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RESIDUAL EFFECTS AND SKILLS RELATED TO DRIVING AFTER A SINGLE ORAL ADMINISTRATION OF DIAZEPAM, MEDAZEPAM OR LORAZEPAM

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1 Psychomotor skills and visual functions related to driving were measured double-blind cross-over in ten healthy volunteers before, and 1, 3, 5 and 7 h after a single oral administration of diazepam (10 mg), medazepam (15 mg) or lorazepam (2.5 mg). The late effects of lorazepam were tested in seven other subjects 12 and 24 h after the administration.

2 Lorazepam impaired almost all the measured skills more ($P < 0.05$ to 0.001) than diazepam, medazepam or the placebo. The lorazepam impairment of reactive skills and flicker fusion discrimination remained statistically significant ($P < 0.05$) for as long as 12 h. Medazepam impaired only reactive skills and flicker fusion, the latter remaining impaired ($P < 0.05$) for as long as 5 h after the administration. The magnitude and duration of the effects of diazepam were intermediate between those of lorazepam and medazepam. Diazepam impaired perceptual speed and reactive and co-ordinative skills as well as flicker fusion discrimination and visual parameters related to driving. Slight impairments in performance were measurable for up to 5 h after administration but at 7 h the results resembled those measured after the placebo.

3 The lack of alterations in adaptation to darkness, sensitivity to brightness or visual discrimination ability in bright counterlight at a time when flicker fusion discrimination was severely depressed suggests that an impaired ability to discriminate flickering light is of no or little clinical significance to driving ability.

4 It is concluded that patients receiving a 2.5 mg dose of lorazepam should not drive or operate machinery for 24 h after the administration. After diazepam (10 mg) or medazepam (15 mg) patients should refrain from driving or participating in skilled performances for only 5 to 7 hours.

Introduction

Benzodiazepines are commonly used as a treatment for anxiety neuroses and as hypnotic agents in outpatient care.

A series of studies on the effects of one benzodiazepine on psychomotor skills related to driving has been in progress in our laboratory (Linnoila, 1973; Linnoila & Mattila, 1973; Linnoila & Häkkinen, 1974; Linnoila, Saario & Mäki 1974; Korttila & Linnoila, 1975a & 1975b). These studies indicate that diazepam impairs driving skills for a variable length of time depending on the dose and the mode of administration.

Hedges, Turner & Harry (1971) and Bell, Dickie, Steward-Jones & Turner (1973) have shown that lorazepam impairs central nervous functions such as flicker fusion frequency, reaction time and visual function, in man, whereas Bernstein, Hughes & Forney (1967) could not demonstrate impairments of human mental or motor performance after the administration of medazepam. Since no report was available on the effect of lorazepam or medazepam on driving skills we conducted the present investigation to study this question and to compare the effects of single oral doses of diazepam, medazepam and lorazepam.

Methods

Subjects

Ten healthy student volunteers, six men and four women, participated in the study. Their characteristics were as follows (means ± s.d.): age, 21 ± 2.5 years; height, 175 ± 8.6 cm and weight, 67 ± 11.0 kg. None of the subjects were on drugs

or had any psychiatric illness. All were moderate users of alcohol and six were smokers. An informed consent was obtained from each subject for the procedure.

Drugs

The four medications were: a lactose placebo, 10 mg diazepam (Diapam®, Orion, Helsinki), 15 mg medazepam (Vegatar®, Orion, Helsinki) and 2.5 mg lorazepam (Temesta®, Leiras/Wyeth, Turku). All the drugs were administered in single doses orally in identical gelatine capsules.

Experimental design

A double-blind cross-over trial design was applied. The sequence of drug administration for individual subjects was randomized according to the Latin Square. Wash-out periods of 1 week were allowed to pass between the sessions.

One day preceding the first test day, the same person explained the tests to all the subjects. The subjects then practiced with each section of the test battery for 1 hour.

On each of the four test days sessions were started between 08.00 h and 09 h 30 min at intervals of 10 min from subject to subject. First we permitted the subjects to make one practice run to ensure their familiarity with the test battery. Then we tested the subjects to establish pre-drug values. The total testing time for the test battery was approximately 20 min. The testing procedure was repeated 1, 3, 5 and 7 h after the ingestion of the capsule.

The subjects fasted overnight before the sessions, and were served a standard lunch 3.5 h after receiving the medication. They were requested to forego coffee, tea, cola, tobacco and alcoholic beverages for 8 h before and during the sessions. In an attempt to maintain motivation we did not inform the subjects of their test scores during the experiment.

