Psychopharmacology (1988) 95:323–328

Psychopharmacology

Objective and subjective assessments of the effects of flupentixol and benzodiazepines on human psychomotor performance

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Abstract. The aim of this double-blind crossover trial was to compare the objective and subjective effects of flupentixol and lorazepam on human performance, and to reveal possible interactions between flupentixol and diazepam. Twelve healthy students received at 1-week intervals oral single doses of flupentixol 1 mg, flupentixol 2 mg, lorazepam 2.5 mg, placebo, and diazepam 15 mg alone and with flupentixol 1 mg. After the baseline measurements, the drugs were given in capsule form, and the tests were repeated 1.5, 3 and 4.5 h later. Diazepam was given at 1.5 h, to time its peak effect to coincide with that of lorazepam. Drug effects were measured objectively (two tracking tests, digit substitution, letter cancellation, flicker fusion, Maddox wing, tapping, memory) and subjectively (visual analogue scales, questionnaire). Blood samples were taken after each test time. Flupentixol 1 mg did not differ from placebo objectively or subjectively. Flupentixol 2 mg proved nearly inert objectively and on visual analogue scales. Lorazepam impaired objectively measured test performance, the clearest effects occurring at 3 and 4.5 h. It also impaired subjectively assessed performance. Diazepam impaired objective performance less than lorazepam, its effects peaking at 1.5 h after intake. Diazepam caused subjective drowsiness, clumsiness, mental slowness etc. as much as or more than lorazepam. The combination of 1 mg flupentixol and diazepam modified performance as much as diazepam alone. After the administration of 1 mg flupentixol, plasma concentrations were undetectable and levels after 2 mg were hardly detectable. Concentrations of lorazepam exceeded those of diazepam in direct bioassay, but they were much lower when bioassayed after solvent extraction. Flupentixol 1 mg did not modify plasma diazepam levels. The clinical anxiolytic effects of lorazepam and flupentixol have not been compared directly, but we conclude that recommended anxiolytic doses of flupentixol have no or negligible influence on psychomotor performance while lorazepam does impair performance. No relevant interaction between 1 mg flupentixol and diazepam was detected.

Key words: Flupentixol – Lorazepam – Diazepam – Human performance – Pharmacokinetics

Benzodiazepines are effective anxiolytics but they also impair psychomotor performance ("man-machine interaction") and may induce tolerance and dependence (Seppälä et al. 1979; Smith and Wesson 1985). Small doses (1–2 mg) of flupentixol have been used in the treatment of anxiety (Jokinen et al. 1984). Since these doses of flupentixol have not caused obvious sedation, the present trial was conducted to measure comparatively the effects on performance of flupentixol (1 mg and 2 mg) and benzodiazepines. Lorazepam was chosen for comparison as it is often administered in the treatment of mixed anxiety and depression, the officially recommended daily dose of lorazepam being 2–5 mg. Therefore, a single dose of 2.5 mg lorazepam was used in this study. To investigate possible interactions of flupentixol and benzodiazepines, 15 mg diazepam was given both alone and in combination with 1 mg flupentixol. This dose of diazepam has been shown to impair psychomotor performance (Mattila et al. 1986) and hence a possible interaction with flupentixol should be detectable. In addition, this dose was chosen because it has quite different effects at 1.5 h and 3 h (Mattila et al. 1986), which has implications regarding subchronic treatment with fixed daily doses of diazepam.

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Material and methods

Subjects

Twelve healthy students, aged 22–27 years and weighing 52–90 kg, volunteered for the trial and were paid for their time. The subjects gave their written informed consent, and the trial protocol was accepted by the departmental committee of ethics. The subjects were trained to the tests before entering the actual trial.

Trial design

In this double-blind crossover trial the subjects received single oral doses of active drug or placebo in randomized order on 6 consecutive Saturdays, each experimental session beginning at 10 a.m.All treatments were given in identical gelatine capsules. To match the peak effects of flupentixol, lorazepam and diazepam, diazepam was given after the first post-drug test round (at 1.5 h) irrespective of whether it was given alone or in combination with 1 mg flupentixol. The other drugs were given after the baseline tests. The same tests were repeated 1.5, 3 and 4.5 h after drug intake. Venous blood was sampled into heparinized vacuum tubes after each test round. A light standard meal (a roll and fruit juice) was served after the test round at 3 h.

Tests

The tests were always done in the same order. Each test round lasted for 25 min, and the subjects began the rounds at 6-min intervals so that the test times (1.5 h, 3 h, 4.5 h) coincided with the middle of the respective test rounds.

