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Lorazepam and Diazepam Differently Impair Divided Attention

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JALAVA, K.-M., M. J. MATTILA, M. TARSSANEN AND J. VANAKOSKI. *Lorazepam and diazepam differently impair divided attention.* PHARMACOL BIOCHEM BEHAV 51(2/3) 189–197, 1995.—Effects of ethanol (EtOH, 0.65 + 0.35 g · kg^{-1}), diazepam (DZ, 15 and 30 mg), lorazepam (LZ, 2 mg) on divided attention were measured in two placebo-controlled crossover studies with healthy young subjects. The test comprised four parallel computer screens with a ball moving along a circular obstacle course on each screen at different rates. When the ball entered an obstacle on any screen, the subject had to press the respective button. The obstacles varied in numbers and shapes, and randomly changed their location every 10 s. Concomitant aural stimuli were responded to by pushing the foot pedals. The primary visual variables were the absolute and percent numbers of correct responses on each screen. Concentrated attention was measured with a symbol digit substitution (SDST) and digit copying (DDCT) tests, for 3 min each. In Study I, with 12 subjects, the tests (4 min) were made before the treatment (placebo, EtOH, DZ) and 1, 3, and 6 h after intake. EtOH impaired attention on the lateral but not on medial screens, with and without aural stimuli, the "special" obstacles of deviating shape being the most sensitive targets to EtOH effects. DZ 15 mg did not modify divided attention whereas it impaired SDST performance and was subjectively slightly more potent than EtOH on visual analog scales. DZ 30 mg impaired attention on the lateral screens, with and without aural stimuli, but without preference to "special" obstacles. It also reduced responses to aural stimuli, strongly impaired SDST and DDCT, and caused subjective sedation. In Study II, with 9 subjects, the test run without aural stimuli was easier but lasted for 15 min. The treatments were placebo, EtOH, and LZ, and the posttreatment tests were 1.5 and 3.5 h after intake. Both EtOH and LZ impaired attention on the lateral screens, at "special" obstacles in particular. EtOH and especially LZ impaired SDST performance and produced subjective sedation on visual analog scales. It appears that the control of varying visual events on parallel screens does not need extra aural events to divide the attention. Considering the effects and plasma concentrations of DZ and LZ, their actions may differ not only quantitatively but also qualitatively.

Divided attention Symbol digit substitution Ethanol Diazepam Lorazepam Human studies

ADEQUATE human skills performance related to driving and some occupational events requires keen attention, controlled reactions without haste, and reasonable coordinative skills (8). The performance models constitute an important obstacle in studies of relationship between the use of drugs and the driving performance. Cognitive perceptual performance consists of concentrated (vigilance) and divided attention. These two components are differentially affected by various drugs, and they are tested separately. The subject's risk-taking behaviour is an important variable, but it is difficult to measure.

When testing concentrated attention, the rate of information processing requirement is low, and these tasks evaluate the architecture of the information-processing system. In a test for divided attention there are two or more subtasks so that the capacity of the human skills performance is overloaded. It follows that one or both subtasks are performed below the level than would be the case if performed alone (5,24–27). Divided attention is an integral requirement of many driving, flying, and occupational situations (25,29,30).

Ethanol dose-relatedly impairs divided attention in various conditions and enhances the effects of drugs, such as cannabis and benzodiazepines (14,18,20,23,25,26,35), that alone do not impair divided attention. The great sensitivity to ethanol (even to 0.15 g · l^{-1}) reported by Moscowitz et al. (26) might result from a good, long-lasting test driven in a low-arousal environment and the nontolerant subjects being paid for the scores. In less precise "natural" conditions, larger doses of alcohol are needed, but they mostly impair divided attention. The complexity of the drug and alcohol effects on divided attention is shown by cannabis, which impairs divided attention

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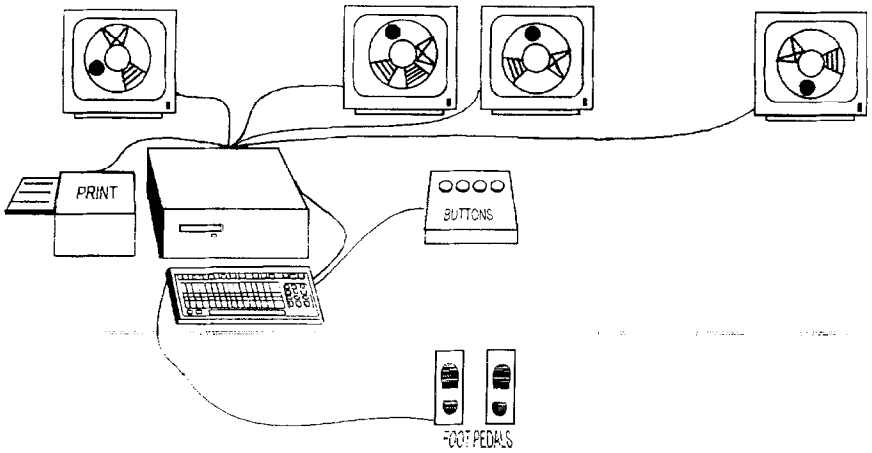

FIG. 1. Composition of the divided attention test shows the division of the four screens to the medial (2 + 3) and lateral (1 + 4) ones. The viewing angle (120°) prevents the adequate observation of the events on the lateral screens at the same time. The subjects are instructed to divide their attention in balanced way to both medial and lateral scores, and to prefer the events at "special" obstacles to the ordinary ones wherever they appear.

under an acquired tolerance to it but not without tolerance (18,25).

Linnoila (15) measured divided attention with a mechanical test composed of four dials in front of the subjects. The lateral dials were at the angle of 120°, the subject being unable to observe all the dials at one glance. Each dial had a pointer revolving at different rates over the obstacles, which varied in numbers in different dials. Every time an arrow touched an obstacle in any dial, the subject had to press the respective button.

Ethanol and an antimuscarinic (glycopyrrolate) impaired the relative performance on the lateral dials (15). In later studies, diphenhydramine (100 mg) but not diazepam (0.3 mg · kg^{-1}) reduced the percent correct responses on the lateral screens (20).

The locations of obstacles were constant in this test, thus allowing learning and prediction of events on these positions. To reduce such a prediction, we computerized that test, and report the effects of alcohol and benzodiazepines on this performance.