Psychomotor tests

Choice-reaction test In the choice-reaction test the subjects were instructed to push a button and press either or both of two foot pedals in response to a series of 32 visual and/or auditory stimuli appearing at intervals of 1.5 s (Linnoila & Mattila, 1973). The interval between the presentation of each stimuli and response was measured with an accuracy of 0.01 sec. The culmulative reaction time and the number of mistakes (= number of incorrect responses) were recorded.

Coordination tests Two tracking tasks were used to measure hand-eye coordination. The number of mistakes (the number of times the subject went off the track) and mistake percentage (percentage of the total length of the track the subject was off) were recorded when the subjects tried to keep a black ball on an illuminated track by turning a steering wheel. Coordination test I was driven with a fixed speed. Coordination test II was driven at a free speed, and the driving time was recorded (Linnoila & Mattila, 1973).

Tests of visual function

Flicker fusion test. Central visual processes were observed by means of critical flicker fusion frequency (Grove-White & Kelman, 1971; Korttila & Linnoila, 1975b). We used a modification of the test in which the subjects wore specially made spectacles (Korttila, Häkkinen & Linnoila, 1976). The spectacles consisted of frames with black, opaque plastic lenses with a hole of 3 mm in diameter to look through and black protectors to prevent surrounding room lights from interfering. Wearing these spectacles the subjects were instructed to announce when a flickering red light (diameter 3 mm) at a distance of 90 cm stopped flickering.

Visual parameters related to driving In order to measure visual functions under simulated night driving conditions, we developed a new test which recorded three other visual parameters. The apparatus was a light proof box (length 80 cm, width 21 cm, height 35 cm) painted black on the inside. Inside the box was a rotating target containing Langhold circles (incomplete circles opening to right, left, up or downwards). Beside the target were two lights directed toward the subject like the lights of an oncoming car. The brightness of this light source and that of the target were independently adjustable. The subjects first remained in total darkness for 5 min in order to adapt to darkness. They then looked at the target inside the box but never toward the opposing lights. *Adaptation to darkness* was measured by adjusting the brightness of the target to the lowest point at which the subjects were able to discriminate the symbols correctly. The brightness of the target was then recorded in linear units from 0 to 100, corresponding to a brightness of 0.03 to 0.3 cd/m^2, respectively. Next the brightness of the target was increased 5%, and the subjects' *sensitivity to brightness* was tested by recording the time before the subjects were unable to discriminate the circles in the target after a 3.6-s exposure to the similated car lights (veiling luminance 0.47 cd/cm^2, caused by two lamps with a brightness of 2000 cd/m^2 each, 80 cm away). The luminance was the average amount of light

directed to the eyes of a driver from the dipped headlights of an oncoming car, as measured by two of the authors (S.H. and M.L.) in 200 passing situations on Finnish concrete two-lane roads. Finally the subjects' *ability to discriminate visually in bright counter-light* was recorded as vision in dim-light conditions by keeping the simulated lights of the oncoming car at 0.47 cd/m^2 all the time.

Bourdon-Wiersma test The Bourdon-Wiersma test of perceptual speed was used according to a modification by Hänninen (1971). Groups of dots were printed in a piece of white paper, 25 cm x 45 cm, and arranged in 50 rows, 25 groups in each. Each group consisted of three, four or five dots. The subjects were told to draw a line through each group with four dots while reading from left to right and down the page. In each row there were eight groups of four dots spaced randomly throughout the row. The subjects were told to work rapidly but without error. The number of lines completed in 8 min and the number of errors were recorded.

Subjective assessments After each sessions the subjects were asked whether they thought they had received a tranquillizer, stimulant or placebo. On every occasion they filled out a questionnaire concerning the subjective estimation of driving ability and feeling of tiredness and dizziness or unsteady gait. The subjects also had the possibility to note other adverse effects on the form. At the end of the entire experiment they were asked which treatment had induced most unpleasant sensations; and which, the least.

Drug levels in serum

During the last two sessions venous blood samples were drawn from a forearm vein at the start of the session and after each test period. The samples were immediately centrifuged and the separated serum stored at -22° C for 1 month prior to the determinations. Serum diazepam and N-desmethyldiazepam levels were assayed according to the method of Heidbrink, Mallach & Moosmayer (1975); and medazepam levels, according to Mallach, Moosmayer & Rupp (1973); each employing electron-capture gas-liquid chromatography. Serum levels of lorazepam were assayed with massspectrometry as aminodichlorbentsophenone with N-desmethyl-aminochlorbentsophenone as the internal standard (Vessman, Ferij & Strömberg, 1972; Knowles, Comer & Ruselius, 1971). The recoveries of the drugs and their metabolites were about 100%.

