ELSEVIER

Sleep Medicine 2 (2001) 323–332

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Original article

Effects of zaleplon or triazolam with or without ethanol on human performance

Timothy Roehrs[a,*], Leon Rosenthal[a], Gail Koshorek[a], Richard M. Mangano[b], Thomas Roth[a]

[a]*Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI, USA*
[b]*Wyeth–Ayerst Research, Radnor, PA, USA*

Received 21 December 1999; received in revised form 20 April 2000; accepted 13 July 2000

Abstract

Objectives and background: Given that non-selective γ-aminobutyric acid (GABA) agonist hypnotics impair performance and potentiate the disruptive effects of ethanol, this study was done to determine the performance-impairing and ethanol-potentiating effects of zaleplon, a new selective GABA agonist hypnotic.

Methods: Eighteen healthy men (12) and women (six), 31.5 ± 5.6 years old, were studied. Each underwent six treatments of 2 days in duration, presented in a Latin square design with 2–12 recovery days between. The treatments were: placebo–placebo; placebo–ethanol; triazolam–placebo; triazolam–ethanol; zaleplon–placebo; and zaleplon–ethanol; with triazolam (0.25 mg) or placebo administered at 08:30 h, zaleplon (10 mg) or placebo at 09:00 h, and ethanol (0.75 g/kg) or placebo consumed from 09:30 h. Performance tests were completed each day at 10:30, 12:00 and 14:30 h.

Results: Breath ethanol concentration (BrEC), tested 0.5, 2.0, 4.5 and 6 h post consumption, did not differ among treatments and peaked at 0.052%, declining to 0.037, 0.009 and 0.001%. Triazolam with and without ethanol impaired digit symbol substitution, symbol copying, simple and complex reaction times and divided attention performance relative to placebo–placebo treatment. It did so consistently at 10:30 and 12:00 h, and less consistently at 14:30 h. Zaleplon without ethanol impaired only digit symbol substitution and divided attention tracking, and only at 10:30 h. Zaleplon with ethanol impaired most measures at 10:30 and 12:00 h, but not at 14:30 h. Zaleplon without ethanol consistently differed from triazolam without ethanol in the extent of performance impairment. Zaleplon with ethanol began to differ from triazolam with ethanol in performance impairment on the 12:00 and 14:30 h test sessions. Ethanol itself impaired most measures at 10:30 h, fewer at 12:00 h and none at 14:30 h. All active drug treatments increased self-rated sleepiness compared with placebo–placebo. Triazolam without ethanol produced greater self-rated sleepiness than zaleplon without ethanol. The addition of ethanol to both drugs generally produced comparable levels of self-rated sleepiness.

Conclusions: In an absolute sense, zaleplon produced less performance impairment and a shorter period of ethanol potentiation than triazolam.

Keywords: Zaleplon; Triazolam; Ethanol potentiation; Performance impairment

1. Introduction

Zaleplon, a short-acting (T_{max}, 1 h; and $T_{1/2}$, 1 h) pyrazolopyrimidine that binds selectively to the benzo-

* Corresponding author. Tel.: +1-313-916-5177; fax: +1-313-916-5167.
E-mail address: taroehrs@aol.com (T. Roehrs).

1389-9457/01/$ - see front matter
PII: S1389-9457(00)00067-8

diazepine (Bz_1) receptor, has been shown to be an effective sedative–hypnotic for the treatment of insomnia [1–4]. In placebo-controlled studies of persons with insomnia, it hastened sleep onset in doses of 5–20 mg and increased sleep time with a 20 mg dose [5–7]. Among the clinical limitations of GABA agonist hypnotics is their tendency to impair performance and cognition and to potentiate the disruptive effects of ethanol [8]. Zaleplon in animal studies showed a reduced likelihood of ethanol potentiation, cognitive impairment and tolerance development [1]. Thus, in humans, the comparative performance-impairing and ethanol-potentiating effects of zaleplon may differ from those of other GABA agonists. To evaluate the performance-impairing and ethanol-potentiating effects of zaleplon, triazolam (0.25 mg) was chosen as the drug of comparison. It was chosen for its similar pharmacokinetics (T_{max}, 1.5 h; and $T_{l/2}$, 2–4 h), although unlike zaleplon, it binds non-selectively to Bz receptors [1,9]. The 0.25 mg triazolam dose was used for its hypnotic equipotency to 10 mg zaleplon as found in a previous laboratory study, in which triazolam (0.25 mg) reduced the nocturnal sleep latency of persons with insomnia by the same amount as zaleplon (10 mg) [10].