METHOD

Subjects

Twelve healthy subjects, seven men and five women, aged 20–28 years and weighing 58–78 kg, volunteered for the study and were paid for their time. The subjects did not use medicines regularly or alcohol in excess; they were free of mental and somatic disease; and five of them had previous experience of single oral doses of zopiclone, suriclone, or diazepam given in psychomotor tests. The study design was approved by the Ethics Committee of the Department of Pharmacology and Toxicology, University of Helsinki. The subjects practised the tests before entering the study, and they were advised to have a light breakfast without coffee in the morning of the test days.

Design

Study I was a double-blind, crossover comparison of ethanol (1 g · kg^{-1}), diazepam (15 mg) and placebo given orally in balanced (Latin square) order at 1-week intervals. Because most of the subjects were diazepam naive, the large dose of 30 mg diazepam was given as the last treatment 1 week after the randomised study. Diazepam was given in gelatine capsules prepared by University Pharmacy from the ground commercial tablets. On each day, the subjects took with water three capsules containing placebo or diazepam. Then they received a drink (6.5 ml · kg^{-1}) containing plain diluted fruit juice or 20% ethanol in the juice. The main volume (2/3) of the drink was served after the capsule intake, and the rest (1/3) 1.5 h thereafter. The drinking times were 30–40 min each.

The subjects were tested in one group and entered the testing rounds at 10-min intervals. Each session began with the baseline round (the first subject at 0830 h) followed by the intake of capsules and drink. Posttreatment testing rounds began 1, 3, and 6 h after the intake of capsules, and each round lasted for 20 min. A standard snack was served after the 3-h test round. Venous blood samples (10 ml) were taken and alcohol concentration in breath was measured at baseline and after every testing round.

Study II, with nine subjects, was driven without aural stimuli, but the test lasted for 15 min. The design was as in Study I, except that 2-mg lorazepam replaced diazepam and the test times were 2 and 4 h after intake. The three best subjects, in terms of stable performances in nondrug conditions, were given an extra fee.

Tests

The *divided attention test* (Fig. 1, Table 1) comprised four screens (size 24 × 17 cm) connected to a PC microcomputer. Two medial screens (2 and 3) were side-by-side whereas the two lateral ones (1 and 4) were at the viewing angle of 120°. Each of the screens showed a ball moving along a circular obstacle course, the obstacles having normal or "special" outlook. To respond to visual signals, the subject had a keyboard with four buttons, one button for each screen. The simultaneous (low- or high-pitched) sounds given via earphones were responded to by pushing the respective foot pedal.

Every time a ball entered an obstacle on any screen, the subject pressed the respective button. If there were several

TABLE 1

THE ADJUSTABLE SCREEN VARIABLES IN THE DIVIDED ATTENTION TEST

Variable	Selected	Options
Width of the obstacles	180	100-300
Minimum distance of two obstacles	100	60-80
Numbers of obstacles		
Screen 1	= 2	1-4
Screen 2	= 4	1-4
Screen 3	= 2	1-4
Screen 4	= 2	1-4
Circling rates of the balls		
Screen 1	= 12	1-50
Screen 2	= 15	1-50
Screen 3	= 12	1-50
Screen 4	= 13	1-50
Numbers of special obstacles		
Screen 1	= yes	yes/no
Screen 2	= yes	yes/no
Screen 3	= yes	yes/no
Screen 4	= yes	yes/no
Duration of the test (min)	= 4	1-15
Interval of location changes (s)	= 10	1-30

The circling rates are relative speeds, the speed 2 referring to one revolution/min; the ball speeds selected thus are 4, 6, 6.5, and 7.5 revolutions/min. The widths of the obstacles are also relative variables, the value 180 equal to the twofold diameter of the ball. The time allowed to press the correct answer refers to the half of ball being inside the obstacle.

closely timed events on different screens, the "special" obstacles (Fig. 1) should be preferred to the normal ones. While observing the events on the screens, the subject also responded to aural signals by pushing the left (low-pitch sound) or right (high-pitch sound) foot pedal. The variables recorded from each screen were the numbers of total stimuli and of correct and incorrect responses. The percent correct responses refer to the correct answers divided by the sum of the total stimuli and incorrect answers; incorrect answers were not included when separating the percent correct responses at "special" obstacles. Except for each of the screens separately, the sums of events on the two medial (2 and 3) and two lateral (1 and 4) screens were recorded. From the pooled aural signals recorded, the percent correct responses were computed by dividing the correct answers by the sum of total stimuli and the incorrect answers.

We first selected an optimal combination of variables (Table 1) to provide sufficient information on the medial screens while retaining the performance on the lateral screens feasibly well. The sound intervals ranged from 2000 ms (minimum) to 5000 ms (maximum). The frequency of the low-pitch sounds was 200 Hz and their duration 500 ms; the values for the high-pitch sounds were 100 Hz and 100 ms, respectively. The time allowed for responding was 1500 ms for either kind of stimuli. In Study II, most of the variables were as in Study I but aural stimuli were withdrawn and the numbers of sectors on the medial screen were reduced from four to two.

Other Tests

The computerized *symbol digit substitution* (SDST) and *digit digit copying* (DCCT) tests (22) lasted for 3 min each. The SDST involved the substitution of simple figures for digits, and it refers to performance under concentrated attention. The numbers of correct substitutions were recorded; matched different codes were used in consecutive tests. The DCCT performance might predominantly refer to the manual component in these computerized tests; the results were recorded as above. Subjective effects were assessed on *visual analog scales* (VAS) using ungraded 100-mm horizontal lines. The subjects located themselves between the two extremes expressed in Finnish and English: drowsy/alert, skillful/clumsy, mentally slow/quick-witted, dizzy/feeling stable, calm/troubled, and very good/very bad performance.

The test rounds always began with divided attention (with or without sounds), followed by DCCT and SDST, and ended with the assessments on VAS. After that, blood alcohol was estimated from breath with Alcolmeter, and venous blood was sampled for the later direct radioreceptor assay (RRA) or plasma for its concentrations of diazepam and lorazepam in diazepam equivalents (19). The role of active metabolites of diazepam within 3 h after intake has been small (nordiazepam 10–15%) or negligible (temazepam, oxazepam).

Statistics

Mean, SEM, and CV values were computed for absolute test performances and for their Δ values (changes from baseline) at each postdrug testing time. Because Study I was partly (diazepam 30 mg) nonrandomized, two-way (subject × drug) ANOVA and Scheffe's test computed for ranked Δ values were used to compare all the treatments of Study I. The randomized part of it (placebo, alcohol, diazepam 15 mg), as well as the data of Study II (Δ values) was analyzed with three-way (subject × week × drug) ANOVA (SAS general linear models), followed by Duncan's multiple comparison. Pearson and Spearman correlations were computed to relate different variables to each other.