Objective tests. These included were digit symbol substitution and letter cancellation (Stone 1984), critical flicker fusion frequency (Smith and Misiak 1976), Maddox wing for heterophoria (Hannington-Kiff 1970), tapping rate, backwards recall of digit spans, and two kinds of tracking test. The "old" tracking test was driven at fixed speed. It lasted for 30 s, and the number of errors and the error percentage (relative length of the track driven off the road) were recorded (Linnoila and Mattila 1973). The "new" computerized tracking test comprised a road moving on the colour TV screen, and the driver had to keep the car or the road by turning the steering wheel (Linnavuo et al. 1987). The driving lasted for 5 min at a fixed, fairly rapid speed. The first (easy) and the latter (difficult) halves were analyzed separately, and the number of errors (deviations off the road) as well as the error percentages were recorded.

A paired associate learning task (Liljequist et al. 1978) was done after the other tests at 4.5 h. Six pairs of syllables were presented to the subject consecutively at intervals of 5–6 s, after which they were given one member of the pair only and asked to complete the pair. The total number of errors and the number of repetitions needed to reach the complete, correct answers were recorded.

Subjective assessments. These used ungraded horizontal visual analogue scales (VAS) (Bond and Lader 1974). A total of 18 pairs of extremes were used: alert/drowsy; calm/troubled; strong/feeble; attentive/dreamy; proficient/incompetent; happy/sad; relaxed/tremulous; interested/bored; sociable/withdrawn; friendly/hostile; quick-witted/mentally slow; satiated/hungry; contended/discontented; clear-headed/muzzy; skilful/clumsy; active/passive; mentally balanced/panicked; and very bad/very good performance. The subjects also filled in a 42-item questionnaire (Seppälä et al. 1982b) for various side effects at the end of each test time.

Statistical handling

Mean ± SEM values of absolute test performances were computed in terms of drug/test time and week/test time. The latter was used in order to reveal possible practice effects in the baselines of the tests. The Δ-values (changes from the respective baselines) indicating actual drug responses were also computed as above. One-way analyses of variance (ANOVA) for repeated measures followed by paired t-tests (Δ-drug versus Δ-placebo) when indicated were computed for objective variables. Non-parametric Kruskal-Wallis and Wilcoxon tests were computed for subjective VAS data, respectively.

Since practice effect was obvious in tracking performance, the objective data was also analyzed with two-way (week × drug effect) repeated measures ANOVA computed for Δ-values at each test time, in order to take sequence effects into consideration. Each individual treatment was separately compared against placebo, and flupentixol 1 mg + diazepam versus diazepam alone were also compared.

Drug concentrations in plasma

Plasma concentrations of flupentixol were measured by radioimmunoassay (RIA) (Jørgensen 1985). To measure the plasma concentrations of the two benzodiazopines in a commensurable way, they were "bioassayed" with a radioreceptor technique (RRA) against drug-free baseline plasma and the same (diazepam) standard. The assay was done both directly from the plasma (Aranko et al. 1985a) and after a single ether extraction (Aranko et al. 1985b). This extraction, followed by evaporation to dryness and dissolution of the residue to methanol, gave a 95–100% recovery for diazepam, while the respective recovery for freshly recovered lorazepam in plasma was 85–90%. After deep-freezing and thawing once, the recovery for lorazepam was 80–85% while the diazepam recovery did not change. ^{3}H-flunitrazepam (0.9 nmol/l) was used as the radioligand, rat cerebral cortex (0.25 mg protein) as the receptor preparation, and three to four concentrations of diazepam ran parallel to the samples in each assay. The results are expressed as diazepam equivalents.

Results

A significant practice effect was seen in the baseline performances in both old and new tracking tests. This effect was not confined to the first weeks but continued over the whole trial period, so that the significant ($P < 0.05$) improvement of performance found at 2–3 weeks increased further to reach a higher level of significance ($P < 0.001$–0.01) during the 6th week. A smaller but statistically significant ($P < 0.05$) practice effect was seen in the backwards recall test from the 4th week on. Despite the considerable practice effect in tracking variables, the two-way ANOVA (drug effect × drug sequence) did not add much significance to the drug responses, as compared with their simpler analysis.

Comparison of flupentixol and lorazepam

A selection of relevant parameters from objective and subjective tests are given in Table 1 and in Figs. 1 and 2. In general, 1 mg flupentixol proved indistinguishable from placebo, and 2 mg flupentixol caused effects which generally did not differ from those recorded after placebo or baseline results. The only exceptions were the significant ($P < 0.05$ versus placebo) reduction of tapping rate and the increased tracking error percentage (old tracking test) recorded 90 min after the intake of 2 mg flupentixol. Both benzodiazepines impaired performance. The new tracking test with longer driving time was slightly more sensitive than the old one in detecting benzodiazepine-induced impairment. Lorazepam impaired objective test functions more than subjective measures.