The objective of this study was to determine, in humans, the performance-impairing and ethanol (0.75 g/kg)-potentiating effect of zaleplon (10 mg), compared with that found for triazolam (0.25 mg). To make these comparisons, the study was conducted in healthy normals with daytime administration.

2. Methods

2.1. Subjects

Eighteen healthy men (12) and women (six), 31.5 ± 5.6 years of age, volunteered to participate. Each had a normal physical examination, were within 15% of their ideal body weights according to Metropolitan Life Insurance Company tables, and the clinical chemistry, hematology and urinalysis laboratory evaluations were all within normal ranges. None had a history of neurological disorders, previous psychiatric conditions, or chronic pulmonary, cardiovascular, gastrointestinal, endocrine, hematological, hepatic, immunological, renal or metabolic diseases.

All participants were asymptomatic regarding sleep–wake function, as verified by a standard screening 8-h sleep recording and a multiple sleep latency test (MSLT) the following day at 09:00, 11:00, 13:00 and 15:00 h [11,12]. Specifically, subjects slept for at least 7 of 8 h in bed and had an average daily sleep latency on the MSLT of >8 min. No participants showed signs of sleep apnea or periodic leg movements.

No participant had a history of alcohol-dependency, a positive breathalyzer result at screening, or a positive result on urine drug screens that included tests for: amphetamines, barbiturates, benzodiazepines, cocaine, morphine/opiates, methaqualone, phencyclidine and tetrahydrocannabinol. No participant had excessive regular intake of caffeine-containing products (greater than the equivalent of five cups of coffee/day) or used any antihistamines, hypnotics, sedatives, stimulants, tricyclic antidepressants, monoamine oxidase inhibitors, or amphetamines within 2 weeks of the study.

The study protocol was approved by the human rights board of the institution. All volunteers consented to participate in the study by reading and signing the informed consent document prior to screening evaluations and following a full explanation of the nature and purpose of the study. They were provided with honoraria for their participation.

2.2. Design

The study was a randomized, double-blind, placebo and active-controlled trial. Zaleplon (10 mg), triazolam (0.25 mg) and placebo were administered in a six-treatment, Latin square study design. The six treatments and their abbreviations used throughout this report were as follows:

ZE: zaleplon (10 mg) + 0.75 g/kg ethanol.
TE: triazolam (0.25 mg) + 0.75 g/kg ethanol.
PE: drug placebo + 0.75 g/kg ethanol.
ZP: zaleplon (10 mg) + ethanol placebo.
TP: triazolam (0.25 mg) + ethanol placebo.
PP: drug placebo + ethanol placebo.

Each subject meeting entry criteria was randomized to one of the treatments. Following the administration of the scheduled treatment, the subjects were assessed by breathalyzer for breath ethanol concentration

(BrEC), and were administered the Stanford sleepiness scale (SSS) and a battery of performance tests. The identical treatment and the same assessments were repeated on the following day (day 2). After a 2–12 day washout period, the subjects continued with the next scheduled treatment, as assigned by the Latin square, until all six treatments were completed.

2.3. Procedures

No more than 14 days following screening, qualified subjects entered the study and resided in the laboratory unit for each 2-day treatment. They reported at 20:00 h the night before the first day of the administration of a treatment and went to bed from 23:00 to 07:00 h. At 08:00 h, they were provided with a standard, light breakfast, which was eaten within 15 min. Vital signs and breathalyzer readings (BrEC) were taken by 08:30 h.

Administration of the treatments on each day was divided into three time periods. At 08:30 h, the subjects were administered triazolam (0.25 mg) or placebo (a single orange/gray #2 capsule). At 09:00 h, the subjects were administered a dose of zaleplon (10 mg) or placebo (two white #4 capsules). At 09:30 h, the subjects were administered ethanol (0.75 g/kg) or ethanol placebo contained in three 8-oz glasses of beverage which was consumed in a 30 min period, 10 min for each 8-oz glass. This dosing regimen was developed based on the knowledge of the absorption characteristics of the three drugs. The intent was for all drugs to be at peak plasma concentration at the initiation of the performance testing. Thus, for example, in the zaleplon (10 mg) + 0.75 g/kg ethanol (ZE) treatment, at 08:30 h, subjects received a single orange/grey #2 capsule (placebo), at 09:00 h, two white #4 capsules (zaleplon 10 mg), and at 09:30 h, the three 8-oz glasses of 0.75 g/kg ethanol. In the triazolam (0.25 mg) + ethanol placebo (TP) treatment, at 08:30 h, subjects received a single orange/grey #2 capsule (triazolam 0.25 mg), at 09:00 h, two white #4 capsules (each placebo), and at 09:30 h, the three 8-oz glasses of the ethanol placebo were administered.

