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Effects of Alcohol, Zolpidem, and Some Other Sedatives and Hypnotics on Human Performance and Memory

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MATTILA, M. J., J. VANAKOSKI, H. KALSKA AND T. SEPPÄLÄ. *Effects of alcohol, zolpidem, and some other sedatives and hypnotics on human performance and memory.* PHARMACOL BIOCHEM BEHAV **59**(4) 917–923, 1998.— Zolpidem (Zol), an ω_1-agonist, acts via $GABA_A$ receptors but may differ qualitatively from diazepam (Dz) and other benzodiazepines (BZDs). We conducted a placebo-controlled, randomized, double-blind, and crossover study to compare the psychomotor and cognitive effects of 15 mg Zol with those of 15 mg Dz, 30 mg oxazepam (Ox), 7.5 mg zopiclone (Zop), and ethanol (EOH; 0.65 + 0.35 $g \cdot kg^{-1}$) given to 12 subjects at 1-week intervals. Psychomotor tests (symbol digit substitution, simulated driving, flicker fusion, body sway) were done before and 1, 3.5, and 5 h after intake; immediate and delayed memory were measured between 1.5 and 3.5 h. The plasma concentrations of drugs were measured by gas chromatography and by radioreceptor assay (RRA). The mean values of EOH in blood at 1.5, 4, and 5.5 h were 0.82, 0.88, and 0.6 $g \cdot l^{-1}$, and the mean values of RRA-assayed plasma Dz were 470, 330, and 210 $\mu g \cdot l^{-1}$, respectively. The corresponding values of other hypnosedatives, in Dz equivalents ($\mu g \cdot l^{-1}$), were 550, 750, and 330 for Ox; 350, 270, and 70 for Zol; and 160, 210, and 70 for Zop. The standard RRA graph for Zol was significantly flatter than those for other hypnotics. Zol impaired coordinative, reactive, and cognitive skills at 1 and 3.5 h more clearly than the other agents did, the most sensitive performance (tracking) still being impaired by Zol at 5 h. Dz and Zop were less active than Zol objectively; subjective sedation after Dz and Zol was stronger than after Zop. Compared to placebo, all active agents tended to impair learning and memory, their decremental effects, in declining order, being Zol, Dz > EOH, Ox > Zop. During the delay, Dz and Zol caused similar losses of material that had been learned. When separating "true" delayed memory from immediate memory (attention important), Dz and Zol had equieffects on delayed memory and were more detrimental than Zop. When contrasting that against the impaired psychomotor performances, it is possible that 15 mg Zol impairs memory relatively less than 15 mg Dz does. © 1998 Elsevier Science Inc.

Diazepam Ethanol Oxazepam Zolpidem Zopiclone Memory Performance Plasma concentrations

THE concept of ω-agonists (12) refers to drugs acting via the $GABA_A$–receptor/chloride channel complex similar to benzodiazepines (BZDs), yet differing in structure from BZDs. The discovery and cloning of $GABA_A$-receptor subunits (17,24) launched the search for hypnotics and anxiolytics having minimal acute (memory impairment) and chronic (dependence) adverse effects. Zolpidem is a short-acting imidazopyridine hypnotic, ω_1-agonist that is able to produce sedation without interfering with muscle coordination (ω_2-effect) and that has negligible if any residual effects 9 h after intake (11,30). This lack of residual effects may result from its rapid metabolism via CYP3A4 and CYP1A2 isoenzymes (23). The affinity of zolpidem to $GABA_A$ receptors is favored by the presence of an α_1-subunit, whereas the presence of an α_5-subunit minimizes the affinity of zolpidem, but not of diazepam, to $GABA_A$ receptors (18). This difference between diazepam and zolpidem has been thought to explain the relatively weak effect of zolpidem on memory reported in the early studies (4). In later studies, however, zolpidem and triazolam have similarly impaired memory after daytime (31) and nighttime (25) administration. The dose–response relationship for zolpidem in human studies has been fairly flat, and its hypnotic doses range from 5 to 20 mg.