Statistics

The three-way analysis of variance (drug, time, subject) which was first applied indicated that subject dependent effects were not significant for any test. Thereafter, having checked additivity and within-cell variances, we used parametric tests, a two-way analysis of variance and Student's *t*-test to make the statistical comparisons between the treatments. Self-ratings were treated according to Fisher's exact probability test (Siegel, 1956) because of the non-parametric nature of the data.

Results

In most tests the effects of lorazepam were still measurable ($P < 0.05$) 7 h after administration, whereas the only significant impairments of psychomotor function after medazepam were noticed in the ability to discriminate the fusion of flickering light (up to 5 h) and in the number of mistakes made on the choice-reaction test. The duration and degree of the impairment caused by diazepam were intermediate between lorazepam and medazepam. In most tests the impairment of performance was significantly ($P < 0.001$) greater after lorazepam than after diazepam, medazepam or the placebo.

Reactive skills

After the placebo, diazepam and medazepam the cumulative reaction times were similar. They decreased with time throughout the session, whereas the reaction time after lorazepam was prolonged for up to 3 h before it began to decrease (Figure 1). At 3 h the reaction time after lorazepam was significantly longer than after the other treatments, but at 7 h the difference was just under the significant level. The number of reaction mistakes increased significantly after every benzodiazepine (Figure 2). Subjects receiving lorazepam made significantly ($P < 0.05$) more mistakes still at 7 h than subjects given the placebo, and there was an impairment of performance for as long as 5 h after diazepam.

Coordinative skills

The results from both coordination tests were parallel. Medazepam did not differ from the placebo (Figure 3). After diazepam the number of mistakes and the mistake percentage were significantly ($P < 0.05$) elevated at 1 h when they were compared with the corresponding results after the placebo. However, lorazepam caused the most increase in coordination mistakes and mistake percentage and in a comparison with the

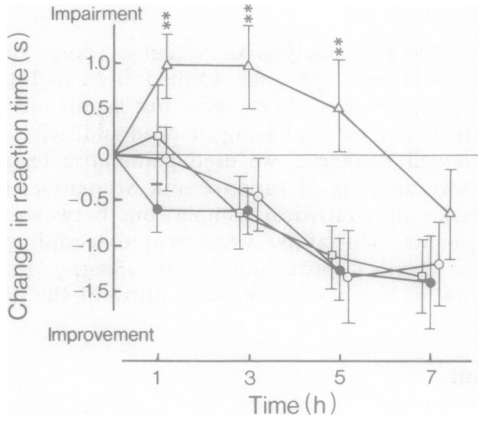

Figure 1 Changes in cumulative reaction time after a single oral administration of a lactose placebo (●), diazepam (○, 10 mg), medazepam (□, 15 mg) or lorazepam (△, 2.5 mg). Points represent mean values of ten subjects; vertical bars are s.e. mean. *t*-test: $**P < 0.01$ in comparison with the placebo. Two-way analysis of variance: Lorazepam *v.* placebo, diazepam or medazepam, $P < 0.01$.

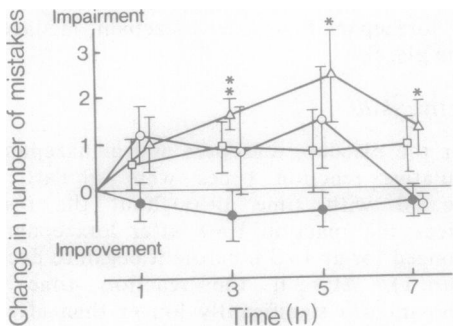

Figure 2 Changes in number of mistakes in a choice-reaction test after a single oral administration of a lactose placebo (●), diazepam (○, 10 mg), medazepam (□, 15 mg) or lorazepam (△, 2.5 mg). Points represent mean values of ten subjects; vertical bars are s.e. mean. *t*-test: $*P < 0.05$; $**P < 0.01$. Two-way analysis of variance: placebo *v.* diazepam, $P < 0.05$; placebo *v.* medazepam, $P < 0.01$; placebo *v.* lorazepam, $P < 0.001$.

placebo results the effects were still significant ($P < 0.05$) at 7 hour. Driving times in co-ordination test II did not alter significantly.