Beginning at 10:30 h, the vital signs and a breathalyzer reading were taken, the SSS was completed and the performance battery was administered. At noon, vital signs, the breathalyzer and SSS were repeated followed by the performance tests. At 14:00 h, the subjects were served a standard lunch. At 14:30 h, vital signs, breathalyzer and SSS testing were repeated again followed by performance testing. Finally, at 16:00 h, vital sign recordings, breathalyzer and SSS tests were repeated once more. On day 2, the subjects received the same treatment and repeated the testing regimen as described for the initial treatment session.

The SSS was used to assess the subjective state of sleepiness following treatment. In the SSS, the subjects were asked to circle a number corresponding to a sentence that most accurately describes his/her current state. The performance assessment consisted of a microcomputer-controlled test battery, in which visual and auditory stimuli were presented, responses to events recorded and the response data were analyzed. The subjects sat in front of a video screen and responded to stimuli on the screen or auditory signals by means of a response pad. The performance battery consisted of the following tests: simple reaction time; complex reaction time; digital symbol substitution; symbol copying; auditory vigilance; and divided attention tests. These tests have been shown to be sensitive to the effects of sedative and stimulant drugs and restrictions or extensions of sleep time from the previous night [13–17]. Each subject underwent two practice sessions on the full test battery on the screening day to ensure the subjects were well practiced and to preclude extensive learning effects during the study proper.

2.4. Data analyses

The digit symbol substitution and symbol copying tests were scored for the number of correct substitutions and copies made. The dependent variables analyzed for the simple and complex reaction time tests were the average reaction times (ms). The divided attention test was analyzed for tracking deviations and reaction times (s) to central and peripheral stimuli (three variables). Finally, on the auditory vigilance test, the reaction times (ms) for each of four 10 min blocks, the whole 40 min test and the total number of errors (false positives and misses) were analyzed (six variables). A total of 13 performance variables at each test session (10:30, 12:00 and 14:30 h) were collected on both days of each treat-

ment. The SSS yields a single score of 1–7. SSS scores and BrECs were assessed on each day at 10:30, 12:00, 14:30 and 16:00 h.

The data for each subject at each test session for performance measures and for BrEC and SSS measures were averaged for both days of each treatment. The analyses revealed no day effects or day by treatment interactions. Thus, these 2-day means were the primary data of the analyses. Each dependent measure for each treatment was submitted to a one factor general linear model, MANOVA (SAS Institute, Cary, NC) that compared the six treatments. Significant effects on a given dependent variable, using the Huynh–Feldt corrected degrees of freedom, were followed by a set of post hoc comparisons among the treatments. Active drugs were compared with the placebo. To assess ethanol potentiation, each drug combined with ethanol was compared with that drug without ethanol and with the placebo ethanol treatment. To assess the differential effects and differential ethanol potentiation, zaleplon with and without ethanol was compared to triazolam with and without ethanol.

3. Results

3.1. Subjects recruited and enrolled

A total of 74 subjects were screened to enroll the 18 subjects who completed the study. Of the 56 subjects failing the screening, 35% showed positive urine drug screens or BrECs. Twenty seven percent did not report for the sleep laboratory screening or were in other ways non-compliant, 16% failed the nocturnal sleep or the daytime alertness screen and 22% had abnormal laboratory values, medical conditions or allergies that prohibited their participation. One subject entered, but did not complete the study, for a non-medical, personal reason. The screening sleep efficiency of the subjects enrolled was $92.4 \pm 3.75\%$ and ranged from 88–98%. The average daily sleep latency on the screening MSLT was 12.2 ± 3.6 min with a range of 8.9–20 min.

3.2. Treatment effects on performance

A summary of the treatment effects and post hoc comparisons on each of the 13 performance measures from each of the three test sessions (10:30, 12:00 and 14:30 h) is presented in Tables 1 and 2. The 2-day means for each measure in the six treatments at each test session are provided in Table 3. Finally, a rank ordering of treatments on each of those seven measures that showed significant treatment effects in the 10:30 h test session, when plasma concentrations of each drug were at their peaks, is provided for all three sessions in Table 4.

3.2.1. Testing at 10:30 h

At the 10:30 h testing, significant treatment effects were found on the digit symbol substitution, symbol copying, simple and complex reaction times, divided attention tracking, central reaction time and peripheral reaction time measures. None of the auditory vigilance variables yielded significant treatment effects.