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Zopiclone is another non-BZD hypnotic, a cyclopyrrolone ω_{1+2} agonist (12) that may differ from zolpidem in vitro (6,9) and in vivo (13). Zopiclone is less selective than zolpidem in binding to the recombinant $GABA_A$ receptor subunits (6). The present study was conducted to determine whether a substantial dose of zolpidem (15 mg) impairs human performance but not necessarily memory, and whether zolpidem differs in these terms from zopiclone (7.5 mg) and from the anxiolytic BZDs, diazepam (15 mg), and oxazepam (30 mg). These two BZDs are occasionally used as hypnotics (22). Oxazepam represented a weak positive control, and ethanol (1 $g \cdot kg^{-1}$ was included in the study owing to its well-known effects on body balance and memory.

METHOD

Subjects

Twelve healthy subjects (five women, seven men), aged 21–28 years and weighing 58–83 kg, gave their written informed consent, practiced the tests, and were paid for their time. The protocol was approved by the Ethics Committee of the Institute of Biomedicine, University of Helsinki. The clinical examination also included relevant clinical chemistry tests of organ functions.

Design and Treatments

In the double-blind triple-dummy crossover study the subjects took 15 mg zolpidem (Zol), 7.5 mg zopiclone (Zop), 15 mg diazepam (Dz), 30 mg oxazepam (Ox), ethanol (EOH; 0.65 + 0.35 $g \cdot kg^{-1}$), and respective placebos in Latin-square order at weekly intervals. The drugs and placebos were given identical gelatin capsules, and ethanol was blended (20%) with orange juice serving as a placebo drink. Oxazepam (and placebo for other drugs) was given at −45 min before the intake of other active treatments; the placebos given at 0 h were placebo capsule, placebo juice, and extra placebo capsule for oxazepam. The second dose of ethanol was given 2 h after the first one. The sessions began at 1000 h, and the 12 subjects entered the testing round at 7-min intervals. The tests were made at baseline and 1, 3.5, and 5 h after intake. The posttreatment tests at 1 and 3.5 h were chosen to enable the inclusion of memory tests; these times may also refer to falling asleep and an occasional wake up, respectively. The deviating times of administration of Ox and EOH were chosen to optimize their concentration–effect relationships for the tests. The gelatine capsules for placebo and active drugs were filled with lactose or/and ground commercial tablets in the Helsinki University Pharmacy. Thus, zolpidem refers to Stilnoct^R (Astra Arcus, Sweden), and zopiclone to Imovane^R (Rhone-Poulenc Rorer, France); both diazepam (Diapam^R) and oxazepam (Opamox^R) came from Orion, Finland. Absolute ethanol was used for alcoholic drinks.

Psychomotor Tests

The computerized symbol digit substitution (SDS) test (20) lasted for 2 min, and the numbers of correct and incorrect substitutions were recorded. New matched codes were administered at consecutive testing rounds. Simulated driving (tracking + mixed reactions) (14) lasted for 6 min. Its first half comprised simple tracking only. During the second half (complex tracking), visual and aural stimuli were given, the responses to be given by pressing the button and pushing the foot pedal according to complex rules. Tracking errors and their severity (percent of time driven off the road) were recorded for both halves separately, and together (TESI = tracking error severity index). Reaction errors and cumulative reaction times were recorded. Body balance was measured on an electronic platform (21) with the eyes open and closed, for 1 min each. The critical flicker fusion frequency (8) was measured by looking at red flickering lights a distance of 80 cm away, the pupil diameter being fixed by special glasses.

Subjective drug effects were assessed on the selected ungraded 100 mm visual analogue scales (VAS), the pairs of adjectives, in Finnish, being drowsy/alert, nervous/calm, clumsy/skilful, uncontented/contented, withdrawn/sociable, quick-witted/mentally slow, and the overall evaluation of very good/very poor performance. Every testing round started with the assessments on VAS.

