's mood scale.

The driving instructors rated the subjects' appearance of being sedated significantly different between the treatments ($F_{2,16} = 3.62$, $P = 0.05$). The subjects appeared significantly more sedated only after zopiclone ingestion compared with placebo ($P = 0.013$). The instructors did not judge the subjects' driving quality to be significantly different between treatments.

Subjective Sleep Quality

Subjective sleep quality was rated significantly different between treatments ($F_{2,16} = 7.91$, $P = 0.004$); the mean (SE) number of complaints decreased significantly from 6.1 (1.2) after placebo to 3.0 (0.7) after zopiclone ($P = 0.011$) and to 1.6 (0.3) after temazepam ($P < 0.001$). The difference in sleep complaints between the 2 hypnotics was significant ($P = 0.025$).

Further differences were found in estimations of time to sleep onset ($F_{2,16} = 6.73$, $P = 0.004$), total sleep time ($F_{2,16} = 5.88$, $P = 0.012$), and number of awakenings ($F_{2,16} = 11.12$, $P < 0.001$) but not in the time awake before rise. The mean (SE) sleep onset time after placebo was 58 (13) minutes. This improved significantly after use of temazepam to 14 (2) minutes ($P = 0.004$) but not after zopiclone 29 (10) minutes. Similarly, total sleep time improved significantly ($P = 0.004$) only after temazepam (436 ± 9 minutes) and not after zopiclone (413 ± 15 minutes) as compared with placebo (373 ± 16 minutes). The mean (SE) number of awakenings dropped significantly from 3.4 (0.6) after placebo to 1.5 (0.4) after temazepam ($P < 0.001$) and 1.1 (0.3) after zopiclone ($P < 0.001$).

DISCUSSION

The present study is the first investigating the residual effects of hypnotics on actual driving performance in elderly drivers. Results show that a single oral dose of temazepam 20 mg does not affect driving performance in elderly individuals 10 hours after bedtime administration. Zopiclone 7.5 mg, on the other hand, impairs driving significantly until 11 hours after intake as indicated by a significant rise in mean SDLP of +2.0 cm compared with placebo, which is almost comparable with the effects found for alcohol when blood alcohol concentrations were around 0.05% as assessed in a previous study.[31] Furthermore, 1 driving test was stopped by the driving instructor because the subject was too drowsy to continue safely after using zopiclone. In line with this, the driving instructors' evaluations showed that the subjects appeared more sedated after using zopiclone than after placebo, yet they did not evaluate driving quality to differ between treatments.

The lack of residual effects on driving after use of temazepam 20 mg in our study is in line with results from previous studies in younger subjects using the same test.[5,32] O'Hanlon and Volkerts[5] treated 11 insomniac women, aged between 26 and 38 years, with temazepam 20 mg, nitrazepam 10 mg, and placebo for 8 nights and assessed the residual effects on driving after the first, third, and seventh dose. Results showed that temazepam's effects were not significant throughout the week. Similarly, Riedel et al[32] found that temazepam 20 mg produced no residual effects on driving in shift workers (aged 24–50 years) as assessed 6.5 hours after the first and the fifth dose. Our data therefore support that temazepam 20 mg is unlikely to produce residual effects on driving in healthy elderly drivers.

The significant residual effect of zopiclone 7.5 mg on driving in elderly drivers was expected based on the findings in younger individuals.[6–8] The increase in SDLP produced by zopiclone in the most recent study with young volunteers was +2.5 cm, whereas it was +2.0 cm in the present study with elderly volunteers.[8] Therefore, the present findings do not support the idea that the residual effects of hypnotics are more pronounced in older drivers.

A similar lack of age differences has been found for the effects of antidepressants on driving as assessed using the same test.[33] The impairing effects of the serotonin reuptake inhibitor nefazodone were found to be comparable in young (age, 28–38 years) and elderly (age, 60–72 years) healthy volunteers. It can therefore be concluded that studies in young volunteers are valid for predicting residual effects of hypnotics in healthy elderly drivers.

The results of the laboratory tests are in line with the effects on driving of both hypnotics. Effects of temazepam were marginal, only slowing response times in word recognition and increasing postural sway as measured by 1 of the 4 parameters in the body sway test. Zopiclone, however, had clear residual effects on memory as measured by delayed recall and speed and accuracy of recognition in the word learning test, inhibitory control in the stop signal task, and postural stability in the body sway test. These effects are in agreement with findings from 2 previous studies using similar tests and procedures.[7,8] Both drugs primarily affected postural sway when eyes were open, which may be due to the order of the measurements. Similar effects were shown previously in a study using the same procedures.[8]

Our results are not in line with those of a study by Hemmeter et al.[12] These investigators found no significant effects of either temazepam 20 mg or zopiclone 7.5 mg on next day performance in 12 healthy elderly volunteers using a battery of laboratory tests and found no significant effects of either temazepam 20 mg or zopiclone 7.5 mg. Although their results support our conclusions that elderly individuals do not seem to be more sensitive to the residual effects of hypnotics than younger individuals, the complete lack of effects of zopiclone is rather unexpected and raises questions about the methodology used. This stresses the importance of the recommendation to include a control drug with moderately impairing effects to demonstrate sensitivity of the methods in studies assessing the effects of medicinal drugs on driving performance.[34]

A limitation of our study with respect to generalization of the results to insomniac patients who drive may be the use of healthy volunteers. Residual effects of hypnotics are expected to be less severe in insomniacs than in healthy volunteers for 2 reasons. First, hypnotics are expected to improve daytime performance in insomniacs since improving sleep, which counteracts drug-induced sedation. Second, most patients use these drugs repeatedly, which may induce the development of tolerance,[35] and as a result, hypnotic-induced daytime impairment may become gradually less severe. With respect to the improving effects on sleep, it should be noted that although the healthy elderly subjects in the present study considered themselves to be good sleepers, their scores on the Groningen Sleep Quality scale indicated that they had a clinically relevant number of sleep complaints during the placebo night, and they evaluated their sleep to be significantly improved after active hypnotic drugs. However, despite improved sleep, driving performance was impaired after zopiclone as compared with placebo. With respect to the development of tolerance, it should be noted that epidemiological studies have shown that the relative risk of becoming involved in a traffic accident is still significantly increased after 1 month of treatment, suggesting that tolerance to residual impairment was not complete.[36] Furthermore, patients using hypnotics on an as needed basis may not develop tolerance and may therefore remain susceptible to the sedative residual effects of hypnotics. Nevertheless, the validity of experimental studies with hypnotics in healthy volunteers for predicting the residual impairment on driving in patients with insomnia remains to be determined, preferably by studies in patients using the same drugs and procedures.

In conclusion, the results of the present study show that temazepam 20 mg is unlikely to produce residual effects on driving 10 hours or more after bedtime administration in healthy elderly aged 75 years or younger. Zopiclone 7.5 mg impairs driving in the elderly at least until 11 hours after administration. The effects were comparable with those found in studies with healthy younger volunteers using the same methods, indicating that older drivers do not have an increased sensitivity to the residual effects of hypnotics.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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