3.2.2. Testing at 12:00 h

At the 12:00 h testing, significant treatment effects were found on the digit symbol substitution, symbol copying, complex reaction time, divided attention tracking, central reaction time and peripheral reaction

Table 1
Treatment effects on performance measures

Variable[a]	10:30 h		12:00 h		14:30 h	
	F	*P* <	*F*	*P* <	*F*	*P* <
DSS	15.8	0.001	8.21	0.001	5.20	0.001
SCC	3.62	0.015	7.99	0.001	3.31	0.009
SRT	4.66	0.015	2.91	0.097	1.43	ns
XRT	4.09	0.021	4.35	0.028	1.16	ns
TRK	5.83	0.001	3.81	0.010	0.45	ns
CRT	7.31	0.001	8.31	0.001	1.08	ns
PRT	10.3	0.001	7.83	0.001	3.52	0.006
VB1	0.79	ns	0.67	ns	1.05	ns
VB2	2.08	0.081	0.28	ns	2.16	0.091
VB3	1.65	ns	0.59	ns	1.34	ns
VB4	1.67	ns	0.67	ns	0.62	ns
VRT	1.25	ns	0.34	ns	1.50	ns
VER	2.15	0.093	0.86	ns	1.07	ns

[a] DSS, digit symbol substitution # cor; SCC, symbol copying # cor; SRT, simple RT (ms); XRT, complex RT (s); TRK, divided attention tracking deviations; CRT, divided attention central RT (s); PRT, divided attention peripheral RT (s); VB1–VB4, auditory vigilance RT (ms) in 10 min blocks; VRT, mean RT (ms) of the four blocks; VER, auditory vigilance errors (misses and false positives).

Table 2
Significant post hoc comparisons on performance measures[a]

Number of significant post hoc comparisons								
PP vs. PE	PP vs. TP	PP vs. ZP	TO vs. TE	TE vs. PE	ZP vs. ZE	ZE vs. PE	TP vs. ZP	TE vs. ZE
10:30 h		Seven measures with significant condition effects						
5	7	2	0	4	5	2	7	0
12:00 h		Six measures with significant condition effects						
2	6	0	1	6	3	4	6	2
14:30 h		Three measures with significant condition effects						
0	2	0	1	2	1	0	3	1

[a] P, placebo; T, triazolam (0.25 mg); E, ethanol (0.75 g/kg); Z, zaleplon (10 mg); PP, placebo, placebo; TP, triazolam, placebo, etc.

Table 3
Two-day means in each treatment[a]

Variable[b]	PP	PE	TP	TE	ZP	ZE
10:30 h						
DSS	201.8 (33.4)	182.3 (35.0)	157.6 (38.1)	154.9 (34.3)	186.2 (34.3)	160.2 (37.5)
SCC	409.7 (88.7)	392.8 (55.3)	346.0 (76.4)	366.3 (106)	396.3 (74.8)	373.4 (88.4)
SRT	468.3 (110)	533.7 (184)	867.8 (537)	942.8 (828)	476.6 (193)	774.6 (500)
XRT	620.2 (114)	665.5 (198)	1211 (869)	1087 (894)	698.7 (387)	1096 (1309)
TRK	28.1 (17.3)	44.9 (42.4)	73.1 (55.3)	74.4 (52.2)	38.9 (38.4)	56.3 (39.5)
CRT	0.60 (0.16)	0.78 (0.29)	0.93 (0.29)	0.85 (0.31)	0.66 (0.20)	0.86 (0.25)
PRT	0.54 (0.12)	0.72 (0.26)	0.89 (0.26)	0.81 (0.32)	0.60 (0.22)	0.82 (0.26)
12:00 h						
DSS	194.9 (42.2)	196.4 (36.4)	173.8 (37.1)	166.2 (41.8)	189.6 (34.3)	178.9 (42.0)
SCC	438.6 (83.5)	434.9 (71.2)	383.9 (77.7)	391.0 (86.6)	424.8 (79.5)	416.4 (82.5)
SRT	474.8 (116)	521.9 (159)	524.7 (143)	782.3 (656)	480.4 (146)	580.5 (202)
XRT	591.9 (124)	630.9 (130)	693.9 (156)	834.7 (324)	624.5 (113)	837.9 (495)
TRK	32.3 (42.1)	29.3 (19.7)	34.9 (17.1)	49.8 (35.1)	23.7 (12.4)	38.9 (28.3)
CRT	0.59 (0.13)	0.66 (0.19)	0.74 (0.22)	0.84 (0.28)	0.58 (0.14)	0.79 (0.26)
PRT	0.55 (0.11)	0.63 (0.18)	0.70 (0.21)	0.79 (0.28)	0.53 (0.11)	0.76 (0.25)
14:30 h						
DSS	201.1 (33.7)	206.3 (33.6)	187.3 (36.0)	188.6 (38.4)	203.9 (35.7)	198.3 (40.5)
SCC	439.9 (81.6)	426.7 (72.4)	405.1 (87.3)	409.1 (90.7)	428.1 (81.8)	433.9 (80.6)
SRT	471.6 (121)	482.5 (118)	506.1 (147)	541.0 (239)	461.6 (129)	774.6 (500)
XRT	596.0 (121)	731.6 (448)	673.2 (211)	680.2 (145)	590.3 (142)	652.9 (139)
TRK	31.3 (23.9)	33.8 (25.4)	34.7 (20.5)	38.5 (21.3)	32.5 (31.7)	34.3 (32.0)
CRT	0.61 (0.14)	0.67 (0.22)	0954 (1.18)	0.72 (0.17)	0.62 (0.17)	0.67 (0.17)
PRT	0.58 (0.12)	0.62 (0.17)	0.63 (0.12)	0.71 (0.16)	0.56 (0.14)	0.65 (0.15)