Memory Test

Verbal memory and learning were tested between the first and second posttreatment psychomotor rounds. The memory task requires the subject to learn a list of 16 unrelated Finnish words over four acquisition trials. The immediate free recall score refers to the sum of all correct responses given in four consecutive administrations of the list, learning effect refers to the increase in score from the first to the last administration, and the delayed free recall score refers to the number of words correctly recalled after 90 min. There were four acquisition trials. The first acquisition took place 1.5 h after the treatment capsule had been taken. As each acquisition trial (and immediate recall) took 4–6 min, all four acquisition trials were completed by 2 h after the treatment capsule had been taken, and the free recall was given at 3.5 h, immediately before the next psychomotor round.

As oxazepam was taken at −45 min, both acquisitions and free recall after oxazepam took place 45 min later than those after the other treatments.

Concentrations of Drugs

Blood ethanol concentrations were estimated from breath using an Alcolmeter. Gas chromatography (GC) was used to

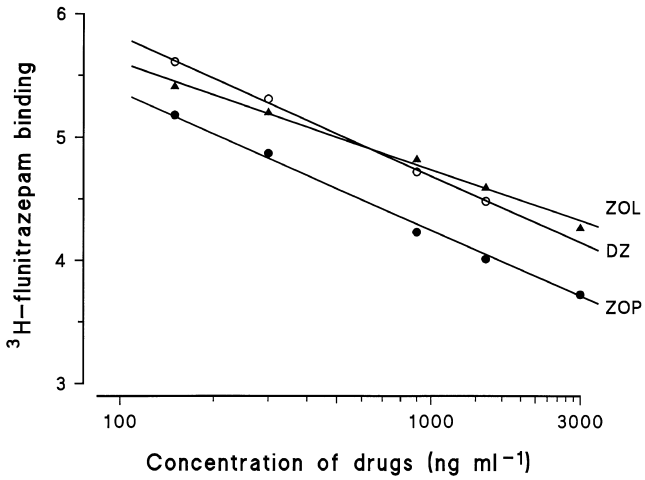

FIG. 1. Displacement of labeled flunitrazepam from the rat brain tissue in vitro by diazepam (DZ), zolpidem (ZOL), zopiclone (ZOP), and oxazepam, added in pooled baseline plasma to the incubation. Graphs refer to reduced concentrations of radioligand present in brain tissue; means of six to eight experiments for each drug. The graph for oxazepam is not shown; it was nearly identical with the DZ graph.

TABLE 1

COMPARATIVE PLASMA CONCENTRATIONS OF HYPNOTICS MEASURED BY GAS CHROMATOGRAPHY (GC) AND BY RADIORECEPTOR ASSAY (RRA) AGAINST DIAZEPAM STANDARD OR THEIR AVERAGE OWN STANDARDS (FIG. 1)

	Mean ± (SEM) Concentrations ($\mu g \cdot l^{-1}$) of Hypnotics in Plasma; $n = 12$					
	Assayed by GC			Diazepam Equivalents by RRA		
Drug/Time	1.5 h	4 h	5.5 h	1.5 h	4 h	5.5 h
Diazepam	342 (42)	228 (27)	213 (13)	480 (70)	330 (50)	210 (30
Oxazepam	190 (19)	255 (34)	213 (13)	550 (70)	750 (90)	330 (60)
Zolpidem	196 (45)	137 (25)	65 (13)	350 (80)	270 (70)	70 (20)
Zopiclone	93 (17)	71 (6)	48 (3)	160 (30)	210 (30)	70 (20)

$n = 11$ for zolpidem.

measure the plasma concentrations of diazepam, oxazepam, and zolpidem (13) and of zopiclone (10). To compare their "commensurable" concentrations expressed in diazepam equivalents, the plasma samples without solvent extraction were assayed for BZD power by using radioreceptor assay (RRA) (19). ^{3}H-Flunitrazepam (0.9 nM) was used as the radioligand, rat cerebral cortex (0.25 mg protein) as the receptor preparation, and the light-protected incubation on ice lasted for 60 min; the nonbound radioligand was removed under machine vacuum. The results (baseline subtracted) were read off the logit standard graph for diazepam (150, 300, 900, and 1500 $ng.ml^{-1}$) made for each subject's baseline plasma. The corresponding graphs were separately produced for oxazepam, zolpidem, and zopiclone as well (Fig. 1).

