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DEVELOPMENT OF TOLERANCE AND CROSS-TOLERANCE TO THE PSYCHOMOTOR ACTIONS OF LORAZEPAM AND DIAZEPAM IN MAN

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1 Development of tolerance and cross-tolerance to lorazepam and diazepam in man was assessed in a double-blind and cross-over trial where eight pretrained healthy students volunteered for four 1 week treatment periods started at 1 month intervals.

2 In each period acute psychomotor responses to oral lorazepam 3 mg and diazepam 15 mg were recorded on day 1, as well as on day 8 after 1 week's treatment twice daily with diazepam 5 mg, lorazepam 1 mg, and placebo. At each session several objective psychomotor tests and subjective assessments were done before the drug intake and 1, 2.5, and 4 h after it.

3 In general, the effects of lorazepam were stronger and of longer duration than those of diazepam at the doses used. When comparing the single-dose responses on days 1 and 8, tolerance to lorazepam effects and some cross-tolerance developed on several functions measured. Tolerance but not cross-tolerance developed on choice reaction errors whereas the opposite was found on flicker fusion. No definite tolerance was found on subjective effects.

4 The results tally with an assumption that tolerance to benzodiazepine actions develops at different rates on various parameters measured.

Introduction

Development of tolerance to the sedative effects of various benzodiazepines has been repeatedly documented both in animals (Margules & Stein, 1968; Cook & Sepinwall, 1975) and in man (Mattila *et al.*, 1977; Church & Johnson, 1979; Seppälä *et al.*, 1980), but the mechanism of tolerance phenomenon has not been convincingly established. A reduction of the benzodiazepine binding sites in the central nervous system after chronic treatment with benzodiazepines has been proposed (Rosenberg & Chiu, 1981; Crawley *et al.*, 1982), yet they used large pretreatment doses as well as the radioligand technique which measures total binding sites rather than really relevant receptors. On the other hand, Elsass *et al.* (1980) and Hendel *et al.* (1980) have suggested that the presence of active metabolites may change the pharmacodynamic profile of the parent compound probably by occupying the receptor binding sites. Further, some tolerance could result from alterations in drug metabolism, but the evidence for this is not hard (File, 1981; Klotz & Reiman 1981).

To elucidate further understanding of the dynamics of prolonged benzodiazepine treatment we have conducted the present human experiment principally focused on lorazepam, a benzodiazepine with intermediate rate of elimination and without active metabolites. Tolerance and cross-tolerance with diazepam were evaluated by measuring the psychomotor responses (Hindmarch, 1980) to this agent initially as well as after pretreatment with lorazepam itself, diazepam or placebo.

Methods

Subjects

Eight healthy students aged 19 to 37 years, and weighing 48 to 78 kg, volunteered for the trial. Exclusions criteria were the history of any psychiatric illness, excessive use of alcohol, and the use of medicines within 2 weeks prior to the experiment. All subjects gave their written informed consent, and were paid for their time.

Drugs

The drugs were administered in identical gelatine capsules containing 5 mg diazepam, 1 mg lorazepam, or lactose placebo. According to clinical practice of using fixed doses in wide range we chose fixed doses

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too, although dosing mg/kg would have been more appropriate.

Design

The subjects were pretrained on the tests to achieve a steady baseline before entering the double-blind and cross-over trial which comprised four consecutive treatment periods (Table 1) with 3 weeks' wash-out intervals. Each treatment period comprised an acute single-dose test session on Day 1, followed by a 1 week subacute treatment twice daily, after which the single-dose test was repeated on Day 8. At these sessions, on Days 1 and 8, a zero test was administered before the drug intake, and the procedure was repeated 60 min, 2.5 h and 4 h after it.

Table 1 Drugs given during the four different treatment periods (D = diazepam and L = lorazepam)

Day 1	*Days 2–7*	*Day 8*
D 15 mg	diazepam 5 mg twice daily	L 3 mg
L 3 mg	lorazepam 1 mg twice daily	L 3 mg
L 3 mg	lorazepam 1 mg twice daily	D 15 mg
Placebo	placebo twice daily	L 3 mg

The treatment schedules are given on Table 1. Thus, the effects of lorazepam 3 mg (L3) after placebo, after lorazepam and after diazepam, as well as the effect of diazepam 15 mg (D15) after lorazepam were studied. The order of various treatment periods was balanced. On the session days the capsules were given to the subjects supervised, while on Days 2–7 the subjects took their treatments at home. The sessions always began between 16.00 h and 17.00 h. Two samples of venous blood were taken at each session, one before the drug intake and the other 180 min after it. Food, coffee, tea, and cola were not allowed for 4 h before and during the first 180 min of the sessions.