Vision

After the placebo the critical flicker fusion frequency remained at the initial level during the

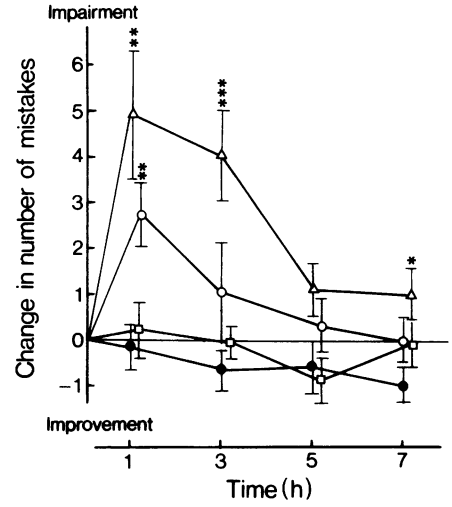

Figure 3 Changes in number of mistakes in co-ordination test I after a single oral administration of a lactose placebo (●), diazepam (○, 10 mg), medazepam (□, 15 mg) or lorazepam (△, 2.5 mg). Points represent mean values of ten subjects; vertical bars are s.e. mean. *t*-test: $*P < 0.05$; $**P < 0.01$; $***P < 0.01$ in comparison with the placebo. Two-way analysis of variance: placebo *v.* diazepam, $P < 0.001$; placebo *v.* lorazepam, $P < 0.001$; diazepam *v.* medazepam, $P < 0.05$; diazepam *v.* lorazepam, $P < 0.01$; medazepam *v.* lorazepam, $P < 0.001$.

entire session. However, all of the benzodiazepines caused a reduction in the ability to recognize a flickering light (Figure 4). After medazepam and diazepam the impaired ability to discriminate flickering light was maximal at 1 h but the effect lasted up to 5 h. After lorazepam the greatest increase occurred at 3 h, and impaired flicker-fusion discrimination was still apparent at 7 h (Figure 4).

Adaptation to darkness was not affected by medazepam, after diazepam it was slightly affected and after lorazepam it was significantly worse up to 5 h when the results were compared with the corresponding placebo values (Figure 5). No treatment changed the subjects' sensitivity to brightness. Visual discrimination ability in bright counterlight was significantly worse at 1 and 3 h after lorazepam than after the placebo (Figure 6).

Perceptual speed

At 1 h after administration diazepam reduced the number of lines completed in the perceptual speed test ($P < 0.05$ *v* placebo), but at 3 h this effect had disappeared (Figure 7). After lorazepam, the

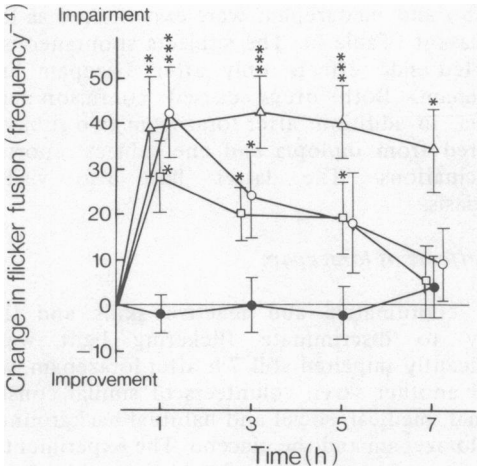

Figure 4 Changes in flicker fusion discrimination after a single oral administration of a lactose placebo (●), diazepam (○, 10 mg), medazepam (□, 15 mg) or lorazepam (△, 2.5 mg). Points represent mean values of ten subjects; vertical bars are s.e. mean. *t*-test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ in comparison with the placebo. Two-way analysis of variance: placebo *v.* diazepam, $P < 0.001$; placebo *v.* medazepam, $P < 0.001$; placebo *v.* lorazepam, $P < 0.001$; diazepam *v.* lorazepam, $P < 0.05$; medazepam *v.* lorazepam, $P < 0.01$.

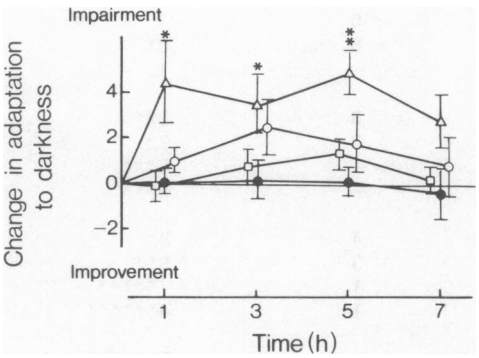

Figure 5 Changes in adaptation to darkness (1×10^{-3} cd/m^2) after a single oral administration of a lactose placebo (●), diazepam (○, 10 mg), medazepam (□, 15 mg) or lorazepam (△, 2.5 mg). Points represent mean values of ten subjects; vertical bars are s.e. mean. *t*-test: * $P < 0.05$; ** $P < 0.01$ in comparison with the placebo. Two-way analysis of variance: placebo *v.* diazepam, $P < 0.05$; placebo *v.* lorazepam, $P < 0.001$; diazepam *v.* lorazepam, $P < 0.05$; medazepam *v.* lorazepam, $P < 0.001$.