Objective tests. Lorazepam impaired simulated driving performance by increasing the number of errors and error percentage in both tracking tests. The effects were most distinct at 3 h after the intake of lorazepam (Table 1). In the new tracking test, lorazepam impaired performance in both the easy first half and the difficult second half, and increased the overall severity of tracking errors. In the digit symbol substitution test and the letter cancellation test (Fig. 1) and the flicker fusion test (Table 1) lorazepam impaired performance, while its effect on muscle tone in the Maddox wing

Table 1. Mean ± SEM values of 12 subjects in some performance tests before and after oral single doses of 1 mg (F1) or 2 mg (F2) of flupentixol, 2.5 mg lorazepam (LZ) and 15 mg diazepam (DZ). Diazepam was given after the tests at 1.5 h had been done. * 11 subjects only. For details see text

Test	Mean ± SEM performance at different test times			
Drug	Baseline	1.5 h	3 h	4.5 h
Tracking errors, first half*				
Placebo	34 ± 3.4	35 ± 3.1	32 ± 3.5	33 ± 3.1
LZ	34 ± 2.8	40 ± 2.5[a]	48 ± 3.5[by]	48 ± 2.2[cz]
F2	29 ± 3.0	33 ± 3.0[a]	33 ± 2.7	32 ± 1.1
F1	36 ± 2.9	33 ± 2.3	33 ± 3.0[a]	32 ± 2.4[a]
F1 + DZ	35 ± 3.0	35 ± 3.6	42 ± 3.3[x]	33 ± 2.5
DZ	34 ± 2.8	34 ± 3.0	43 ± 4.4[ax]	35 ± 3.0
Tracking errors, second half*				
Placebo	58 ± 5.1	54 ± 4.2	53 ± 4.5	51 ± 4.6
LZ	58 ± 4.1	65 ± 3.9[ay]	74 ± 3.3[bz]	71 ± 1.9[cz]
F2	57 ± 4.8	55 ± 3.9	52 ± 4.4	53 ± 3.4[a]
F1	58 ± 3.5	53 ± 2.8	51 ± 3.7[a]	51 ± 2.9
F1 + DZ	59 ± 5.6	53 ± 5.4[a]	59 ± 3.8	53 ± 4.5
DZ	55 ± 4.5	57 ± 4.5	57 ± 4.9	51 ± 3.8[a]
Flicker fusion (Hz × 10)				
Placebo	262 ± 7	258 ± 8	247 ± 9[a]	240 ± 7[b]
LZ	258 ± 6	240 ± 8[a]	219 ± 8[cz]	220 ± 7[cx]
F2	261 ± 5	249 ± 6[a]	248 ± 5	244 ± 5[b]
F1	266 ± 8	262 ± 7	254 ± 8	245 ± 7[c]
F1 + DZ	268 ± 6	256 ± 7[a]	228 ± 6[cz]	232 ± 6[ax]
DZ	260 ± 9	251 ± 8[a]	226 ± 8[cy]	225 ± 5[cx]
Bad/good performance (mm VAS)				
Placebo	69 ± 5	64 ± 4[a]	65 ± 6	69 ± 5
LZ	70 ± 6	64 ± 6[a]	54 ± 5[b]	53 ± 6[ax]
F2	69 ± 5	63 ± 6	65 ± 6	66 ± 6
F1	59 ± 6	63 ± 5	62 ± 6	62 ± 6
F1 + DZ	66 ± 6	66 ± 6	52 ± 5[a]	53 ± 7[bx]
DZ	65 ± 7	63 ± 6	44 ± 5[a]	47 ± 6[a]

[a] $P<0.05$; [b] $P<0.01$; [c] $P<0.001$ vs baseline
[x] $p<0.05$; [y] $p<0.01$; [z] $p<0.001$ vs Δ-placebo