Objective tests

Hand-to-eye coordination was measured by a tracking task driven at fixed speed for 30 s (Linnoila & Mattila, 1973). The number of deviations from the track and the cumulative length of the deviations in per cent of total track length were recorded. An attention test (Linnoila & Mattila, 1973) consisted of four dials with revolving pointers, two dials at the central part and two dials at the peripheral parts of the subject's vision field. The test driven for 10 min provided a supra-maximal stimulus flow (84/min), and a background white noise was added to stress the subject. The cumulative number of responses and the number of correct responses to both central and lateral dials were counted. An extra bonus was paid for the best performance to motivate the subjects. In a choice reaction test sound stimuli of two different pitches and light stimuli of three different colours were given both alternately and simultaneously for 10 min. The subject had to respond to them by pushing a button or pressing either or both of the two foot pedals. The total number of stimuli, spaced at 1.5 s intervals, was 250. Cumulative reaction times and reaction errors were recorded separately for visual (40), auditory (20), and mixed (190) stimuli. Conventional critical flicker fusion test comprised recording of the maximal frequency of a red flickering light (2 mm) distinguished at a fixed distance (1 m) under standard background illumination. The subjects wore special spectacles to eliminate changes in pupillary diameter (Seppälä *et al.*, 1976). Coordination of the extra-ocular muscles was measured by Maddox wing (Hannington-Kiff, 1970), the relative deviation of eyes being expressed in prism diopters. Reflex rate was measured by a finger tapping task (Hindmarch, 1980). The number of taps per 30 s was recorded. The body sway was measured by an electronic platform in both lateral and sagittal directions (Savolainen & Linnavuo, 1979). Body movements during 20 s were recorded with both eyes open and closed.

Subjective assessments

At every test time the subjects were asked to assess their ability to perform the tests as well as for some psychological effects of treatments by the visual analogue scales (Seppälä *et al.*, 1982). A 32-item questionnaire was employed to report eventual side-effects.

Statistics

Raw data were employed mainly to reveal possible learning effects during the whole trial. Most results were computed as changes from the baseline values of the test day concerned. The two acute L3 groups on Day 1 did not differ significantly from each other and their results were pooled for analysis. Two-way analysis of variance (ANOVA) drug (seven different drug conditions) and time as factors, and paired *t*-tests were used to analyse the parametric data. The scores of the visual analogue scales were transformed to ratios of predrug/postdrug scores. These ratios were roughly normally distributed and parametric analyses were used (Stubbs, 1979).

Results

As a rule, baseline performance of the subjects remained stable throughout the trial, but the baseline values (Day 1) of the critical flicker fusion as well as

the number of correct responses in the attention test showed significant ($P < 0.05$ and 0.01 respectively; ANOVA) fluctuations between the periods. The overall drug effect was statistically significant on reactive skills, flicker fusion, coordinative skills, attention, body sway, and on visual analogue scales 'alert-drowsy' and 'antagonistic-friendly', but not on Maddox wing or tapping (Tables 2 and 3). The effect of time always remained nonsignificant. The results from flicker fusion test, body sway, attention test, reaction test, as well as from subjective assessments on the scale 'alert-drowsy' are visualized in Figures 1 and 2.

Table 2 F-values (d.f. 6/161) and the level of confidence (overall drug effect) for objective measurements

Parameter	*F*
Reaction mistakes (auditive signals)	3.929***
Reaction mistakes (visual signals)	2.367*
Reaction mistakes (mixed signals)	3.929***
Critical flicker frequency	14.498***
Correct responses in attention test	
left lateral dial	5.986***
left central dial	6.056***
right central dial	4.728***
right lateral dial	4.016***
Tracking mistakes	2.520*
Tracking mistakes (%)	4.153***
Lateral body sway, eyes open	3.078**
Lateral body sway, eyes closed	8.520***
Sagittal body sway, eyes open	4.739***
Sagittal body sway, eyes closed	6.704***
Tapping speed	1.313
Maddox wing	1.518

* = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$

Results on Day 1

Placebo proved inactive on most parameters measured. However, some improvement of performance was seen in attention test and tracking task after the intake of placebo.

Table 3 F-values (d.f. 6/161) and the level of confidence (overall drug effect) for visual analogue scales

Scales	*F*
Feeling of performance	0.952
Alert — drowsy	2.818*
Lethargic — energetic	0.471
Antagonistic —friendly	2.372*

* = $P < 0.05$

Effects of lorazepam L3 was the most effective treatment. It impaired significantly almost all objective parameters when compared with placebo ($P < 0.01$ to 0.001; paired *t*-test). Maddox wing and tapping were exceptions; they were insensitive to lorazepam. With regard to reactive and attentive skills the impairment after L3 was clearest at 1 and 2.5 h, whilst flicker recognition, coordination, and body balance were still affected at 4 h (Figures 1 and 2). The critical flicker frequency proved the most sensitive parameter for lorazepam.