RESULTS

Study I

The mean percent correct responses to visual stimuli, pooled from all screens during the placebo condition, remained similar over the whole session. The correct responses were more frequent in the absence (52%) than in the presence (46%) of aural stimuli. As a whole, the subjects responded to aural stimuli (71%) better than to visual stimuli. The average CV values of correct responses to visual stimuli after placebo were 16–20% in the presence of sounds and 15–19% without them. ANOVA showed significant subject effects in about 20% of the tests computed.

The mean concentrations of blood alcohol ($g \cdot l^{-1}$) were 0.72 at 1 h, 0.92 at 3 h, and 0.46 at 6 h. The mean concentrations ($\mu g \cdot l^{-1}$) of diazepam were 470 at 1 h, 420 at 3 h, and 310 at 6 h after diazepam 15 mg. The respective values after diazepam 30 mg were 680, 880, and 600 $\mu g \cdot l^{-1}$. One male subject (75 kg) showed low concentrations of diazepam in plasma after either dose of diazepam. He responded strongly to diazepam 30 mg but only fairly to diazepam 15 mg in the SDST test, and was excluded from Trial II. The large variation in plasma diazepam and its somewhat blunted absorption could have modified the test results; diazepam 15 mg was slightly less active than usually on the SDST performance.

Because *diazepam 30 mg* was given nonrandomized as the last treatment, an insignificant practice effect (+5–10% compared with other treatments) was noted at the baselines of

objective, but not subjective, tests. When analyzed together with the randomized treatments, it did not modify significantly the events on the medial screens, with or without sounds, but reduced the correct responses to aural stimuli ($p < 0.05$) at 3 h (Table 2). On the lateral screens, diazepam 30 mg impaired attention both in the presence (Table 2) and absence of sounds at 3 h. As to the latter, diazepam 30 mg and ethanol differed from placebo and diazepam 15 mg, without clear preference to the "special" obstacles (F_D values 7.71 for "special" and 9.15 for all obstacles). Relating the medial and lateral "special" obstacle performances (AM%S/AL%S) within each subject, neither dose of diazepam differed from placebo whereas ethanol did (F_D 4.22, $p < 0.05$) at 3 h.

The randomized treatments (placebo, diazepam 15 mg, ethanol) were also analyzed separately. In the presence of sounds, ethanol, but not diazepam 15 mg, reduced the numbers of pooled percent correct responses to visual stimuli at 1 h (F_D 4.80, $p < 0.05$) and 3 h (F_D 4.01, $p < 0.05$) whereas the responses to aural stimuli remained uninfluenced. The same variable without sounds was impaired by ethanol at 3 h (F_D 5.03, $p < 0.05$). Considering the numbers of correct responses in particular, ethanol effects in the presence of aural stimuli were clearer ($p < 0.01$) at 1 and 3 h, referring to increased numbers of incorrect responses after ethanol. Combining the data from all three posttreatment times for ANOVA did not add much significance to the drug effects.

The correct percent responses on the lateral screens (AL%) were sensitive to drug effects whereas those on the medial screens (AM%) were not (Fig. 2), irrespective of the sounds being present or absent. The significant drug effects were attributable to ethanol, which was more effective in the absence than in the presence of aural stimuli. Diazepam 15 mg did not impair divided attention. As to the events at the "special"

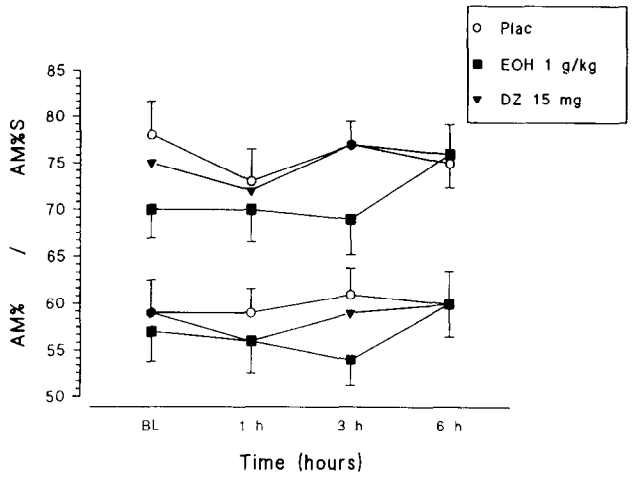

FIG. 2. Total correct percent responses on the medial screens (AM%), and their special fraction recorded at the "special" obstacles (AM%S) in Study 1. Mean ± SEM values are given. The number of "special" obstacles was small and the percent correct responses at them were high. No significant changes by ethanol (EtOH) or diazepam 15 mg (DZ) were noted.

TABLE 2

EFFECTS OF ETHANOL (EtOH) AND DIAZEPAM (DZ) ON THE SYMBOL DIGIT SUBSTITUTION (SDST), LATERAL ATTENTION WITH SOUNDS (ARL%), AND CORRECT REACTIONS (REAC)

	Values of Performances (N = 12)			
Test	Baseline	1 h	3 h	6 h
SDST				
Plac	143 (8)	138 (5)	134 (6)	131 (4)
EtOH	142 (7)	120 (4)*†	115 (5)*	126 (5)‡
DZ15	144 (8)	125 (6)‡	120 (6)‡	124 (5)*
DZ30	158 (8)	127 (5)*†	115 (5)†§	124 (5)†§
F_D		8.89 (S)	9.23 (S)	3.75 (S)
ARL%				
Plac	32 (1.7)	35 (1.7)	31 (1.4)	35 (2.5)
EtOH	33 (1.3)	27 (2.5)*†	27 (2.0)*	32 (2.6)
DZ15	34 (2.0)	31 (2.1)	34 (1.6)	37 (2.1)
DZ30	37 (2.9)	33 (3.2)†‡	31 (3.1)	32 (2.1)
F_D		5.67	NS	NS
REAC				
Plac	41 (2)	43 (2)	43 (2)	41 (3)
EtOH	42 (2)	45 (2)	43 (2)	42 (3)
DZ15	43 (2)	41 (3)	40 (3)	43 (3)
DZ30	47 (1)	43 (2)*	39 (3)*†	42 (3)‡
F_D		3.48	5.90	NS

Values are mean with SEM in parentheses. F_D refers to drug effects and (S) to significant subject effects in two-way ANOVA computed for ranked Δ values.

*Difference from baseline, $p < 0.01$.