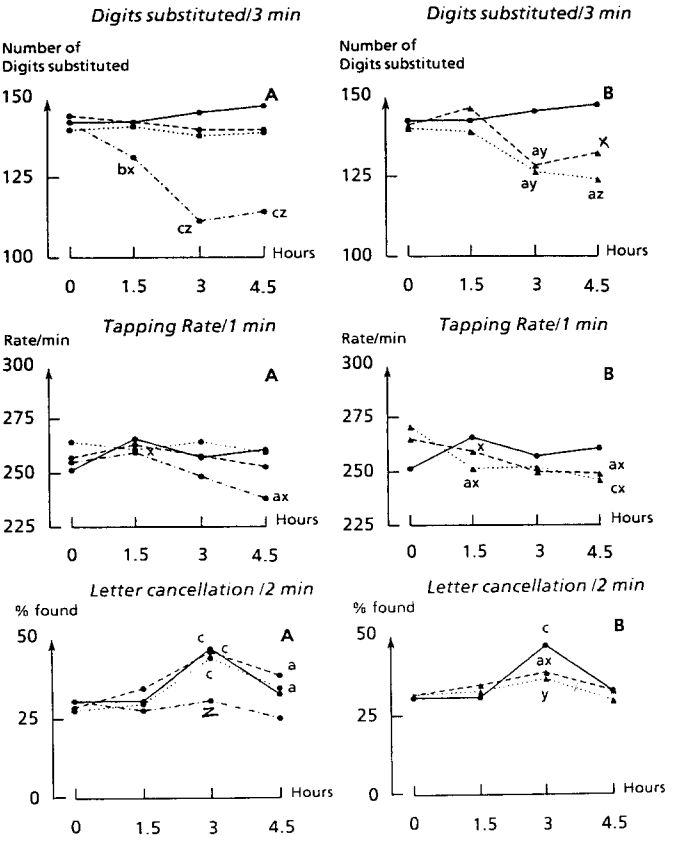

Fig. 1 A, B. Absolute values of performance of 12 subjects in some objective tests, as modified by oral single doses of (**A**) flupentixol 1 mg or 2 mg and lorazepam 2.5 mg, and (**B**) diazepam 15 mg and diazepam + flupentixol 1 mg. Diazepam was given after the tests at 1.5 h had been done. Statistical significances are: a = $P<0.05$; b = $P<0.01$; c = $P<0.001$ vs baseline (paired t-test); x = $P<0.05$; y = $P<0.01$; z = $P<0.001$ vs Δ-placebo (two-way ANOVA). **A** ●——● Placebo; ●---● Flupentixol 1 mg; ●...● Flupentixol 2 mg; ●-.-.-● Lorazepam 2,5 mg. **B** ●——● Placebo; ▲---▲ Diazepam; ▲...▲ Diazepam + flupentixol

test was less consistent. Lorazepam impaired learning acquisition by increasing the numbers of errors and repetitions ($P<0.01$; two-way ANOVA) as compared with placebo.

Flupentixol showed little activity in objective tests, and a 1 mg dose showed a non-significant trend towards improved tracking. Flupentixol 2 mg proved relatively inert on various performance tests, with two exceptions mentioned above. Both numerically (Table 1) and graphically (Fig. 1), the results show that the subjects were more affected by 2.5 mg lorazepam than by either 2 mg flupentixol or placebo.

Subjective findings. Flupentixol 1 mg did not differ from placebo on any of the 18 VAS variables. Flupentixol 2 mg did not differ from placebo either, except for the VAS variable "proficient/incompetent", showing that the subjects felt less competent at 3 h as compared with the respective baseline and Δ-placebo. This difference might have resulted from a low baseline value. After the intake of lorazepam the subjects reported feeling drowsy, feeble, dreamy and mentally slow, and they considered their performance as impared (Fig. 2, Table 1).

The results of the other subjective test, the 42-item questionnaire, showed that 1 mg flupentixol did not differ from placebo in either the number or the degree of side effects, except that, perhaps, there were even fewer side effects. Only in one item (drowsiness) out of the 42 items on the questionnaire did 2 mg flupentixol increase the score as compared with placebo. This effect of 2 mg flupentixol was not confirmed by the other subjective rating, the VAS "alert/drowsy". Lorazepam caused drowsiness, fatigue, dizziness and heavy headedness, differing significantly from placebo both at 3 and 4.5 h.

Comparison of diazepam and diazepam-flupentixol

The single oral dose of 15 mg diazepam served as a model for the study of both acute and subchronic effects of benzodiazepines. After rapid absorption it impaired performance both objectively and subjectively at 1.5 h, whereas mainly subjective impairment remained at 3 h. Thus, prolonging the objective effects of diazepam by concomitant drugs may reveal important interactions, as previously reported in another connection (Mattila and Mattila 1987). In order to compare the peak effects of the robust doses of 2.5 mg