Statistics

Mean ± SEM values were computed for absolute and Δ-performances (changes from baseline). Three-way (drug × subject × week) ANOVA, Newman–Keuls and paired *t*-tests

TABLE 2

EFFECTS OF ETHANOL (EOH), OXAZEPAM (OX), DIAZEPAM (DZ), ZOLPIDEM (ZOL), AND ZOPICLONE (ZOP) ON COORDINATIVE, REACTIVE, AND COGNITIVE PERFORMANCES OF HEALTHY SUBJECTS

	Mean ± (SEM) Values of Performance ($n = 12$, except 11 for Zol)						
Test/Time	Placebo	EOH	Ox	Dz	Zol	Zop	F_D
SDS (2 min)							
BL	97 (7)	94 (5)	95 (7)	98 (7)	96 (7)	97 (8)	ns (SW)
1 h	84 (5)*	74 (4)‡	79 (5)*	71 (4)‡§	57 (4)‡¶,**,††	70 (4)‡§	5.77 (S)
3.5 h	87 (6)	75 (4)‡§	75 (5)†§	79 (4)‡§	78 (4)†§	76 (5)‡§	2.45 (S)
5 h	89 (6)	81 (5)‡	82 (5)*	82 (4)‡	83 (5)†	85 (6)†	ns (SW)
TESI							
BL	15 (3)	15 (2)	17 (2)	16 (3)	14 (3)	15 (3)	ns (SW)
1 h	15 (2)	25 (4)*	21 (4)	35 (6)†	104 (20)‡¶,‡‡	41 (7)‡§	18.04
3.5 h	14 (3)	32 (5)†¶	23 (5)	15 (3)**	46 (11)†¶,‡‡	21 (3)*	9.24
5 h	13 (2)	24 (4)*	17 (3)	12 (2)**	23 (4)†¶	17 (3)	6.30 (W)
Reaction time (s × 10)							
BL	497 (17)	484 (14)	480 (11)	488 (18)	503 (24)	482 (14)	ns (S)
1 h	489 (16)	497 (17)	510 (15)†	574 (21)‡§,**,††	691 (45)†¶,††	574 (21)‡¶,**,††	13.64 (S)
3.5 h	496 (18)	519 (14)*	521 (13)*	532 (24)*	561 (30)*	573 (62)	ns
5 h	499 (18)	498 (21)	512 (20)*	522 (18)†	518 (20)	539 (17)‡	ns (S)
Poor performance on VAS (mm)							
BL	21 (4)	27 (5)	26 (6)	26 (5)	30 (5)	24 (5)	ns (SW)
1 h	24 (5)	37 (6)	31 (5)	55 (7)‡¶,**,††	53 (4)‡§,††	39 (6)	6.65 (S)
3.5 h	22 (5)	39 (7)	39 (6)	45 (5)†§	51 (4)†¶	42 (6)	3.56 (S)
5 h	22 (5)	43 (6)§	33 (6)	29 (5)	32 (4)	22 (5)	2.50 (S)

SDS = symbol digit substitution; TESI = tracking error severity index; RT = cumulative reaction time; VAS = visual analogue scale. S and W refer to subject and week effects in three-way ANOVA.

*$p < 0.05$, †$p < 0.01$ and ‡$p < 0.001$ vs. baseline; §$p < 0.05$ and ¶$p < 0.01$ vs. placebo; **$p < 0.05$ vs. EOH; ††$p < 0.05$ vs. Ox; ‡‡$p < 0.05$ vs. any other treatment.

were computed for Δ-values. The differences of the slopes of graphs for hypnotics in the RRA were analyzed with 95% confidence intervals.

RESULTS

Concentrations of Drugs and Alcohol

Mean concentrations of ethanol in blood at 1.5, 4, and 5.5 h were 0.82, 0.88, and 0.60 l^{-1}, and the mean values of plasma diazepam assayed by RRA were 470, 330, and 210 $\mu g \cdot l^{-1}$. The concentrations of other hypnotics as diazepam equivalents, and those obtained by the GC are given in Table 1. It appears that the GC-assayed concentrations were lower than the diazepam equivalents (BZD "power"). When correlating (Pearson) these two assays (GC vs. RRA) at the time of peak responses (3.5 h for oxazepam and 1 h for the others), the *r*-values were 0.500 for diazepam, 0.870 for oxazepam, 0.730 for zolpidem, and 0.426 for zopiclone.