Effects of diazepam D15 proved rather ineffective; it only impaired critical flicker frequency and coordinative skills (increased mistake % in the tracking task) at 1 h when compared with placebo ($P < 0.01$ and 0.05 respectively; paired *t*-test) (Figure 1).

Subjective assessments The subjects reported that single-doses of either active drug were felt as tranquillisers. This refers particularly to D15 which produced side-effects already at 1 h, whereas three subjects misinterpreted L3 as placebo at 1 h. This indicates that the subjective effect of L3 was somewhat delayed. Analysis of visual analogue scores revealed that the subjects rated their performance after either benzodiazepine as skillful as after placebo. This opinion disagrees with other visual analogue scale data which indicated that the active drug caused more drowsiness. As a whole, D15 caused most side-effects early at 1 h whereas the side-effects after L3 proved more sustained (Table 4).

Results on Day 8

The predrug baseline on Day 8 did not differ significantly from the objective and subjective measures on Day 1 (Table 5) and suggest a development of tolerance.

L3 after placebo On Day 8 the acute effects of L3 were similar to those observed on Day 1 (Figures 1 and 2). This indicates that pretreatment with placebo did not modify the effects of L3.

L3 after lorazepam After 7 days' pretreatment with lorazepam (1 mg twice daily) the subjects' responses to L3 were less than those measured on Day 1 as to reaction errors, attention errors, mistake % in tracking task, and body sway ($P < 0.05$ to 0.01, ANOVA). This suggests that treatment with lorazepam had developed tolerance to lorazepam itself (Figures 1 and 2). However, full L3 responses in the flicker fusion test on Day 8 suggest that no actual tolerance to lorazepam had been developed on this parameter (Figure 1).

L3 after diazepam The choice reaction errors to the

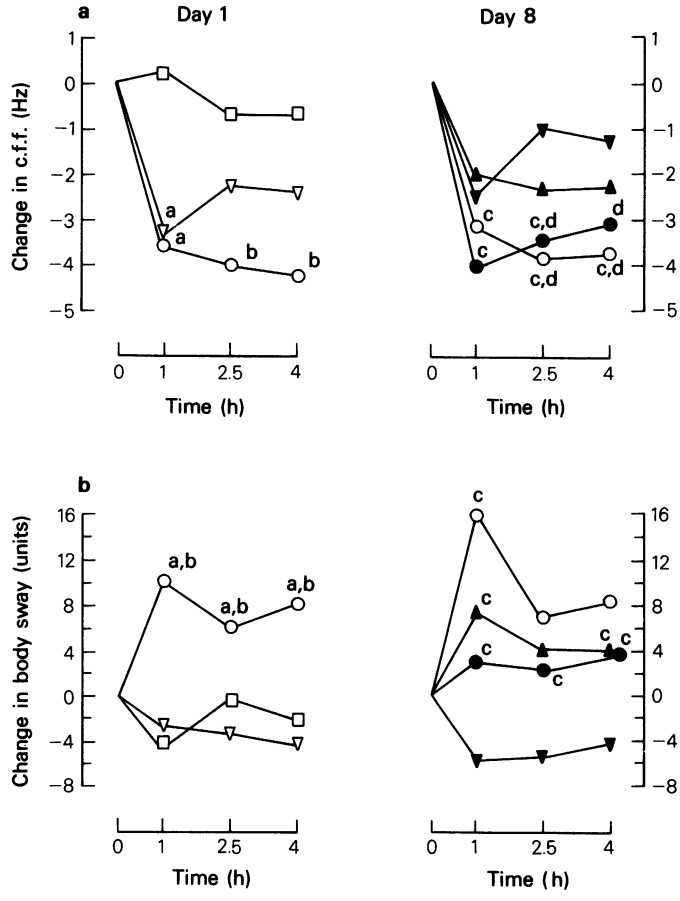

Figure 1 (a) Change in the critical flicker frequency (c.f.f.). Paired *t*-test: a = significantly ($P < 0.05$–0.001) different from placebo, b = significantly different from D15, c = significantly different from L3 after diazepam, d = significantly different from D15 after lorazepam.
(b) Change in body sway. Paired *t*-test: a = significantly different from placebo, b = significantly different from D15, c = significantly different from D15 after lorazepam.
□ = placebo, ▽ = D15, ○ = L3, ○ L3 after placebo, ● L3 after lorazepam 1 mg twice daily, ▲ L3 after diazepam 5 mg twice daily, and ▼ D15 after lorazepam 1 mg twice daily.

mixed stimuli were equally increased by L3 on Day 1 and on Day 8 after pretreatment with diazepam (5 mg twice daily). Similarly, pretreatment with diazepam failed to alter the L3 effect on mistake % in the tracking task. But pretreatment with diazepam reduced the L3 effects on critical flicker frequency, body sway, and attention (Figures 1 and 2) thus suggesting a development of cross-tolerance between these benzodiazepines.