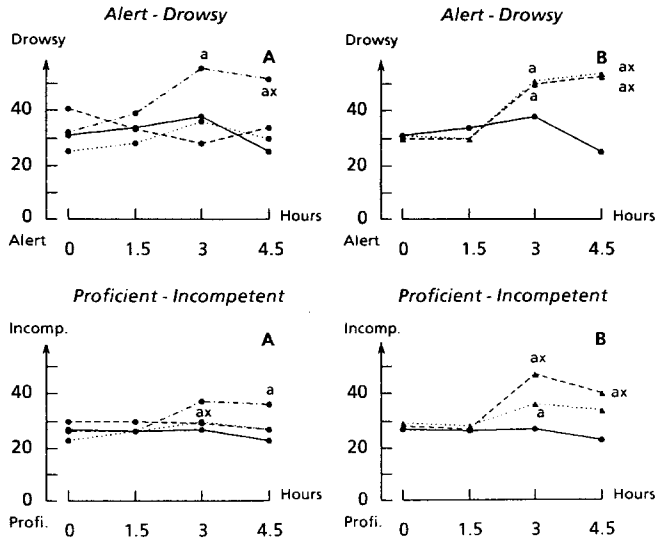

Fig. 2A, B. Absolute values of 12 subjects in some visual analogue scale (100 mm) assessments. For symbols see Fig. 1. Statistical significances: a = $P<0.05$ vs baseline (paired t-test); x = $P<0.05$ vs Δ-placebo (Kruskal-Wallis and Wilcoxon texts). **A** ●——● Placebo; ●---● Flupentixol 1 mg; ●···● Flupentixol 2 mg; ●-·-·-● Lorazepam 2.5 mg. **B** ●——● Placebo; ▲---▲ Diazepam; ▲···▲ Diazepam + flupentixol

Table 2. Concentrations of benzodiazepines (BZs) in plasma when assayed with radioreceptor technique directly from plasma or after its extraction with ether. Both diazepam and lorazepam are expressed as diazepam equivalents. Diazepam was given 1.5 h after 1 mg flupentixol or placebo. For more details see text

Treatment	BZs in plasma as ng/ml of diazepam; mean ± SEM	
Time	Direct assay	After ether extraction
Lorazepam		
1.5 h	870 ± 191	34 ± 12
3 h	1440 ± 229[a]	65 ± 12
4.5 h	860 ± 104	82 ± 13[b]
Diazepam alone		
3 h	370 ± 39	550 ± 73
4.5 h	220 ± 37	450 ± 40[c]
Diazepam + flupentixol 1 mg		
3 h	400 ± 74	510 ± 56
4.5 h	140 ± 56	370 ± 32[c]

[a] $P<0.01$ vs respective concentrations at 1.5 and 4 h
[b] $P<0.05$ vs respective concentrations at 1.5 h
[c] $P<0.01$ vs respective direct assay (paired t-test)

lorazepam and 15 mg diazepam, the latter was given 1.5 h later.

Objective tests. Diazepam impaired tracking performance, particularly at 3 h (1.5 h after the intake of diazepam). In the digit symbol substitution, flicker fusion and letter cancellation (Fig. 1, Table 1) tests, diazepam also impaired performance; less consistent effects were observed on muscle tone in the Maddox wing test. In some tests (Fig. 1) 1 mg flupentixol in combination with diazepam tended to prolong the effects of diazepam and increase the level of statistical significance as compared with placebo. However, no significant differences were found when diazepam and the combination diazepam + flupentixol 1 mg were compared with two-way ANOVA tests.

Subjective findings. The data recorded on VAS lines indicated that after treatment with diazepam, the subjects considered themselves drowsy, feeble, dreamy and mentally slow, and their performance was impaired (Fig. 2, Table 1). The effect of diazepam on the subjective tests lasted longer than its effect on the objective tests. In combination with 1 mg flupentixol, diazepam did not show prolonged effects, and occasionally flupentixol even decreased the subjective sedative effects of diazepam.

Measurements on the 42-item questionnaire did not show any difference between the effects of diazepam alone and in combination with flupentixol.

Concentrations of drugs in plasma

The anxiolytic doses of flupentixol are small and its concentrations after the 1 mg dose were mostly below the thresholds of detection by the radioimmunoassay (RIA) used. Measurable but low concentrations (mean ± SEM) of flupentixol were found after the 2 mg dose at 3 h (0.5 ± 0.12 ng/ml) and at 4.5 h (0.5 ± 0.09 ng/ml) but not at 1.5 h.

The concentrations of lorazepam and diazepam, measured with a radioreceptor (RRA) method and expressed as ng/ml of diazepam, are given in Table 2. It appears that the plasma benzodiazepine concentrations after lorazepam were definitely larger than the respective concentrations after diazepam when assayed directly from plasma without previous solvent extraction. The time-courses of concentrations of benzodiazepines were as expected: lorazepam reached peak concentrations at 3 h and diazepam at 1.5 h after administration, respectively. The wide standard deviation for lorazepam indicates a wide range of concentrations recorded; they may be attributable to differences in binding to plasma proteins.