†Difference from placebo (Scheffe's test), $p < 0.05$.

‡Difference from baseline, $p < 0.05$.

§Difference from baseline, $p < 0.001$.

obstacles, the ethanol-induced impairment of attention did not reach statistical significance on the medial screens (AM%S), with or without aural stimuli. The respective variable on the lateral screens (AL%S) showed a trend towards ethanol-induced impairment when the sounds were present. Without sounds, the lateral screens showed significant drug effects at 3 and 6 h (Fig. 3) and when the test times were combined (F_D 12.37, $p < 0.001$). These effects referred to ethanol, which differed from placebo, and also from diazepam 15 mg, which did not affect these variables.

When the above variables were interrelated, within the same subjects and testing rounds, the drug effects in the presence of sounds were few and of low significance. Without sounds, the repeated-measures drug effects for AL%/AM% (F_D 5.33, $p < 0.01$) resulted from ethanol-induced impairment of attention on the lateral screens. The respective relationships for the "special" obstacles (AL%S/AM%S) showed even more pronounced drug effect (F_D 12.41, $p < 0.001$), indicating a clear ethanol-induced impairment ($p < 0.01$) on the lateral screens whereas diazepam 15 mg proved inert. Similar but less significant effects appeared separately at 3 and 6 h, and also diazepam 15 mg produced a borderline impairment ($p < 0.05$) at 6 h.

The effects on *concentrated attention* (SDST) are seen in Table 2 and Fig. 4. It appears that the SDST performance declined during the session, even after the intake of placebo. When all four treatments were analyzed together, diazepam 30 mg dominated the drug effects up to 6 h (Table 2). When analyzing the randomized placebo, diazepam 15 mg, and ethanol separately, the combined posttreatment test times showed a drug effect on SDST (F_D 7.71, $p < 0.001$), both ethanol and diazepam ($p < 0.01$) impairing the performance. Significant drug effects at individual test times were found at 1 h only (Fig. 4).

The DDCT performance, which refers to manual dexterity, easily improves during the placebo session (22). It remained constant, the mean values being 273, 278, 273, and 279 at baseline, 1, 3, and 6 h, respectively. This suggests that the testing rounds were overall strenuous. The respective values

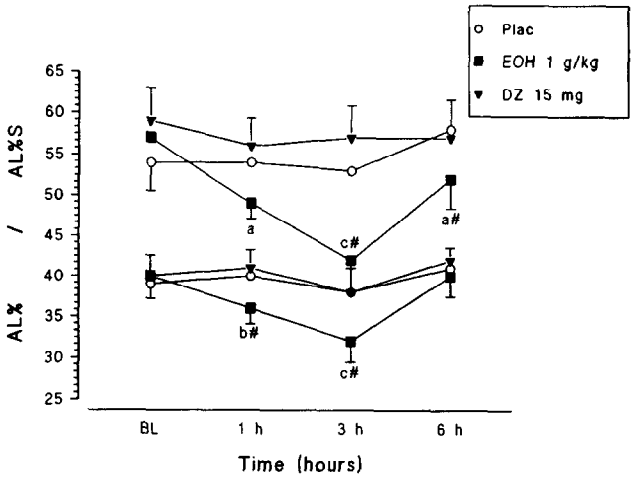

FIG. 3. Total correct percent responses on the lateral screens (AL%), and their special fraction at the "special" obstacles (AL%S) in Study I. [a,b,c]Changes from baseline at 5%, 1%, and 0.1% levels; #difference from placebo, $p < 0.01$. Ethanol (EtOH) was active whereas diazepam 15 mg (DZ) was not.

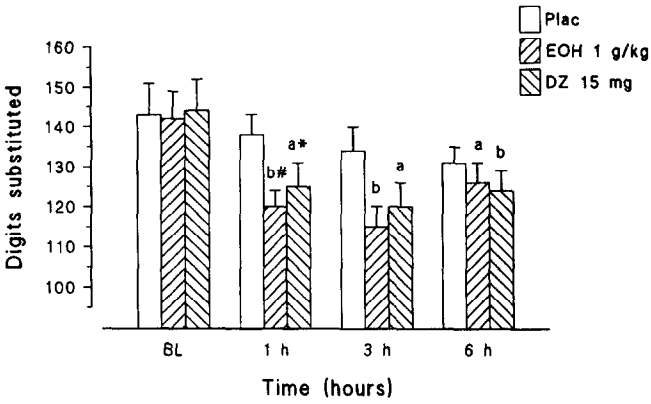

FIG. 4. Effects of ethanol (EtOH) and diazepam 15 mg (DZ) on the symbol digit substition in Study I. [a,b]Changes from baseline at 5% and 1% levels; differences from placebo, *$p < 0.05$; #$p < 0.01$.

were for ethanol 271, 245, 246, and 268; for 15 mg diazepam 272, 259, 256, and 268; and for 30 mg diazepam 288, 280, 258, and 276. Diazepam 30 mg reduced DCCT performance ($p < 0.05$ vs. placebo) at 1 and 3 h, whereas ethanol did so at 1 h only, and diazepam 15 mg did not differ from placebo.

Diazepam, but not ethanol, produced drowsiness and mental slowness whereas both of the drugs produced clumsiness, dizziness, and feeling of impaired performace. The two doses of diazepam differed from each other subjectively less than objectively.

A Pearson correlation was computed for all variables, treatments, and weeks included, using analysis of covariance and the *pooled absolute data* for placebo, ethanol, and diazepam 15 mg. The correct percent responses to aural stimuli did not correlate to any visual variable of divided attention or to SDST or DDCT tests. The correct percent responses to visual stimuli in the presence or absence of sounds correlated to each other ($p < 0.001$) on both the medial ($r = 0.794$) and lateral ($r = 0.745$) screens. The respective correlations computed for the "special" obstacles gave slightly lower r values on the medial (0.622) and lateral (0.638) screens. Relating the correct percent responses on the medial (AM%) and lateral (AL%) screens, the r values were 0.689 for all obstacles and 0.586 for the "special" ones. The subjective variables showed significant correlations to each other but not to the objective measures.