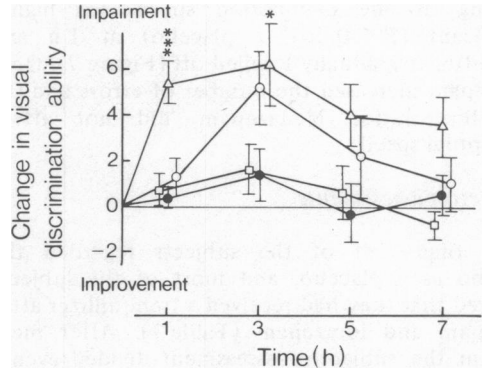

Figure 6 Changes in visual discrimination ability (1×10^{-3} cd/m^2) in bright counterlight after a lactose placebo (●), diazepam (○, 10 mg), medazepam (□, 15 mg) or lorazepam (△, 2.5 mg). Points represent mean values of ten subjects; vertical bars are s.e. mean. *t*-test; * $P < 0.05$; *** $P < 0.001$ in comparison with the placebo. Two-way analysis of variance: placebo *v.* diazepam, $P < 0.05$; placebo *v.* lorazepam, $P < 0.001$; diazepam *v.* medazepam, $P < 0.05$; diazepam *v.* lorazepam, $P < 0.05$; medazepam *v.* lorazepam, $P < 0.001$.

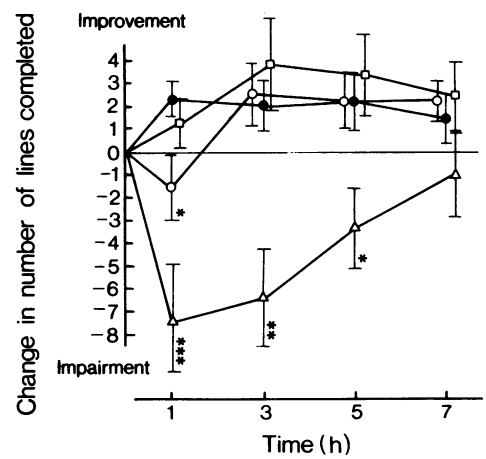

Figure 7 Changes in number of lines completed in Bourdon-Wiersma test of perceptual speed after a lactose placebo (●), diazepam (○, 10 mg), medazepam (□, 15 mg) or lorazepam (△, 2.5 mg). Points represent mean values of ten subjects; vertical bars are s.e. mean. *t*-test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ in comparison with the placebo. Two-way analysis of variance: lorazepam *v.* placebo, diazepam or medazepam, $P < 0.001$.

slowing of the completion speed was highly significant ($P < 0.001$ *v* placebo) at 1 h and thereafter it gradually levelled off (Figure 7). Only lorazepam increased the number of errors and the error/line ratio. Medazepam did not affect perceptual speed.

Subjective assessments

More than half of the subjects regarded the placebo as a placebo, and most of the subjects believed that they had received a tranquillizer after diazepam and lorazepam (Table 1). After medazepam the subjective assessment divided evenly between placebo and tranquillizer (Table 1). The volunteers' conceptions of their driving abilities were the most pessimistic after lorazepam throughout the sessions. After diazepam and lorazepam eight subjects out of ten reported fatigue at 1 to 3 h, but after diazepam this sensation then disappeared more rapid than after lorazepam. There was a high incidence of dizziness or unsteady gait 1 h after diazepam and from 1 to 7 h after lorazepam. Both of these agents also induced the most unpleasant sensations, while the placebo and medazepam were experienced as less unpleasant (Table 1). The subjects spontaneously reported side effects only after diazepam and lorazepam. Both drugs caused confusion and nausea. In addition, after lorazepam two subjects suffered from diplopia and one subject reported hallucinations. The latter had also visible mydriasis.

Late effects of lorazepam

Since coordinative and reactive skills and the ability to discriminate flickering light were significantly impaired still 7 h after lorazepam, we tested another seven volunteers of similar constitutional, medical, social and habitual backgrounds with lorazepam and the placebo. The experimental setting was the same as in the original study. Each subject participated in two sessions, 7 days apart. The initial scores were recorded one evening prior to the administration of the drug and the tests were then repeated 12 and 24 h later, i.e. the next morning and the following evening. Twelve hours after lorazepam the ability to discriminate flickering light was significantly ($P < 0.05$) im-

Table 1 The number of subjects, out of ten, estimating the nature of treatment, reporting the side effect, and evaluating the unpleasantness of the treatment