The mean concentrations of diazepam assayed after solvent extraction were 50–100% larger than those assayed directly from plasma. Irrespective of the assay used, 1 mg flupentixol did not modify plasma diazepam concentrations significantly. Unexpectedly, plasma lorazepam levels were low or negligible when bioassayed against diazepam standards after extraction with ether. The recovery in the extraction process after deep-freezing and thawing was 95–100% for diazepam and 80–85% for lorazepam. Measurements of plasma lorazepam from the same refrozen and rethawed samples by gas chromatography (Seppälä and Korte, personal communication) gave the following (mean ± SEM) values: 19 ± 4 ng/ml at 1.5 h, 32 ± 6 ng/ml at 3 h, and 31 ± 4 ng/ml at 4.5 h. These values are very similar to those previously measured in our laboratory after oral doses of 2.5 mg lorazepam (Seppälä et al. 1976).

When looking tentatively for linear correlations of various objective responses (Δ-values) to drugs and their respective plasma log concentrations (direct radioreceptor assay), most correlations were negligible. Lorazepam showed

a low (0.466; $P > 0.05$) positive correlation at 3 h on per cent tracking error during the difficult second half of the track. With digit symbol substitution the respective correlation was even lower ($r = 0.261$). No correlation was detected on these variables at 1.5 or 4.5 h. When the respective correlations were calculated for diazepam at 3 h (1.5 h after intake), the log concentrations of diazepam correlated significantly with impairment of digit substitution ($r = 0.596$; $P < 0.05$) but not with the increase of tracking error percentage ($r = 0.377$). In the presence of 1 mg flupentixol these correlations for diazepam effects fell to zero.

Discussion

Patients with depression and/or anxiety often express an obvious alteration in their psychomotor performance as well as their cognitive functions, such as attention, perception, memory and intellectual performance (Siegfried and O'Connolly 1986). In addition, side effects induced by psychotropic drugs may interfere with cognitive functions. It can be difficult for a patient treated with such drugs to state whether impaired function is related to the disease or is an effect of the drug (Siegfried and O'Connolly 1986). It is known that in depressive patients sedative antidepressants improve rather than impair psychomotor performance along with the amelioration of depression (Seppälä et al. 1978). In spite of this, it is wise to choose a compound with a minimum of the above-mentioned untoward side effects, provided that the doses used are clinically effective.

The data presented indicate that neither 1 mg nor 2 mg flupentixol impaired performance. Flupentixol 1 mg differed neither objectively nor subjectively from placebo. Flupentixol 2 mg proved inert objectively but caused a mild subjective sedation, as reported in answer to the questionnaire. This effect was not confirmed by the respective VAS rating. In its lack of impairment of performance, flupentixol differed strikingly from lorazepam, which definitely impaired performance both objectively and subjectively. Furthermore, 1 mg flupentixol did not enhance the decremental effects of diazepam on human performance. In this way it differs from larger, antipsychotic doses of neuroleptics which, in similar circumstances, may increase diazepam-induced impairment (Mattila and Mattila 1987).

It may be argued that our single-dose study lacks validity as it was conducted with healthy volunteers. However, the results obtained in healthy volunteers have previously been applicable to subacute (2 weeks) treatments of outpatients with anxiety (Saario et al. 1976) and depression (Seppälä et al. 1978). Saario et al. (1976) documented an impairment of psychomotor functions both with diazepam (15–30 mg daily) and with thioridazine (75–150 mg daily).

The two tracking tests are a measure of speed and accuracy of eye-to-hand coordination, while cognitive functions were evaluated with digit symbol substitution, letter cancellation and memory tests. Critical flicker fusion is a test for non-specific cortical arousal, and the Maddox wing test refers to central coordination of the muscle tone. All these functions were without doubt impaired by 2.5 mg lorazepam; the present findings are in accord with our previous results obtained with single doses of 2.5 mg lorazepam (Seppälä et al. 1976, 1982a, b; Aranko et al. 1985a) on a similar set of laboratory tests. Our present finding of the decremental effect of lorazepam on learning acquisition at 4.5 h is, likewise, in accord with other reports of lorazepam-induced, dose-related impairment of memory (Shader et al. 1986).

Objectively, 15 mg diazepam was somewhat less decremental than 2.5 mg lorazepam in terms of affecting fewer functions and causing quantitatively less impairment of performance recorded at 3 h only (1.5 h after diazepam administration). However, diazepam was subjectively perhaps more sedative than lorazepam, and this sedation lasted for at least 3 h. This pattern of diazepam action is in accord with our previous results obtained with single 0.3 mg/kg doses of diazepam (Mattila et al. 1986). The short duration of objective impairment of performance after a single dose of diazepam might be a result of acute receptor tolerance (Ellinwood et al. 1983) and/or of rapid (even intracerebral) redistribution. Obviously, lower concentrations of diazepam are needed in the brain for subjective sedation than for objective impairment of performance.