[a] P, placebo; T, triazolam (0.25 mg); E, ethanol (0.75 g/kg); Z, zaleplon (10 mg); PP, placebo, placebo; TP, triazolam, placebo, etc.
[b] DSS, digit symbol substitution # cor; SCC, symbol copying # cor; SRT, simple RT (ms); XRT, complex RT (ms); TRK, divided attention tracking deviations; CRT, divided attention central RT (s); PRT, divided attention peripheral AT (s).

Table 4
Rank ordering of means in each treatment[a,b]

Variable[c]	PP	PE	TP	TE	ZP	ZE
10:30 h						
DSS	1	3	5	6	2	4
SCC	1	3	6	5	2	4
SRT	1	3	5	6	2	4
XRT	1	2	6	5	3	4
TRK	1	3	5	6	2	4
CRT	1	3	6	4	2	5
PRT	1	3	6	4	2	5
12:00 h						
DSS	2	1	5	6	3	4
SCC	1	2	6	5	3	4
SRT	1	3	4	6	2	5
XRT	1	3	4	5	2	6
TRK	3	2	4	6	1	5
CRT	2	3	4	6	1	5
PRT	2	3	4	6	1	5
14:30 h						
DSS	3	1	5	6	2	4
SCC	1	4	5	6	3	2
SRT	2	3	5	6	1	4
XRT	2	6	4	5	1	3
TRK	1	3	5	6	2	4
CRT	1	4	6	5	2	3
PRT	2	3	4	6	1	5

[a] P, placebo; T, triazolam (0.25 mg); E, ethanol (0.75 g/kg); Z, zaleplon (10 mg); PP, placebo, placebo; TP, triazolam, placebo, etc.
[b] 1, best; 6, worst performance.
[c] DSS, digit symbol substitution # cor; SCC, symbol copying # cor; SRT, simple RT (ms); XRT, complex RT (ms); TRK, divided attention tracking deviations; CRT, divided attention central RT (ms); PRT, divided attention peripheral RT (ms).

time measures. Again none of the auditory vigilance variables yielded significant treatment effects.

3.2.3. Testing at 14:30 h

At the 14:30 h testing, significant treatment effects were found on the digit symbol substitution, symbol copying and divided attention peripheral reaction time measures. As in the other test sessions, none of the auditory vigilance variables yielded significant treatment effects.

3.3. Drugs versus placebo

At the 10:30 h testing in post hoc comparisons with placebo–placebo, the performance of triazolam with and without ethanol treatments on each of the seven variables was impaired. Zaleplon without ethanol impaired performance only on digit symbol substitution and divided attention tracking, while zaleplon with ethanol performance impairment was seen on all measures except the complex reaction time.

At the 12:00 h testing, triazolam with ethanol impaired the performance, relative to the placebo treatment, on each of the six variables, and triazolam without ethanol impaired the performance on all but divided attention tracking. Zaleplon without ethanol no longer differed from the placebo treatment on any measure, and zaleplon with ethanol impaired the performance on all but divided attention tracking.

Finally, on the 14:30 h testing, triazolam with ethanol impaired the performance relative to the placebo on each of the three variables showing treatment effects, and triazolam without ethanol impaired the performance on all but the divided attention peripheral reaction time. Zaleplon, both with and without ethanol, did not differ from the placebo on any measure.

3.4. Ethanol versus placebo

3.4.1. BrECs

The BrECs for the placebo, triazolam and zaleplon treatments at the four times tested (0.5, 2.0, 4.5 and 6.0 h post ingestion) are presented in Table 5. The BrEC peak and decline was similar among the treatments. There was no significant difference among treatments and no significant treatment by time difference. There was a significant time post ingestion effect ($F = 262.0$; $P < 0.001$), with BrEC differing significantly at each test from that of the preceding test.