A simple Pearson correlation matrix was computed for the *drug responses* (changes from baseline), including all four treatments and the variables AL%, AL%S, the pooled A% and A%S, SDST, and DDCT at each posttreatment time separately and combined. When combining the test times, the clearest correlations ($p < 0.001$) *after placebo* were found for AL%S related to pooled A%S values ($r = 0.809$), and AL% related to pooled A% values ($r = 0.513$), the correlations improving with time. SDST and DDCT did not correlate to the divided attention variables. *After ethanol*, the correlations within divided attention were as above, but SDST correlated ($p < 0.001$) to AL%S ($r = 0.545$) and to DDCT ($r = 0.661$). These occurred at 1 and 3 h but no more at 6 h. *After diazepam 15 mg*, the correlations within divided attention were similar to or lower than after placebo. SDST correlated to DDCT ($r = 0.508$, $p < 0.01$) and to AL%S ($r = 0.394$, $p < 0.05$), mainly resulting from the diazepam effects at 1 h. *After diazepam 30 mg*, the correlations within divided attention were as after placebo, but SDST correlated ($r = 0.346$–0.597,

p <0.05-0.001) not only to DDCT but also to the variables of divided attention. These correlations were clearest at 1 and 6 h.

Study II

This study, using the test with less information (no sounds, two obstacles on each screen) but of longer duration (15 min), was carried out with nine subjects tested at baseline and 1.5 and 3.5 h after the capsule intake. The mean concentrations of blood alcohol ($g \cdot l^{-1}$) were 0.65 at 2 h and 0.75 at 4 h. The respective mean concentrations of plasma lorazepam ($\mu g \cdot l^{-1}$ in diazepam equivalents) were 510 at 2 h and 380 at 4 h.

There were no significant drug effects on the pooled data from all the screens, irrespective of the correct responses being analyzed in numbers or percent numbers. However, both ethanol ($p < 0.05$) and lorazepam ($p < 0.01$) reduced the correct percent responses at the pooled "special" obstacles at 1.5 and 3.5 h. These drug effects were predominantly on the lateral screens (AL%S), on which the correct responses and percent responses revealed clear-cut drug effects and medial screens did not (Figs. 5 and 6). These significant drug effects on the lateral screens partly resulted from an improved performance during the placebo session; such an improvement was not seen on the medial screens.

When interrelating the above variables within the subjects, as made in Study I, the mean significant drug effects were found at 1.5 h but no more at 3.5 h. Again, AM%S/AL%S gave the clearest drug effects (F_D 6.78, $p < 0.01$); both ethanol ($p < 0.05$) and lorazepam ($p < 0.01$) differed from placebo.

In regard to the *concentrated attention*, the SDST remained stable before and after the intake of placebo. Ethanol and lorazepam caused pronounced decrements in the correct substitutions (Fig. 7). The mean values of DDCT performance under placebo were 282 at baseline, 278 at 1.5 h, and 292 at 3.5 h; the respective values for ethanol were 281, 267, and 264, and for lorazepam they were 289, 254, and 251. Thus, lorazepam impaired this performance ($p < 0.01$ vs. placebo) at 1.5 and 3.5 h whereas ethanol effects reached significance ($p < 0.05$) at 3.5 h only. Both of these agents caused significant ($p < 0.01$-0.05) shifts towards sedation on the VAS, yet significant drowsiness after ethanol appeared late.

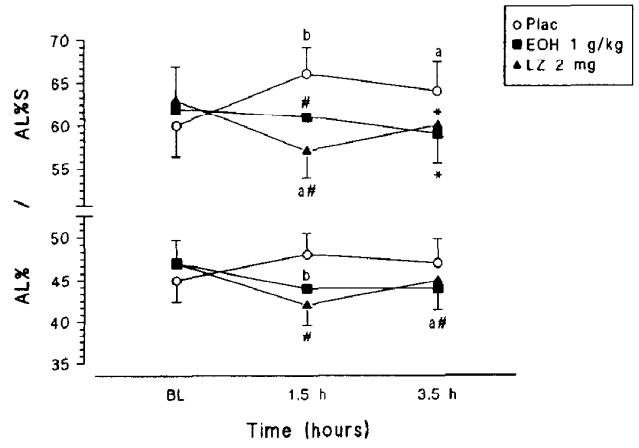

FIG. 5. Effects of ethanol (EtOH) and lorazepam (LZ) on total correct percent responses on the lateral screens (AL%), and their special fraction at the "special" obstacles (AL%S) in Study II. [a,b]Changes from baseline at 5% and 1% levels; difference from placebo, *p < 0.05; #p < 0.01.

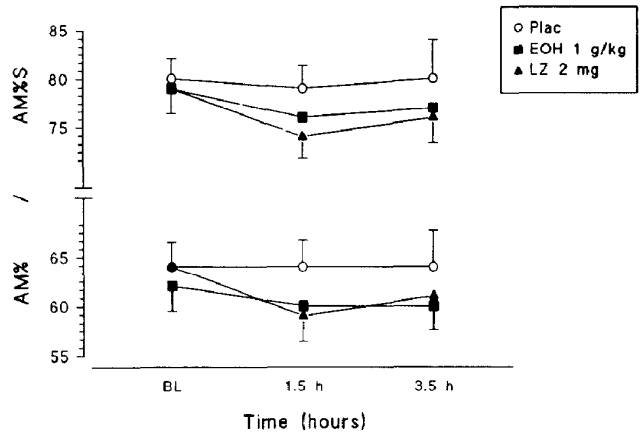

FIG. 6. Total correct percent responses on the medial screens (AM%), and their special fraction at the "special" obstacles (AM%S) in Study II. No significant changes by ethanol (EtOH) or lorazepam (LZ) were noted.

Simple Pearson correlation matrices computed for drug responses (changes from baseline) from pooled results showed that AL% and AL%S correlated to SDST and DDCT at 1.5 h (r = 0.626-0.795, $p < 0.001$) but not at 3.5 h (r = 0.301-0.403, $p < 0.1$). When analyzing the treatments separately, there were no significant correlations after placebo or ethanol. After lorazepam, SDST correlated to AL%S at 1.5 h (r = 0.750, $p < 0.05$) and 3.5 h (0.821, $p < 0.01$). Also, DCCT correlated to AL% (r = 0.882, $p < 0.01$) and AL%S (r = 0.758, $p < 0.05$) at 1.5 h but not later.