The standard RRA-assayed graphs for diazepam, zolpidem, and zopiclone (Fig. 1) show that zopiclone is more effective than the other drugs. The pairwise comparisons of the graphs ($df = 1, 7$) showed that the graph for zolpidem (angle 0.813; 95% f.l. 0.979–0.647) was flatter ($p < 0.05$) and crossed that for diazepam (angle 1.149; 95% f.l. 1.288–1.0099) (Fig. 1). The corresponding angles of the graphs for oxazepam and zopiclone did not differ from the diazepam graph, respectively.

Psychomotor Performances

The baseline performances showed definite subject effects for all variables and a week effect for several variables but no treatment effect for any variable (Table 2). The tracking errors and their severity recorded for simple tracking were only half of those for the complex tracking, indicating a division of attention during the latter half of driving. At the placebo baseline, for example, the mean number of errors (13) in plain tracking differs from that (23) recorded in complex tracking, $t(22) = 2.55$, $p < 0.05$, unpaired *t*-test. There was a placebo effect on the symbol digit substitution and body sway tests, but not for driving variables or subjective assessments.

As seen in Table 2, zolpidem-induced decrements in coordinative and reactive performances were greater than those recorded after other hypnotics or ethanol. The peak effects of zolpidem were measured at 1 h. Ethanol-induced increases in tracking errors during the first and second halves of the tests at 3.5 and 5 h roughly matched those recorded after zolpidem at these times. The divided attention during the complex tracking (second half) was relatively similar to that seen at baseline. Impairments in the cognitive component of performance (SDS) were more evenly recorded after the active drugs, yet zolpidem had a stronger effect than the others (Table 2). As to flicker fusion, its threshold was significantly lowered at 1 h, $F(5, 71) = 5.57$, $p < 0.001$, and at 3.5 h, $F(5, 71) = 3.59$, $p < 0.05$. These changes were attributable to diazepam at 1 h ($p < 0.01$), oxazepam at 3.5 h ($p < 0.05$) and zolpidem ($p < 0.01$) at both 1 and 3.5 h.

Upon processing the Δ-values of TESI (tracking error severity index) with repeated measures contrast ANOVA, all posttreatment times together, zolpidem, $F(5, 207) = 62.31$, $p < 0.001$, zopiclone, $F(5, 207) = 4.85$, $p < 0.05$, and ethanol, $F(5, 207) = 5.66$, $p < 0.05$, differed from placebo. Zolpidem differed from all other active treatments as well. Similar treatment of the SDS data showed that zolpidem, $F(5, 207) = 15.59$, $p < 0.001$, diazepam, $F(5, 207) = 8.16$, $p < 0.01$, and zopiclone, $F(5, 207) = 7.21$, $p < 0.01$, differed from placebo. As to the cumulative reaction times, Zolpidem, $F(5, 207) = 20.83$, $p < 0.001$, zopiclone, $F(5, 207) = 18.32$, $p < 0.001$, and diazepam, $F(5, 207) = 8.71$, $p < 0.01$, differed from placebo.

The body sway (Fig. 2) with the eyes open was significantly increased at 1 and 3.5 h after ethanol and after zolpidem, while zopiclone increased body sway at 1 h only. With the eyes closed, the baseline sway was twofold that measured for the sway with the eyes open. The individual variations were great, but the prominent sway after zolpidem at 1 h differed from those measured after the other treatments, ethanol included (Fig. 2). In terms of the repeated measures contrast ANOVA against placebo, the body sway with the eyes open and closed were increased by zolpidem, $F(5, 207) = 14.95$ and 21.08, $p < 0.001$, and by ethanol, $F(5, 207) = 8.06$ and 7.67, $p < 0.01$, only.