Table 5
BrEC (%) in each treatment[a]

Test time	PE	TE	ZE
10:30 h	0.051 (0.017)	0.052 (0.018)	0.053 (0.015)
12:00 h	0.039 (0.008)	0.037 (0.014)	0.033 (0.014)
14:30 h	0.009 (0.010)	0.012 (0.011)	0.006 (0.007)
16:00 h	0.001 (0.002)	0.002 (0.003)	0.001 (0.002)

[a] P, placebo; E, ethanol (0.75 g/kg); T, triazolam (0.25 mg); Z, zaleplon (10 mg); PE, placebo, ethanol, etc.

3.4.2. Ethanol effects and potentiation

Relative to placebo–placebo, ethanol alone impaired performance in the 10:30 h testing on every measure but symbol copying and complex reaction time. By the 12:00 h testing, ethanol impairment was only detected with the three divided attention measures. No ethanol effects on performance were detected in the 14:30 h testing.

As for potentiation, in the direct comparison of triazolam with ethanol versus that without ethanol, greater impairment was found only on the complex reaction time at 12:00 h and on the divided attention peripheral reaction time at 14:30 h. The rank ordering of means shows that triazolam with and without ethanol had similar ranks of 5 or 6, the worst performance (see Table 4). In the direct comparison of zaleplon with ethanol versus zaleplon without ethanol, impairment with ethanol was seen on digit symbol substitution, simple reaction time and the three divided attention measures in the 10:30 h test, again on the three divided attention measures in the 12:00 h test, and finally, on the divided attention peripheral reaction time measure in the 14:30 h test. Again, note that the zaleplon–placebo treatment rarely differed from the placebo treatment. The rank ordering of means shows that zaleplon without ethanol usually ranked second best in performance, while zaleplon with ethanol ranked fourth or fifth, but always better than triazolam without ethanol and typically better than triazolam with ethanol (see Table 4).

3.5. Zaleplon versus triazolam

For comparison of single drug effects, analysis of the 10:30 h data eliminates the confound of differential pharmacokinetics. Each drug is compared at its predicted peak plasma concentration. Triazolam without ethanol differed from zaleplon without ethanol on all seven measures and from ethanol alone on four measures. On each measure, triazolam produced greater impairment. In contrast, zaleplon differed from ethanol on two measures and it was less impairing in both cases.

Additionally, the drugs differed in the duration of effects. Zaleplon without ethanol differed from triazolam without ethanol on all seven measures that showed treatment effects in the 10:30 h testing, again on all six measures showing treatment effects in the 12:00 h testing, and finally on all three measures showing treatment effects in the 14:30 h testing. In each case, zaleplon performance was better than that of triazolam.

Zaleplon with ethanol differed significantly from triazolam with ethanol only on the digit symbol substitution and symbol copying measures at 12:00 h and the divided attention peripheral reaction time measure at 14:30 h. In each case, zaleplon performance was better.

3.6. SSS

The SSS data for the assessments at 10:30, 12:00, 14:30 and 16:00 h are presented in Table 6. There were significant treatment effects on the SSS at each test: (1), $F = 8.72$, $P < 0.002$; (2), $F = 13.0$, $P < 0.001$; (3), $F = 8.23$, $P < 0.001$; and (4), $F = 4.22$, $P < 0.002$. In the post hoc comparisons, a greater self-rated sleepiness at 10:30 h was found for each active drug treatment relative to placebo–placebo. By the 12:00 and 14:30 h assessments, zaleplon without ethanol no longer differed from placebo–placebo. Finally, by 16:00 h, both triazolam and zaleplon without ethanol no longer differed from placebo–placebo. All ethanol treatments (i.e. ethanol alone and

Table 6
Stanford sleepiness scores in each treatment[a]

Time	PP	PE	TP	TE	ZP	ZE
10:30 h	1.78 (0.90)	2.64 (1.34)	3.28 (1.10)	3.14 (1.52)	2.19 (1.14)	3.00 (1.51)
12:00 h	1.89 (0.88)	3.11 (1.49)	3.14 (1.43)	3.92 (1.73)	2.13 (0.95)	3.19 (1.44)
14:30 h	1.61 (0.88)	2.17 (0.82)	2.14 (1.00)	2.92 (1.34)	1.58 (0.62)	2.28 (1.29)
16:00 h	1.58 (0.73)	2.25 (0.97)	1.89 (1.17)	2.33 (1:22)	1.64 (0.76)	2.22 (0.94)

[a] P, placebo; E, ethanol (0.75 g/kg); T, triazolam (0.25 mg); Z, zaleplon (10 mg); PP, placebo, placebo; PE, placebo, ethanol, etc.

in combination with both active drugs) showed greater self-rated sleepiness on each of the four assessments. Triazolam with and without ethanol rarely differed, the exception being the 14:30 h assessment. Zaleplon with ethanol consistently increased self-rated sleepiness compared with zaleplon without ethanol. Triazolam without ethanol compared with zaleplon without ethanol also consistently increased self-rated sleepiness, and with the addition of ethanol to either drug, there were rarely differences, again, the exception being the 14:30 h assessment.