DISCUSSION

Our results tally with the view that both ethanol and diazepam impair concentrated attention whereas ethanol, but less so diazepam, impairs divided attention as well (23,25). Unexpectedly, lorazepam 2 mg impaired not only concentrated but also divided attention, even at 3.5 h when the plasma lora-

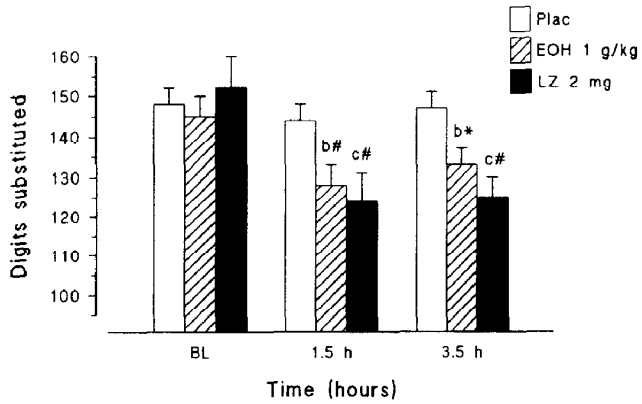

FIG. 7. Effects of ethanol (EtOH) and lorazepam (LZ) on the symbol digit substition in Study II. [b,c]Changes from baseline at 1% and 0.1% levels; differences from placebo, *p < 0.05; #p < 0.01.

zepam concentrations were declining. It thus differed from diazepam 15 mg, although their commensurable plasma concentrations were similar; the twofold dose (30 mg) of diazepam caused decrements more in concentrated than in divided attention. Our visual test for divided attention, with variations (screens, circling rates, obstacle shapes, and locations) in the events, proved satisfactory to detect the effects of alcohol and lorazepam. The presence of sounds did not modify the test except for rendering it more strenuous.

Compositions of divided attention tests vary in different laboratories, depending on the investigator's interests, such as basic research, aging, and drug and alcohol effects (3,5, 10,17,18,25-30,36). As a rule, two or more different, relatively easy subtasks are administered simultaneously. The subjects' fluctuating preference to one subtest creates problems difficult to solve (21). The long duration of the test, up to 1 h, has been considered mandatory for the proper division of attention, but it can jeopardize the subjects' motivation unless they are paid for the scores. Increased load and complexity of information to be processed render especially the aged subjects prone to poor performance not compensated by the practice effect (10,17,27,28). In general, long-lasting monotonous tests are often preferred to the sets of short-lasting tests when measuring drug effects (11,12,25,29), and they may represent quiet driving in low-density traffic. Such tests suit less well to acute single-dose studies for the time courses of drug actions, and might not refer to dynamic occupational tasks or driving in hectic city traffic.

We used the SDST (22) to evaluate concentrated attention, because keen attention is an important factor in simple data-spaced cognitive tests. Although the linear Pearson correlations are subject to arguments, we used them to relate SDST and its manual component (DDCT) to divided attention variables. Changes in SDST performance moderately correlated to respective changes in periferal attention after active drugs, the power order of drugs being lorazepam > ethanol > diazepam 30 and 15 mg. DDCT did not correlate to the visual attention variables, suggesting that the manual dexterity on the buttons did not limit the divided attention performance in our test. The only exception was 1.5 h after lorazepam, when the effects recorded were strong and motor performance might have modulated the results.

The main instruction was to divide the attention in a balanced way to both medial and lateral scores, and to prefer the events at "special" obstacles for the ordinary ones in closely simultaneous events. The amount of information to be processed was supramaximal, and obviously more adequate in Study II than in Study I. Kimchi et al. (10) analyzed dichoptic and binocular viewing in focused and divided attention. They found that divided attention impaired the discrimination of finer details, but there were no major differences between dichoptic and binocular viewing, at least with discrete tasks and short durations of exposure. The binocular viewing of simple events on the set of screens in our test (Fig. 1) thus represents an adequate approach to measure divided attention. The duration of our tests was fairly short, but it provided information of attentive performance differently on the central and peripheral screens, and may not need to be longer than 10–15 min. The order of administration of different tests, strenuous or stimulatory, and the character of the subjects (extroverts vs. introverts) may need extra notion (11,12).

We previously used our test with more visual load, without sounds and "special" obstacles, and the test lasting 5 min, to measure drug actions and interactions on attention. In these terms, 600 mg carbamazepine impaired divided attention (lateral screens) but had less effect on digit symbol substitution; 7.5 mg zopiclone acted vice versa, and the drug combination impaired divided attention less than carbamazepine alone (13). When measuring the effects of 15 mg diazepam, 50 mg amitriptyline, and 15 mg mirtazepine, alone and in combinations (Mattila, unpublished, 1988), both of these sedative antidepressants alone each impaired digit symbol substitution and also attention on the medial but not the lateral screens. In combination with diazepam they impaired both digit substitution and attention on lateral screens, but without preference to "special" obstacles. These effects differed from the effects of ethanol and lorazepam, but not from the nonspecific effects of 30 mg diazepam in the present study.

Corbetta et al. (3) showed with positron emission tomography that attention to shape in visual stimuli specifically activated fusiform and parahippocampal gyri, and temporal cortex along the superior temporal sulcus. Because selective and divided attention also activated structures outside the visual system, impairment of divided attention at the "special" obstacles of our test could depend, more or less, on the characteristics of the drugs concerned.

Linnoila (15) reported that, by using the old model of our test, both ethanol and glycopyrrolate, an antimuscarinic, impaired attention on the lateral obstacles. In our present test, 50 mg amitriptyline did not impair attention on the lateral screens, although it had a considerable antimuscarinic component of action. Liu and Wickens (17) found that spatial uncertainty in the visual scanning subtask, added to tracking, definitely divides the attention and can be crucial to it. Considering our test, random changes in the location of obstacles reduce the role of learning and memory in performing the test, which might render it less sensitive to antimuscarinics, and may be important to the whole test when producing uncertainty.

Is the unexpected difference between lorazepam and diazepam more than a quantitative one? It could result from different testing details in Study I and Study II, but ethanol behaved similarly in these two studies. This suggests that the tests were essentially similar whereas diazepam (15 and 30 mg) and lorazepam 2 mg differently affected attention. These two drugs have seldom, if ever, been challenged to rigorous scrutiny in a human study, and the comparative doses used in animals and man need not be correct. The "equipotent" human doses of diazepam and lorazepam remain uncertain, and anxiolytic efficacy during maintenance may not be commensurable with impaired attention in single-dose studies.