There was a poor correlation between "bioassayed" concentrations of benzodiazepines and their effects as analyzed in this study. This poor correlation has likewise been demonstrated with chemically assayed lorazepam (Lister et al. 1983). Single-dose effects may correlate with plasma benzodiazepine concentrations if the function measured is fairly simple, e.g., saccadic eye movements (Bittencourt et al. 1981). With such complex functions as the performance tests measure, such positive correlations are not expected, as the rate of penetration of benzodiazepines into the brain varies (Tedeschi et al. 1983) and is, at its best, slow and incomplete with lorazepam (Aaltonen et al. 1980). As a whole, there was a positive correlation between the concentrations and certain effects of diazepam when given alone. However, when given together with 1 mg flupentixol, these correlations could not be detected even though there was no major modification in either the individual effects or concentrations.

The difference between the objective effects of lorazepam and diazepam is reflected in their concentrations bioassayed directly from plasma as diazepam equivalents. In order to demonstrate this difference between the doses of the benzodiazepines used, we employed the direct RRA technique and diazepam as a commensurable standard for both benzodiazepines. In these terms, single doses of 2.5 mg lorazepam and 15 mg diazepam are not equipotent. This difference is not always appreciated, since the recommended clinical doses of lorazepam are not necessarily correct. Dutch investigators have recently estimated that the traffic risks caused by lorazepam 1 mg t.i.d. are comparable with those caused by blood alcohol concentrations of about 1.5 mg/ml. On their scale, diazepam 5 mg t.i.d. was comparable with 0.5 mg/ml alcohol in blood (Brookhuis et al., Report to Second International Symposium on Medicinal Drugs and Driving, Maastricht, 1987). These estimates were based on measurements by using special cars on the road.

We have repeatedly observed relatively high plasma benzodiazepine activity with lorazepam in radioreceptor assays. We attribute this phenomenon to the fact that lorazepam has a lower level of binding to plasma proteins (below 90%) than diazepam (over 95%). The different effect of plasma on the displacement of ^{3}H-flunitrazepam from benzodiazepine receptors in vitro by lorazepam and diazepam, respectively, can be documented (Aranko et al. 1985a). The reasons why plasma lorazepam concentrations were low when bioassayed after ether extraction remain obscure, but an alteration of the active molecule during extraction is

possible. This phenomenon is, of course, not seen when lorazepam is assayed against a lorazepam standard (Aranko et al. 1985b).

The doses of the drugs used prompt the question of their relative clinical equipotency; BZs and neuroleptics are not qualitatively similar and their effects may not be commensurable (Rickels 1983). There are no direct comparative trials of flupentixol versus lorazepam to establish their anxiolytic efficacy in neurotic disorders. Indirect comparison is possible, since both substances have been used in several controlled trials, mainly on a multicenter basis. Jokinen et al. (1984) found that a daily dose of 1–2 mg flupentixol proved comparable with diazepam 5–10 mg daily, but their spectra of actions were somewhat different. Rickels et al. (1976) used 3 mg lorazepam daily and concluded, after evaluation of the results, that this dose may be too high for mildly anxious patients. This conclusion is in agreement with our present data on the actions and concentrations measured after a single oral dose of 2.5 mg lorazepam. Although this dose of lorazepam thus seems relatively larger than the doses of flupentixol used, the present study indicates that 1 and 2 mg flupentixol in practice have less effect on skilled performance and memory.

In this study, neither 1 mg nor 2 mg flupentixol had significant untoward effects, which is in clear contrast to the marked impairment caused by lorazepam. As it is well known that lorazepam also has a tendency to produce dependence in long-term use, it seems that flupentixol would be a valuable alternative to lorazepam and other benzodiazepines. As no relevant interaction between diazepam and flupentixol 1 mg was found, these two drugs can be combined, according to the patients' needs, without major impairment of skilled performance.

Acknowledgements. The authors owe Dr A Jørgensen, Lundbeck A/S, their thanks for the assay of plasma concentrations of flupentixol. The technical assistance of Mrs Katri Eklund in the radioreceptor assay is greatly appreciated.

References

Aaltonen L, Kanto J, Salo M (1980) Cerebrospinal fluid concentrations and serum protein binding of lorazepam and its conjugate. Acta Pharmacol Toxicol 46:156–158

Aranko K, Seppälä T, Pellinen J, Mattila MJ (1985a) Interaction of diazepam or lorazepam with alcohol. Psychomotor effects and bioassayed serum levels after single and repeated doses. Eur J Clin Pharmacol 28:559–565

Aranko K, Mattila MJ, Nuutila A, Pellinen J (1985b) Benzodiazepines, but not antidepressants or neuroleptics, induce dose-dependent development of tolerance in psychiatric patients. Acta Psychiatr Scand 72:436–446

Bittencourt PRM, Wade P, Smith AT, Richens A (1981) The relationship between peak velocity of saccadic eye movements and serum benzodiazepine concentration. Br J Clin Pharmacol 12:523–533