Attempts were made to correlate (Pearson) plasma log concentrations (GC and RRA) each separately to the corresponding effects (SDS, TESI, reaction times, and body sway with the eyes open) at the time of the peak effect. Because the

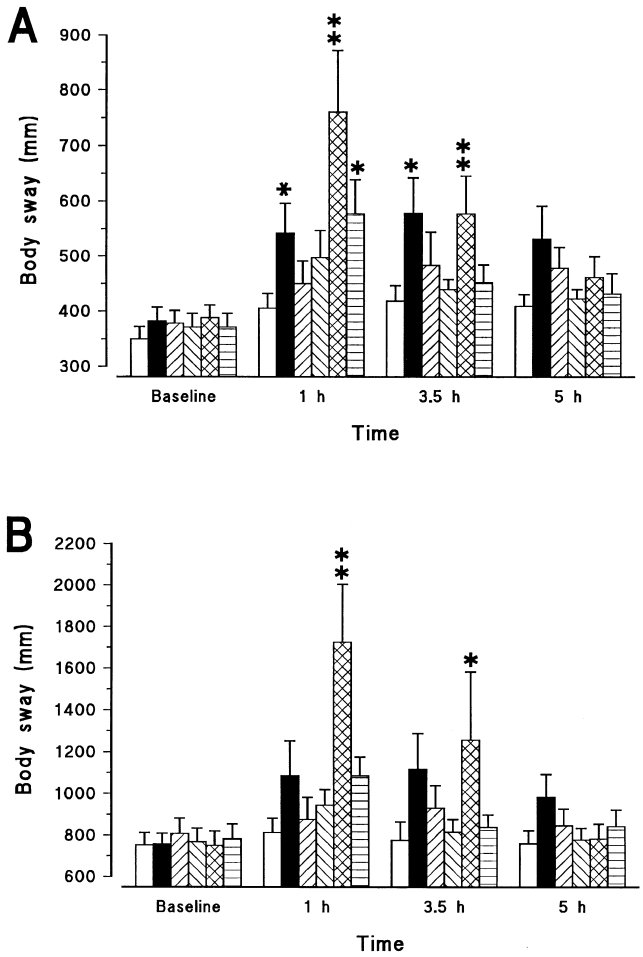

FIG. 2. Effects of zolpidem, zopiclone, and ethanol on the body balance (length of the gravity point movements). The subjects stood on an electrical platform without shoes, with the eyes open (A) and closed (B), for 1 min each. The mean ± SEM values of 12 subjects (11 for zolpidem) are given. The symbols of treatment columns (from left to right) refer to placebo (open), ethanol (solid), oxazepam (rising stripes), diazepam (declining stripes), zolpidem (crosshatched), and zopiclone (horizontal stripes). Asterisk * and ** refer to significant differences from Δ-placebo at $p < 0.05$ and $p < 0.01$ levels, respectively.

responses (Δ-values) varied considerably, the *r*-values were low, irrespective of GC or RRA assays being tested. The two largest *r*-values were 0.653 (reaction time/RRA; diazepam) and 0.640 (body sway/RRA; zolpidem).

Memory Tests

Compared to placebo, active treatments tended to impair acute and delayed memory (Table 3), zolpidem being the most potent in impairing acute memory and learning. As to the spontaneous recalls of words after the delay, diazepam and zolpidem differed from placebo; zolpidem also differed from ethanol and oxazepam. Comparison of the delayed recalls with the last learning recalls (Memo ID in Table 3) revealed that diazepam impaired memory slightly but not significantly more than zolpidem. On the Memo ID, two subjects scored 16 words after zolpidem, while the subject with the lowest memory scores recalled only 10 words after placebo.

Subjective Effects

The shifts on VAS were subject to great variations. Partly due to this deviation, no significant drug effects were found, for example, in alertness although diazepam, zolpidem, and zopiclone induced definite drowsiness and many of the subjects fell asleep. There were no shifts towards calmness, contentedness, or being sociable. Oxazepam differed from placebo only in producing clumsiness at 3.5 h, whereas diazepam and zolpidem, to a lesser extent also zopiclone, produced clumsiness, mental slowness, and overall poor performance.