The clinically adopted anxiolytic doses of lorazepam are often too large compared to those of diazepam, and the commonly used dose ratio of 1 : 5 should be 1 : 8–1 : 10 in single-dose studies. It is known that the highly lipophilic diazepam is absorbed and passes through the blood–brain barrier more rapidly than the less lipophilic lorazepam (9,31). Lorazepam, in turn, binds to plasma proteins less (below 90%) than diazepam (over 95%), thus being better available for tissue penetration. The RRA-assayed plasma concentrations of diazepam and lorazepam in our study suggest that single oral 2 mg lorazepam and 15–20 mg diazepam might produce similar concentrations into plasma. Volkerts et al. (34) found that lorazepam (1 mg thrice in 8 h) impaired driving on the road as much as, or more than, ethanol ($1.5\ g \cdot l^{-1}$ in blood) did. In these conditions, diazepam 5 mg thrice has corresponded to $0.5\ g \cdot l^{-1}$ of ethanol. We have found 2 mg lorazepam slightly more active than $1\ g \cdot kg^{-1}$ of ethanol in impairing simulated driving performance (21).

Acute pharmacodynamic tolerance develops to the effects of diazepam ("clockwise hysteresis"), but not to lorazepam

effects, which can even increase with time ("counterclockwise hysteresis") after robust IV doses (4). We did not find such a sensitization to 2 mg lorazepam within 6 h after oral intake (21). The members of 1,4-benzodiazepines have been considered to differ from each other in their potency and pharmacokinetics, their effects depending on the occupancies at the $GABA_A$-BZD receptors in the brain, without real qualitative differences in the postbinding events (6). The acute tolerance to diazepam is considered to result from the shift of diazepam from the central receptors and the brain tissue back to plasma, the central and peripheral concentrations being in equilibrium; lorazepam is much slower in this redistribution (7). It is not known if such results obtained in mice and using large doses of lorazepam are relevant to man. Further, the interpretation quoted does not seem to fit to our diazepam data. An intracerebral redistribution and deviating receptor effects as a cause of acute tolerance to, for example, diazepam have attracted little interest.

Evidence from mouse studies indicates that tolerance developed to lorazepam little reduces the binding of [^{3}H]diazepam to its binding sites in brain membranes, and GABA effect on chloride channel remained unaltered. However, the coupling of flunitrazepam, ethanol, and barbiturate to the chloride channel was reduced whereas increased coupling between the channel and the inverse agonist site was found (1). In a rat study (27), GABA-induced increase of benzodiazepine binding was reduced and the benzodiazepine/Cl coupling in the cortex or hippocampus was not changed by oral diazepam acutely or flurazepam chronically. The authors considered the interaction of benzodiazepine recognition sites with GABA essential for the actions of the benzodiazepines used. These small differences can, in principle, result from real mechanistic differences between the drugs used.

Itil et al. (9) compared intravenous diazepam (5 mg) and lorazepam (1 mg) using the quantitative pharmaco-EEG (multilead brain mapping) in patients with anxiety. They found that diazepam effects appeared immediately, 10–15 min before the appearance of lorazepam effects, which reached full effect within 30–40 min. There were quantitative (lorazepam more potent), qualitative (diazepam "more anxiolytic"; lorazepam "more antidepressant or stimulant"), and interindividual differences. The onset of diazepam's action was in the frontal area whereas lorazepam effects appeared in the occipital area. Although the report was not exact and the variables measured may not represent attention, the study did show differences between diazepam and lorazepam given IV to man. The greater potency of lorazepam probably resulted from its relatively larger dose.

In another human study (33), intravenously injected lorazepam (0.05 mg · kg^{-1}) given to dental patients impaired pegboard performance more than diazepam (0.25 mg · kg^{-1}) and midazolam (0.1 mg · kg^{-1}) did; lorazepam was less anxiolytic but caused more giddiness/dizziness than diazepam, respectively. Lista et al. (16) compared diazepam and lorazepam in rats under chloralose anaesthesia. Electrical stimulation of ascendic 5-HT pathways suppressed the firing activity of C3 pyramidal neurons. Diazepam and lorazepam injected IV dose-relatedly enhanced this response, without direct effects on pyramidal neurons. Lorazepam shared the diazepam action but was twofold less potent, although it otherwise is 10-fold more potent than diazepam. This suggests that the "equipotent" anxiolytic/sedative effects of ordinary doses of lorazepam and diazepam are differently composed, and they might show deviating effects in some tests.

A robust oral test dose of 3 mg lorazepam impaired attention both in medial and lateral dials of our old test (2). Its RRA-assayed concentrations in diazepam units were over 1000 $\mu g \cdot l^{-1}$, and it was far more potent than 15 mg diazepam (about 500 $\mu g \cdot l^{-1}$ in plasma) in various tests, thus resembling 30 mg diazepam in the present study. In the same old test, oral diazepam 0.3 mg · kg^{-1} failed to impair lateral attention at 1.5 or 3 h; the RRA-assayed mean plasma diazepam concentrations were 640 and 520 $\mu g \cdot l^{-1}$, respectively (20).

We conclude that: i) the doses of benzodiazepines used were ordinary yet not optimal for comparison; ii) there are real pharmacodynamic differences between diazepam and lorazepam; iii) these differences may have been contributed by different distribution of these drugs; and iv) lorazepam resembles ethanol more than diazepam does in their effects on attention, provided their doses are reasonably matched.

REFERENCES

1. Allan, A. M.; Baier, L. D.; Zhang, X. Effects of lorazepam tolerance and withdrawal on $GABA_A$ receptor-operated chloride channels. J. Pharmacol. Exp. Ther. 261:395–402; 1992.
2. Aranko, K.; Mattila, M. J.; Seppälä, T. Development of tolerance and cross-tolerance to the psychomotor actions of lorazepam and diazepam in man. Br. J. Clin. Pharmacol. 15:545–552; 1983.
3. Corbetta, M.; Miezin, F. M.; Dobmayer, S.; Shulman, G. L.; Petersen, S. E. Selective and divided attention during visual discriminations of shape, color, and speed: Functional anatomy by positron emission tomography. J. Neurosci. 11:2383–2402; 1991.
4. Ellinwood, E. H., Jr.; Heatherly, D. G.; Nikaido, A. M.; Bjornsson, T. D.; Kilts, C. Comparative pharmacokinetics and pharmacodynamics of lorazepam, alprazolam and diazepam. Psychopharmacology (Berlin) 86:392–399; 1985.
5. Eriksen, C. W.; Goettli, B.; St. James, J. D.; Fournier, L. R. Processing redundant signals: Coactivation, divided attention, or what? Perception Psychophys. 45:356–370; 1989.
6. Greenblatt, D. J.; Miller, L. G.; Shader, R. I. Neurochemical and pharmacokinetic correlates of the clinical action of benzodiazepine hypnotic drugs. Am. J. Med. 88(3A):18S–24S; 1990.
7. Greenblatt, D. J.; Sethy, V. H. Benzodiazepine concentrations in brain directly reflect receptor occupancy: Studies of diazepam, lorazepam, and oxazepam. Psychopharmacology (Berlin) 102: 373–378; 1990.
8. Häkkinen, S. Traffic accidents and psychomotor test performance: A follow-up study. Mod. Probl. Pharmacopsychiatry 11: 51–56; 1976.
9. Itil, T.; Shapiro, D.; Itil, K. Z.; Eralp, E.; Bergamo, M.; Mucci, A. Discrimination of mode of action of anxiolytics using an integrated computer data bank and dynamic brain mapping (CNS effects of diazepam and lorazepam). Int. Clin. Psychopharmacol. 4:273–283; 1989.
10. Kimchi, R.; Gopher, D.; Rubis, Y.; Raij, D. Performance under dichoptic versus binocular viewing conditions: Effects of attention and task requirements. Hum. Factors 35:35–55; 1993.
11. Koelega, H. S. Extraversion and vigilance performance: 30 years of inconsistencies. Psychol. Bull. 112:239–258; 1989.
12. Koelega, H. S. Benzodiazepines and vigilance performance: A review. Psychopharmacology (Berlin) 98:145–156; 1989.
13. Kuitunen, T.; Mattila, M. J.; Seppälä, T.; Aranko, K.; Mattila, M. E. Actions of zopiclone and carbamazepine, alone and in combination, on human skilled performance in laboratory and clinical tests. Br. J. Clin. Pharmacol. 30:453–461; 1990.
14. Kunsman, G. W.; Manno, J. E.; Przekop, M. A.; Manno, B. R.; Kunsman, C. M. The effects of temazepam and ethanol on hu-