Bond A, Lader M (1974) The use of analogue scales in rating subjective feelings. Br J Med Psychol 47:211–218

Ellinwood EH, Linnoila M, Easler M, Molter DW (1983) Profile of acute tolerance to three sedative anxiolytics. Psychopharmacology 79:137–141

Hannington-Kiff JG (1970) Measurements of recovery from outpatient anaesthesia with simple ocular test. Br Med J 3:132–135

Jokinen K, Koskinen T, Selonen R (1984) Flupentixol versus diazepam in the treatment of psychosomatic disorders: a double-blind, multicentre trial in general practice. Pharmatherapeutica 2:573–581

Jørgensen A (1978) A sensitive and specific radioimmunoassay for *cis*(Z)-flupentixol in human serum. Life Sci 23:1533–1542

Liljequist R, Seppälä T, Mattila MJ (1978) Amitriptyline- and mianserin-induced changes in acquisition on paired-associated learning task. Br J Clin Pharmacol 5:149–153

Linnavuo M, Ylilääkkölä P, Mattila MJ, Mäki M, Seppälä T (1987) A new device to measure drug-induced changes in coordinative and reactive skills related to driving. Pharmacol Toxicol 61:142–147

Linnoila M, Mattila MJ (1973) Drug interaction on psychomotor skills related to driving: diazepam and alcohol. Eur J Clin Pharmacol 5:186–194

Lister RG, File S, Greenblatt DJ (1983) Behavioural effects of lorazepam are poorly related to its concentrations in the brain. Life Sci 32:2033–2040

Mattila MJ, Mattila ME (1987) Actions and interactions with ethanol or diazepam of remoxipride on psychomotor skills and mood in healthy volunteers. Pharmacol Toxicol [Suppl III] 60:56

Mattila ME, Seppälä T, Mattila MJ (1986) Combined effects of buspirone and diazepam on objective and subjective tests of performance in healthy volunteers. Clin Pharmacol Ther 40:620–626

Rickels K (1983) Nonbenzodiazepine anxiolytics: clinical usefulness. J Clin Psychiatry 44:38–43

Rickels K, Case WG, Chung HR, Morris RJ, Pereira-Ogan J, Rosenfeld H, Segal A (1976) Lorazepam and diazepam in anxious outpatients. A controlled study. Int Pharmacopsychiatry 11:93–101

Saario I, Linnoila M, Mattila MJ (1976) Modification by diazepam or thioridazine of the psychomotor skills related to driving: a subacute trial in neurotic outpatients. Br J Clin Pharmacol 3:165–171

Seppälä T, Korttila K, Häkkinen S, Linnoila M (1976) Residual effects and skills related to driving after a single oral administration of diazepam, medazepam or lorazepam. Br J Clin Pharmacol 3:831–841

Seppälä T, Linnoila M, Mattila MJ (1978) Psychomotor skills in depressed outpatients treated with *l*-tryptophan, doxepin, or chlorimipramine. Ann Clin Res 10:214–221

Seppälä T, Linnoila M, Mattila MJ (1979) Drugs, alcohol and driving. Drugs 17:389–400

Seppälä T, Aranko K, Mattila MJ, Shrotriya RC (1982a) Effects of alcohol on buspirone and lorazepam actions. Clin Pharmacol Ther 32:201–207

Seppälä T, Dreyfus JF, Saario I, Nuotto E (1982b) Zopiclone and flunitrazepam in healthy subjects: hypnotic activity, residual effects on performance and combined effects with alcohol. Drugs Exp Clin Res 8:35–47

Shader RI, Dreyfuss D, Gerrein JR, Harmatz JS, Allison SJ, Greenblatt DJ (1986) Sedative effects and impaired learning and recall after single oral doses of lorazepam. Clin Pharmacol Ther 39:526–530

Siegfried K, O'Connolly M (1986) Cognitive and psychomotor effects of different antidepressant in the treatment of old-age depression. Int Clin Psychopharmacol 1:231–243

Smith JM, Misiak H (1976) Critical flicker frequency (CFF) and psychotropic drugs in normal human subjects – a review. Psychopharmacology 47:175–182

Smith DE, Wesson DR (1985) The benzodiazepines. Current standards for medical practice. MTP Press, Lancaster

Stone B (1984) Pencil and paper tests – sensitivity to psychotropic drugs. Br J Clin Pharmacol 18:15S–20S

Tedeschi G, Smith AT, Dhillon S, Richens A (1981) Rate of entrance of benzodiazepines into the brain determined by eye movement recording. Br J Clin Pharmacol 15:103–106

Received September 7, 1987 / Final version January 20, 1988