DISCUSSION

The data presented indicate, as expected, that 15 mg zolpidem was more effective than the comparator drugs in producing decrements on psychomotor performance and immediate memory and learning. However, 15 mg diazepam matched 15 mg zolpidem on subjective sedation on VAS, and on the decrements in delayed recalls of learned material. This discrepancy between the decrements on psychomotor performance and delayed memory suggest that these two drugs have qualitative differences.

The GC-assayed plasma concentrations of drugs related to their doses used tallied with those published previously (10,13, 19,27). The "commensurable" RRA-assayed diazepam equivalents proved more complex, owing to an active metabolite (nordiazepam) and from somewhat different receptor events of zolpidem (6,18) and zopiclone (5,6). The amount of nordiazepam is not important during the first hours (19). Although the correlation of the log concentration of drugs with drug effects showed low *r*-values, this took place with both GC- and RRA-assayed concentrations tested. The flat log concentration/effect graph for zolpidem (Fig. 1) suggests its character of partial agonism; this tallies with the benign course of monointoxications following high doses of zolpidem (7).

The high plasma concentrations of oxazepam, as diazepam equivalents, were contradictory to its relatively mild effects on performance and memory, yet the GC and RRA concentrations in plasma moderately correlated with each other. Because the RRA-assayed log concentration/effect graphs for diazepam and oxazepam in vitro were almost identical, the dose of 30 mg of oxazepam should produce plasma concentrations higher than those after diazepam 15 mg, unless their pharmacokinetic differences cloud the issue. The large concentrations of oxazepam in diazepam equivalents, compared with its lower GC-assayed concentrations (Table 1) could be an outcome of its pharmacokinetics; a possible role of oxazepam glucuronide cannot be excluded. Compared with diazepam, oxazepam's milder effects could result from its well-known slower absorption and brain penetration.

Does zolpidem differ qualitatively from the other hypnosedatives studied? In a number of appropriate studies, with two or three equiactive doses for both zolpidem and the comparator drug, zolpidem has proved similar to the other BZDs tested. Thus, zolpidem (5, 10, and 15 mg) and triazolam (0.125, 0.25, and 0.5 mg) proved similar when compared after bedtime, performance and memory being measured 1.5 h after intake (25,31). In a daytime study (26) with escalating doses of zolpidem (5, 10, and 20 mg) it was revealed that zolpidem resembles triazolam (0.125, 0.25, and 0.5 mg) and temazepam (10, 20, and 40 mg) as to their decremental objective and subjective behavioral effects in healthy subjects (26). In studies using only one dose of zolpidem (10 mg) and equiactive comparator drug(s) have showed that the effects of zolpidem 10 mg after are comparable with triazolam 0.25 mg (2,25). In a recent comparative bedtime study (1), zolpidem 10 mg, zopiclone 7.5, and flunitrazepam 1 mg similarly impaired psychomotor performance and memory during 4 h after intake; some impairment was still found at 7 h.

Plausibly, there is no major qualitative pharmacodynamic difference between zolpidem and zopiclone in their acute ef-

TABLE 3

IMMEDIATE (MEMO I) AND DELAYED (MEMO II) RECALLS OF WORDS (MAX 16)

	Mean ± (SEM) Values of Performance (n = 12, Except 11 for Zol)						
Test/Time	Plac	EOH	Ox	Dz	Zol	Zop	F_D
Memo IA	7.9 (0.8)	7.3 (0.5)	6.4 (0.7)	6.6 (0.5)	5.6 (0.7)*	7.3 (0.5)	2.80 (S)
Memo IB	11 (0.6)	10 (0.6)	10 (0.9)	9.3 (0.7)	8.4 (1.0)*	9.8 (0.7)	ns (S)
Memo IC	13 (0.8)	11 (0.9)	11 (1.0)*	11 (0.8)*	9.5 (1.3)†	11 (0.7)	3.23 (SW)
Memo ID	14 (0.7)	12 (0.9)*	13 (0.9)¶	13 (0.6)¶	11 (1.0)†§	12 (0.8)	4.32 (SW)
Memo I Σ	45 (3)	41 (3)	40 (3)	39 (2)	34 (4)†	41 (2)¶	4.13 (S)
Delay 1.5h							
Memo II	12 (0.2)	9.0 (1.2)	10 (1.1)	7.6 (1.3)†‡§	6.7 (1.5)†‡§	9.3 (1.3)¶	7.17 (S)
(ID–II)	2.0 (0.7)	3.0 (0.7)	2.3 (0.7)	4.2 (0.8)†§	4.0 (0.8)*	2.9 (0.8)	3.70 (S)