Nature of treatment or side effect	*Time after treatment (h)*	*Treatment*			
		Placebo	*Diazepam (10 mg)*	*Medazepam (15 mg)*	*Lorazepam (2.5 mg)*
Placebo		6	1	5	1
Tranquillizer		3	8*	5	8*
Stimulant		1	1	–	1
Feeling of reduced driving ability	1	3	8**	3	8**
	3	2	6	3	7*
	5	2	2	–	5***
	7	2	–	–	4****
Fatigue	1	3	8*	4	8*
	3	3	8**	3	8**
	5	2	3	1	7*****
	7	2	–	1	4******
Dizziness or unsteady gait	1	2	8*******	–	9********
	3	2	4	1	8*****
	5	–	1	1	5*
	7	–	1	1	4*
Most unpleasant		1	5***	–	4***
Least unpleasant		5******	–	4******	1

* $P < 0.05$ *v.* placebo; ** $P < 0.05$ *v.* placebo and *v.* medazepam; *** $P < 0.05$ *v.* medazepam; **** $P < 0.05$ *v.* diazepam and *v.* medazepam; ***** $P < 0.05$ *v.* placebo and $P < 0.01$ medazepam; ****** $P < 0.05$ *v.* diazepam; ******* $P < 0.05$ *v.* placebo and $P < 0.05$ medazepam; ******** $P < 0.05$ *v.* placebo and *v.* medazepam (Fisher's exact probability test).

paired as compared to the placebo, but at 24 h the difference was no longer significant (Table 2). The cumulative reaction time was also worse ($P < 0.05$) 12 h after lorazepam but no longer affected at 24 h (Table 2). The differences in the number of reaction mistakes were not significant. The parameters measured in the coordination tests did not differ from pre-administration values.

Drug concentrations in serum

The highest concentrations of diazepam (299 ± 64 ng/ml) and medazepam (173 ± 41 ng/ml) in serum (means ± s.d.) were measured 1 h after drug administration. Thereafter, the medazepam concentrations declined regularly as a function of time, while the diazepam concentrations showed a

Table 2 Changes in cumulative reaction time (s), number of reaction mistakes and critical flicker fusion frequency (frequency^{-1}) in seven subjects 12 h and 24 h after a placebo or lorazepam (2.5 mg) as compared to the values before administration

		Change in measurement					
Treatment		*Cumulative reaction time*		*Number of mistakes*		*Flicker fusion*	
		12 h	*24 h*	*12 h*	*24 h*	*12 h*	*24 h*
Placebo	Mean	−0.50	−0.51	−0.29	−0.43	−1.43	−2.86
	s.e. mean	0.31	0.27	0.29	0.37	3.40	6.06
Lorazepam	Mean	0.81*	−0.76	0.14	−0.58	27.14*	5.71
	s.e. mean	0.37	0.45	0.26	0.61	8.92	5.71

* *t*-test between lorazepam and placebo: $P < 0.05$.

Table 3 Serum levels of lorazepam (ng/ml) 1, 3, 5, 7, 12 and 24 h after a single oral administration of lorazepam (2.5 mg). Individual values and means ± s.e. mean

			Time after administration (h)					
Subject	*Weight (kg)*	*Height (cm)*	*1*	*3*	*5*	*7*	*12*	*24*
1	67	179	29	26	19	13	–	–
2	73	179	31	28	17	17	–	–
3	52	164	33	58	44	54	–	–
4	80	181	24	26	22	23	–	–
Mean ± s.e. mean*			29 ± 1.9	34 ± 7.8	26 ± 6.3	27 ± 9.3	–	–
1	76	185	–	–	–	–	15	15
2	70	178	–	–	–	–	19	13
3	50	160	–	–	–	–	13	61
4	63	180	–	–	–	–	16	14
5	54	174	–	–	–	–	20	50
Mean ± s.e. mean							17 ± 1.3	30 ± 10

* Four subjects for 1 to 7 h and five subjects for 12 and 24 h.
– not available.

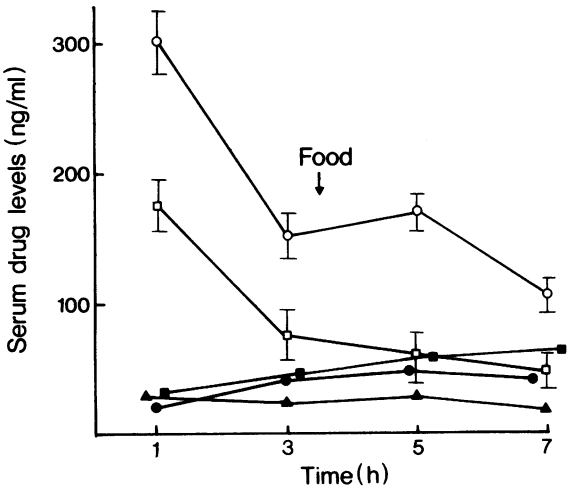

Figure 8 Serum diazepam (○) and N-desmethyldiazepam (●) levels after oral diazepam (10 mg) ($n = 6$); serum medazepam (□), diazepam (▲) and N-desmethyldiazepam (■) concentrations (mean ± s.e. mean) after oral medazepam (15 mg) ($n = 5$).