4. Discussion

To summarize the results, treatment effects were found on the digit symbol substitution, symbol copying, simple and complex reaction time and all three divided attention measures at 10:30 h, the predicted peak plasma concentrations of the active drugs. The treatment effects remained on six of the measures in the 12:00 h testing and on three measures at 14:30 h. None of the auditory vigilance measures showed effects. The BrECs did not differ among treatments and peaked at 0.052%, declining to 0.037, 0.009 and 0.001%. Ethanol itself impaired most measures at 10:30 h, fewer at 12:00 h and none at 14:00 h. Triazolam with and without ethanol impaired digit symbol substitution, symbol copying, simple and complex reaction times and divided attention performance relative to placebo–placebo. It did so consistently at 10:30 and 12:00 h, and less consistently at 14:30 h. Zaleplon without ethanol only impaired digit symbol substitution and divided attention tracking at 10:30 h. Zaleplon with ethanol impaired most measures at 10:30 and 12:00 h, but not at 14:30 h. Zaleplon without ethanol consistently differed from triazolam without ethanol in the extent of performance impairment. With ethanol, zaleplon began to differ from triazolam with ethanol in performance impairment on the 12:00 and 14:30 h test sessions.

In interpreting these results, recall that the two objectives of this study were to compare the performance-impairing and the ethanol-potentiating effects of zaleplon and triazolam at peak plasma concentrations of equipotent sedative doses. Zaleplon without ethanol had a smaller impairing effect than triazolam without ethanol at predicted peak plasma concentrations. However, this differential impairment makes it difficult to interpret the ethanol potentiation data. The issue is whether absolute or relative effects are considered. The addition of ethanol to zaleplon produced greater impairment than the addition of ethanol to triazolam. Triazolam and ethanol compared with triazolam alone did not differ on any measure, while zaleplon and ethanol produced poorer performance than zaleplon alone on two of the seven measures. This apparently greater ethanol potentiation of zaleplon may merely be an artifact of ceiling effects of triazolam. That is, the performance battery was incapable of detecting further impairment than that with triazolam alone. This failure to differentiate the effects of triazolam alone from those of triazolam combined with ethanol is a limitation of this study. On the other hand, in terms of the absolute level of performance, the zaleplon and ethanol performance was consistently better than that of triazolam and ethanol.

The interpretation of these results also depends on the hypnotic equipotency of zaleplon (10 mg) and triazolam (0.25 mg). In a previous study, we reported that nocturnal sleep latency was similarly reduced by l4 min with zaleplon and triazolam at these doses in insomniacs [10]. In previous studies, we found that, at estimated peak plasma concentrations, a one-to-one correspondence is seen among drugs and doses in their hypnotic–sedative effects and their performance-impairing effects [18]. However, the present data show a disparity in sedative versus performance-impairing effects. Some possibilities that might explain the disparity are: (1), there is no real equipotency of these doses; (2), there is a differential hypnotic equipotency at night versus daytime; (3), equipotency is different in insomniacs versus normals; and finally, (4), the receptor non-specificity of triazolam versus the specificity of zaleplon. Firstly, the differential receptor specificity of zaleplon versus that of triazolam does not appear to be a likely explanation. In a previous study comparing the receptor specific Bz agonist, zolpidem, with the non-specific agonist, triazolam, similar amnestic effects were found over a range of equipotent hypnotic doses of each drug [17]. The same would be expected for other performance tasks and for another receptor specific Bz_1 agonist.

The data of this study must also be interpreted with the appreciation that the performance tasks used in this study have differential sensitivities to the impairing effects of the drugs and ethanol. Thus, for some of the measures, the presence of effects changed over time. Effects were not detected at peak plasma concentrations, but were found at later time points. However, the global picture is presented in Table 4, and it does show consistencies in the rank ordering of means for the various measures across time and across the six treatments.

One limitation of this study was that subjective assessments (i.e. the SSS) of sedative effects were carried out. A direct assessment of sedative effects using the MSLT may have more precisely indicated the relative sedative effects of these drugs in these subjects at peak plasma concentrations and in combination with ethanol. On the SSS, zaleplon without ethanol produced less subjective sleepiness than triazolam, but similar sleepiness when combined with ethanol. In contrast, consistently less performance impairment was associated with zaleplon than triazolam, both with and without ethanol. The extent to which a subject's performance ability may have influenced that subject's assessment of their state of sleepiness can not be known. A direct physiological measure of sleepiness would have avoided this problem. Additionally, in attempts to replicate this study, the use of multiple doses of each drug will be important in establishing sedative equipotency.