Memo IA, IB, IC, and ID refer to the four consecutive immediate tests. Statistical symbols as in Table 2.
*$p < 0.05$ and †$p < 0.1$ vs. placebo; ‡$p < 0.05$ vs. EOH; §$p < 0.05$ vs. Ox; ¶$p < 0.05$ vs. Zol.

fects in human beings, although differences have been found in vitro (6) and in rodents (3,28). Schmid et al. (29) studied the binding of zolpidem to BZD receptors in vivo by using positron emission tomography and ^{11}C-labeled flumazenil. Although the displacement of radiotracer by zolpidem was monophasic in the neocortex and the cerebellum, two different kinds of binding sites (high and low affinities) were detected in several subcortical regions. The latter finding contrasts with the corresponding rodent data and thus emphasizes species differences. Zopiclone may have substantial advantages over the BZDs in terms of dependence and abuse potential (11), but similar advantages with zolpidem have not been sufficiently documented thus far.

The results with temazepam vs. zolpidem (26) might imply that diazepam is comparable to these atypical hypnotics in acute human studies. The largest dose of temazepam (40 mg), however, showed some ceiling effects, and diazepam in our study matched zolpidem subjectively but not objectively (Table 2). The "equiactive" anxiolytic/sedative effects of BZDs can be differently composed, as suggested by the diazepam-induced enhancement of serotonergic activation in rats under chloralose anesthesia. Lorazepam shared the diazepam action but was twofold less potent (15). It may be that differences between BZDs are not only pharmacokinetic but sometimes pharmacodynamic as well.

The definite impairment of body balance by zolpidem in our study (Fig. 2) was unexpected because the mild effect of 15 mg diazepam on body sway, particularly with the eyes closed, has been a common finding in our laboratory. Without speculating the mechanisms of the zolpidem-induced body sway in young subjects, the elderly should avoid large doses at bedtime, for not to encounter unexpected dizziness at an occasional wake up after a 3–4 hour sleep.

The different affinity of zolpidem vs. diazepam to $GABA_A$ receptors (18) has raised the question of whether this difference might reduce mnesic impairments in favor of zolpidem. However, in several studies zolpidem, triazolam, and flunitrazepam have proved qualitatively analogous in producing anterogradic amnesia on different memory tests. As to the effects of the BDZs on episodic memory, poor learning is largely due to impaired attention, whereas the loss of material that has been learned, as the difference Memo ID—Memo II in our study (Table 3), might represent an impairment in consolidation processes (16). In these terms, the numerally same 15 mg dose of diazepam and zolpidem caused similar losses in the material learned, while zolpidem was more decremental on learning acquisition, presumably due to impaired attention, which also caused even deep impairments in psychomotor tests (Table 2). However, an assumption of zolpidem impairing "true" memory relatively less than diazepam does should be taken with reservation, because these drugs started the 1.5 h delay at different levels (Table 3).

In conclusion, the moderately high 15 mg dose of zolpidem given during daytime caused definite impairments of coordinative, reactive, and cognitive performances. As to the RRA-assayed plasma concentrations of hypnosedatives, they correlated moderately with the GC-assayed concentrations while the concentrations–effect correlations were low for both. RRA-assayed diazepam and zopiclone, as the groups, tallied fairly well in their effects and constructed standard graphs. The responses to zolpidem were strong but not in every subject. Compared to 7.5 mg zopiclone, another type of ω-agonist, zolpidem, in a dose of 15 mg, was quantitatively more effective, and it definitely impaired performance and memory. There was no clear qualitative overall differences on the memory impairment by diazepam, zopiclone, and zolpidem, but the relative effect of zolpidem on delayed memory was, perhaps, milder than that of diazepam. However, unexpected response levels after zolpidem vs. comparator drugs may be partly due to different dose levels of the drugs used.

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