slight peak at 5 h (Figure 8). Diazepam is a metabolite of medazepam, and, accordingly, small amounts of diazepam were found after the treatment with medazepam. Both the diazepam and the medazepam administrations produced N-desmethyldiazepam, the serum concentrations of which rose up to 7 h to the level of 50 ng/ml (Figure 8). The highest mean (± s.d.) concentrations of lorazepam were observed 3 h after administration (34 ± 15.7 ng/ml), and at 7 h they were still 80% (27 ± 9.3) of the peak values (Table 3). At 12 h after administration the mean concentration of lorazepam was still 50% of the peak value, and at 24 h two subjects had 2.5 and 5 times as much lorazepam in their serum as 12 h after ingestion.

Discussion

We wanted to investigate the effects of diazepam, medazepam and lorazepam on psychomotor performance since the use of these drugs may lead to traffic or occupational hazards.

Drug doses

The literature dealing with clinically equipotent doses of diazepam and lorazepam in the treatment of anxiety is controversial. Eaves, Jain & Swinson (1973) reported that lorazepam in 1.0 mg and 1.5 mg dosages was superior to diazepam (5 mg) in relieving anxiety. Most studies (Haider, 1971; DeBuck, Boon & Pelc, 1972; Höffkes, 1972; Borenstein, Scoret & Cujor, 1973; Nanivadekar, Wig, Khorana, Master & Kulkarni, 1973; Sing & Saxena, 1974) suggest that diazepam (10 mg) is equipotent to lorazepam (2 mg or 2.5 mg) when the two are used as hypnotic drugs and as a treatment for anxiety neuroses. The dose of medazepam used in this study was based on the study of Kerry & McDermott (1971) on treatment of anxiety with medazepam.

Trial design and tests

The study was carried out with a small group of healthy volunteers after single drug administrations. It is possible that the action of psychotropic drugs on psychomotor skills is different in normal and neurotic or psychotic patients, and the results must therefore be interpreted with care (Silverstone, 1974). However, in one hundred psychiatric mental, but otherwise healthy, patients receiving psychotropic drugs, psychomotor functions were worse than in suspected drunken drivers whose blood contained very little or no alcohol (Penttilä, Lehti & Lönnqvist, 1975).

A poor performance of drivers on the choice-reaction and coordination tests used in our study has been shown to correlate with a liability to encounter traffic accidents (Häkkinen, 1958, 1976; Eklund 1970). Our previous result, that impaired ability to discriminate the fusion of flickering light did not correlate with the measured visual parameters related to driving (Korttila, Häkkinen & Linnoila, 1975a) was confirmed in this study. Thus impaired flicker fusion is presumably of little clinical significance as regards psychomotor or visual functions related to driving.

The modification of the Bourdon-Wiersma test used in the present study has proved to be a very sensitive test of perceptual speed in evaluating the harmful effects of manifest and latent carbon disulphide poisoning (Hänninen, 1971) and the effects of anaesthetic gases on the psychomotor performance of operating room personnel (Gamberale & Svensson, 1974).

Effects of diazepam

Linnoila & Mattila (1973) found no impairment in psychomotor performance on the same choice-reaction and coordination tests used in the present study 30-150 min after orally administered diazepam (5 mg or 10 mg), nor did they find any residual effects when the tests were performed in the morning 10 h after a 10 mg dose of diazepam (Linnoila, 1973). Later, Linnoila & Häkkinen

(1974) noticed that a single oral dose of diazepam (10 mg) impaired simulated driving, and Korttila & Linnoila (1975a, 1975b) found that diazepam (10 mg), given i.m. or i.v., impairs psychomotor performance for as long as 5 to 7 hours.

One result of the present study, that the duration of action of a 10 mg dose of diazepam was 5 h, agrees with Linnoila & Häkkinen's (1974) and Korttila & Linnoila's (1975a, 1975b) findings but not with those of Linnoila & Mattila (1973). Linnoila & Mattila (1973) did not employ a training period before drug administration whereas the subjects of the other studies trained on the test apparatus. In addition the present study was done in cross-over manner which allowed the subjects to become fully acquainted with the test battery. The results indicate that the effects of diazepam on psychomotor performance is beneficial when a presumably exciting or anxious situation is to come, but, if the subject is fully acquainted with the task to be performed, diazepam impairs performance.