Another critical factor may be the time-of-day at which sedation and performance-impairment is tested. The choice of drug dose for this study was based on the previous study which used a night-time administration. The drugs were administered and assessed during the daytime in this study. An earlier study found that the sedative and performance-impairing effect of ethanol varied as a function of time-of-day [17]. Night-time versus daytime testing may yield somewhat differential sedative and performance-impairing effects of these two drugs.

Acknowledgements

This research was supported by NIAAA, grant #ROl-AA07147, NIMH, grant #ROl-MH59338 and Wyeth–Ayerst Research.

References

[1] Beer B, Clody DE, Mangano R, Levner M, et al. A review of the preclinical development of zaleplon, a novel non-benzodiazepine hypnotic for the treatment of insomnia. CNS Drug Rev 1997;3:207–224.

[2] Rosen AS, Fournie P, Darwish M, Danjou P, et al. Zaleplon pharmacokinetics and absolute bioavailability. Biopharm Drug Dispos 1999;20:171–175.

[3] Greenblatt DJ, Harmatz JS, von Moltke LL, Ehrenberg BL, et al. Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. Clin Pharmacol Ther 1996;64:553–561.

[4] Sanger DJ, Morel E, Perault G. Comparison of the pharmacological profiles of the hypnotic drugs, zaleplon and zolpidem. Eur J Pharmacol 1996;313:35–42.

[5] Beer B, Leni JR, Wu WH, Clody D, et al. A placebo-controlled evaluation of single, escalating doses of zaleplon (CL 248,846), a non-benzodiazepine hypnotic. J Clin Pharmacol 1994;43:335–344.

[6] Fry J, Scharf MB, Berkowitz DV, Brown DW, et al. A phase 111, 28 day, multicenter, randomized, double-blind, comparator- and placebo-controlled, parallel-group safety, tolerability, and efficacy study of 5, 10, and 20 mg zaleplon, compared with 10 mg of zolpidem or placebo in adult outpatients with insomnia (Abstract). Sleep 1998;21:S262.

[7] Walsh JK, Fry J, Erwin CW, Scharf M, et al. Efficacy and tolerability of 14-day administration of zaleplon 5 mg and 10 mg for the treatment of primary insomnia. Clin Drug Invest 1998;16:347–354.

[8] Roth T, Roehrs TA, Vogel GW, Dement WC. Evaluation of hypnotic medications. In: Prien RF, Robinson DS, editors. Clinical evaluation of psychotropic drugs, principles and guidelines, New York: Raven Press, 1995. pp. 579–592.

[9] Nicholson A. Hypnotics: clinical pharmacology and therapeutics. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine, 2nd ed., Philadelphia, PA: W.B. Saunders, 1994. pp. 355–363.

[10] Roth T, Roehrs TA, Fortier J, Koshorek G, et al. Dose response effects of a new hypnotic in insomniacs (Abstract). Sleep Res 1995;24:53.

[11] Rechtschaffen A, Kales A. A manual of standardized, techniques and scoring system for sleep stages of human sleep. Los Angeles, CA: Brain Information Service/Brain Research Institute, University of California at Los Angeles, 1968.

[12] Carskadon MA, Dement WC, Mitler MM, Roth T, et al. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1968;9:519–528.

[13] Bishop C, Roehrs T, Rosenthal L, Roth T. Alerting effects of methylphenidate under basal and sleep-deprived conditions. Exp Clin Psychopharmacol 1997;5:344–352.

[14] Roehrs T, Timms V, Zwyghuizen-Doorenbos A, Buzenski R, et al. Polysomnographic, performance, and personality differences of sleepy and alert normals. Sleep 1990;13:395–402.

[15] Roehrs T, Merlotti L, Zorick F, Roth T. Sedative, memory and performance effects of hypnotics. Psychopharmacology 1994;116:130–134.

[16] Roehrs T, Beare D, Zorick F, Roth T. Sleepiness and ethanol effects on simulated driving. Alcohol Clin Exp Res 1994;18:154–158.

[17] Roehrs T, Zwyghuizen-Doorenbos A, Knox M, Moskowitz H, et al. Sedating effects of ethanol and time of drinking. Alcohol Clin Exp Res 1992;16:553–557.

[18] Roth T, Kramer M, Lutz T. The effects of hypnotics, performance, and subjective state. Drugs Exp Clin Res 1977;1:279–286.