man psychomotor performance. Eur. J. Clin. Pharmacol. 43: 603-611; 1992.
15. Linnoila, M. Drug effects on psychomotor skills related to driving: Interaction of atropine, glycopyrrhonium and alcohol. Eur. J. Clin. Pharmacol. 6:107-112; 1973.
16. Lista, A.; Blier, P.; de Montigny, C. Benzodiazepine receptors modulate 5-hydroxytryptamine neurotransmission in the rat hippocampus: In vivo electrophysiological evidence. J. Pharmacol. Exp. Ther. 254:318-323; 1990
17. Liu, Y.; Wickens, C. D. Visual scanning with or without spatial uncertainty and divided and selective attention. Acta Psychol. (Amst.) 79:131-153; 1992.
18. Marks, D. F.; MacAvoy, M. G. Divided attention performance in cannabis users and non users following alcohol and cannabis separately and in combination. Psychopharmacology (Berlin) 99: 397-401; 1989.
19. Mattila, M. E. Acute and subacute effects of diazepam on human performance: Comparison of plain tablet and control release capsule. Pharmacol. Toxicol. 63:369-374; 1988.
20. Mattila, M. J.; Mattila, M.; Konno, K. Acute and subacute actions on human performance and interactions with diazepam of temelastine (SK&F 93944) and diphenhydramine. Eur. J. Clin. Pharmacol. 31:291-298; 1986.
21. Mattila, M. J.; Kuitunen, T.; Veilahti, J. Related coordinative, reactive and cognitive performances as impaired by drugs and alcohol: Comparison with clinical test for driving fitness. J. Traffic Med. 21:101-114; 1993.
22. Mattila, M. J.; Aranko, K.; Mattila, M. E.; Paakkari, I. Effects of psychotropic drugs on digit substitution: Comparison of the computerized symbol-digit substitution and traditional digit-symbol substitution tests. J. Psychopharmacol. 8:81-87; 1994.
23. Maylor, E. A.; Rabbitt, P. M.; James, E. H.; Kerr, S. A. Effects of alcohol and extended practice on divided-attention performance. Perception Psychophys. 48:445-452; 1990.
24. McDowd, J. M. The effects of age and extended practice on divided attention performance. J. Gerontol. 41:764-769; 1986.
25. Moskowitz, H. Attention tasks as skills performance measures of drug effects. Br. J. Clin. Pharmacol. 18:51S-61S; 1984.
26. Moscowitz, H.; Burns, M.; Williams, A. F. Skills performance at low blood alcohol levels. J. Stud. Alcohol 46:482-485; 1985.
27. Plude, D. J.; Hoyer, W. J. Age and the selectivity of visual information processing. Psychol. Aging 1:4-10; 1986.
28. Ponds, R. W.; Brower, W. H.; van Wolffelaar, P. C. Age differences in divided attention in a simulated driving task. J. Gerontol. 43:P151-156; 1988.
29. Sanders, A. F. Drugs, driving and the measurement of human performance. In: O'Hanlon, J. F.; deGier, J. J., eds. Drugs and driving., London: Francis & Taylor; 1986:1-16.
30. Stokes, A. F.; Banich, M. T.; Elledge, W. C. Testing the tests—an empirical evaluation of screening tests for the detection of cognitive impairments in aviators. Aviat. Space Environ. Med. 62:783-788; 1991.
31. Tedeschi, G.; Smith, A. T.; Dhillon, S.; Richens, A. Rate of entrance of benzodiazepines into the brain determined by eye movement recording. Br. J. Clin. Pharmacol. 15:103-107; 1983.
32. Tietz, E. I.; Chiu, T. H.; Rosenberg, H. C. Regional GABA/benzodiazepine receptor/chloride channel coupling after acute and chronic benzodiazepine treatment. Eur. J. Pharmacol. 167: 57-65; 1989.
33. Van der Bijl, P.; Roelofse, J. A.; Joubert, J. J.; van Zyl, J. F. Comparison of various psychologic and psychomotor parameters in patients sedated with intravenous lorazepam diazepam, or midazolam during oral surgery. J. Oral Maxillofac. Surg. 49:672-678 (discussion 678-679); 1991.
34. Volkerts, E. R.; Brookhuis, K. A.; O'Hanlon, J. F. The effects of treatment with buspirone, diazepam and lorazepam on driving performance in real traffic. In: Noordzij, P. C.; Rosbach, R., eds. Alcohol, drugs and traffic safety—T86. Amsterdam: Elsevier; 1987:217-222 (Excerpta Medica Int. Conf. Ser. 721).
35. Yap, M.; Mascord, D. J.; Starmer, G. A.; Whitfield, J. B. Studies on the chronopharmaccology of ethanol. Alcohol Alcohol. 28: 17-24; 1993.
36. Zeef, E. J.; Kok, A. Age-related differences in the timing of stimulus and response processes during visual selective attention: Performance and psychophysiological analyses. Psychophysiology 30:138-151; 1993.