As regards the magnitude and duration of impaired performance in this study the effects of a 10 mg dose of diazepam fell between the deleterious effects of lorazepam (2.5 mg) and the slight effects of medazepam (15 mg).

Effects of medazepam

Bernstein *et al.* (1967) found no impairment in motor or mental performance when they assessed medazepam with a delayed auditory feedback apparatus after single oral administration of a 10 mg dose either alone or in combination with alcohol.

In our study medazepam showed only minor effects. The 15 mg dose of medazepam used did not cause more fatigue or dizziness than the placebo, a finding which agrees with the small incidence of drowsiness and ataxia associated with treating anxiety with a 10 mg t.i.d. dosage of medazepam (Kerry & McDermott, 1971). Contrary to other benzodiazepines (Korttila & Linnoila, 1974) there was no impairment of coordinative skills after medazepam, and there was only a slight increase in the inaccuracy of reaction mistakes.

Effects of lorazepam

After a 2.0 mg dose of lorazepam tracking in the handeye coordination test (Bell *et al.*, 1973), flicker fusion discrimination, disc-dotting scores and reaction times (Hedges *et al.*, 1971) were significantly impaired, the maximum effect being seen mostly at 4 to 6 h after administration. The same investigators noticed that the effects of lorazepam (1 mg) were considerably less severe although still measurable. The reaction test used by Hedges *et al.* (1971), in which the subjects react to the same visual stimulus, is less likely to reveal the impairment of reactive skills than a choice-reaction test (Tetsch, Machtens & Voss, 1972; Tetsch, 1973).

In the present study the effects of lorazepam (2.5 mg) on psychomotor performance were greater and more prolonged than those of diazepam (10 mg) or medazepam (15 mg). Subjective fatigue and dizziness or unsteady gait were still reported by four of ten subjects 7 h after the administration, and reactive skills and the ability to see a flickering lighg were significantly impaired for as long as 12 h after the administration. This finding suggests that, if lorazepam (2.5 mg) is taken as a hypnotic agent in the evening, driving should not be allowed the next morning. The high incidence of the harmful and side-effects of this drug on psychomotor performance agrees with recent reports from clinical practice, in which comparable dosages were used (Wätzig & Michaelis, 1973), and with the potential central nervous system toxicity of this drug in children suffering from mild to moderate degrees of overdosage (Jeffrey & Whitfield, 1974). On the other hand in some reports (Haider 1971; Silverstone 1973) side-effects, particularly drowsiness have been less common with 1 mg of lorazepam (1 mg, t.i.d.) than with diazepam (5 mg t.i.d.).

On the basis of the present results it is not possible to say how smaller doses of diazepam and lorazepam would impair psychomotor performance. Since medazepam (15 mg) had relatively few effects in this study it is unlikely, however, that smaller doses would have any clinically significant effect on psychomotor skills.

Drug concentrations in blood

As suggested by our previous study (Korttila, Mattila & Linnoila, 1976) the observed elevation of serum diazepam after food intake is presumably due to the remobilization of diazepam from its storage site in the gastrointestinal wall. In this study late elevation of serum diazepam coincided with the slight impairment of reactive skills, but it was not recognized subjectively by the volunteers. Such a rebound in serum diazepam and a recurrence of impaired performance is not clinically significant after a 10 mg dose of diazepam given orally or i.m. (Korttila & Linnoila, 1975b), but if an i.v. dose of 20 mg is administered, there is a possibility of traffic or occupational hazards (Korttila *et al.*, 1976).

Medazepam disappeared fairly rapidly from the

serum, and the level of its metabolite diazepam was also too low to impair psychomotor performance. The other main metabolite of medazepam, N-desmethyldiazepam, seems not to impair psychomotor performance or flicker fusion discrimination, as was also suggested in a recent study in which N-desmethyldiazepam was administered orally (Palva & Linnoila, 1976).

The slow disappearance of lorazepam from the serum coincided with its long duration of action and agreed with previous reports (Knowles *et al.*, 1971; Elliot, Nomof, Navarro, Ruselius, Knowles & Comer, 1971). The late elevation of serum lorazepam, noticed in two subjects 24 h after the administration, had not been reported before and we have no explanation for it.

There was no general rebound in the serum concentrations of medazepam or lorazepam after food intake. This finding agrees with the differences in the pharmacokinetics of different benzodiazepines (Korttila & Linnoila, 1976).

One must remember that the present results were obtained from young, healthy subjects. The effects of the drugs on an old patient may be more severe and have a longer duration.

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