D15 after lorazepam The modest effect of D15 on Day 1 clouds the assessment of the development of tolerance to it. The effects of D15 on Day 8 were approximately the same as on Day 1. A statistically nonsignificant trend towards reduced effects was seen when D15 was given after 7 days' treatment with lorazepam. This suggests that some cross-tolerance had been developed (Figures 1 and 2).

Subjective assessment One subject rated L3 as placebo after pretreatment with lorazepam, and another subject after diazepam. However, pretreatment with diazepam but not with lorazepam diminished drowsiness rated after L3 ($P < 0.05$ L3 after diazepam *vs* L3 after placebo at 2.5 h, paired *t*-test) (Figure 2). Subjects treated with lorazepam felt drowsiness for a shorter period after D15 on Day 8 than on Day 1. The number of side-effects reported

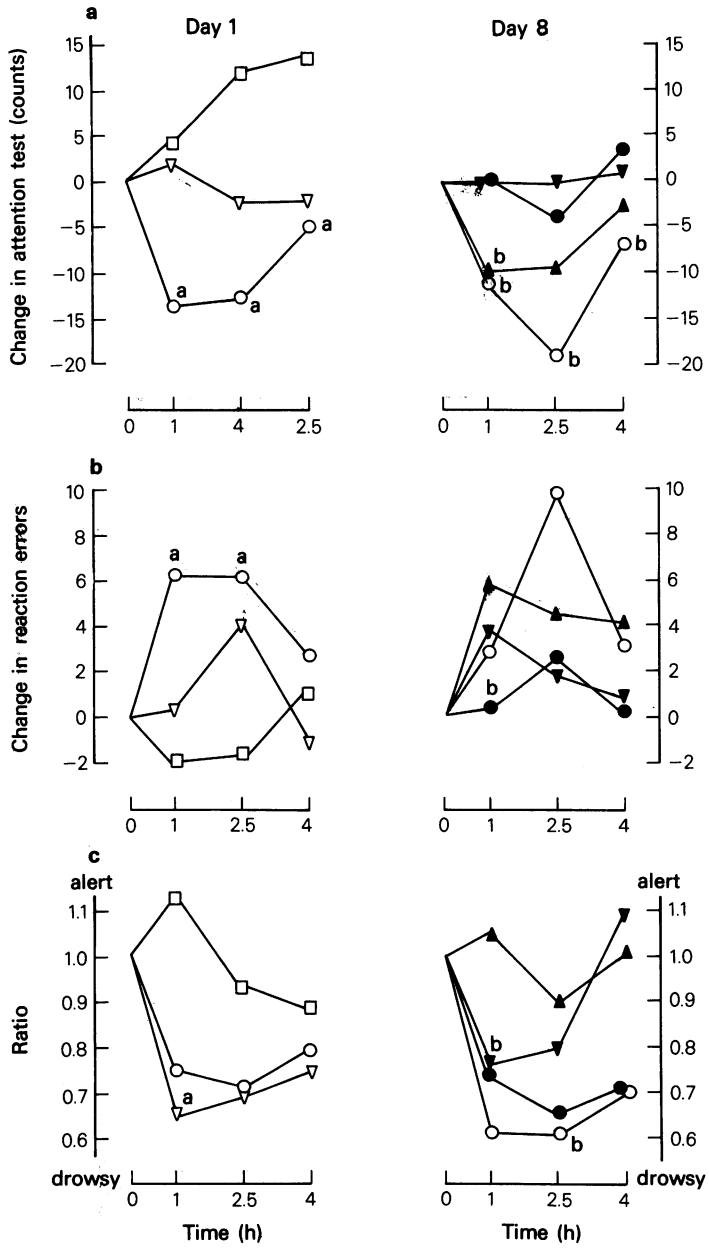

Figure 2 (a) Change in attention test. For symbols see Figure 1. Paired *t*-test: a = significantly different from placebo, b = significantly different from L3 after lorazepam.
(b) Change in reaction errors. Paired *t*-test; a = significantly different from placebo, b = significantly different from L3. (c) Change in scale 'alert-drowsy'. Data are represented as a change in ratio predrug/postdrug values. Paired *t*-test: a = significantly different from placebo, b = significantly different from L3 after diazepam.

after L3 on Day 8 depended on pretreatment so that L3 caused side-effects at 1 h significantly more ($P < 0.001$; paired *t*-test) after the diazepam treatment than after lorazepam pretreatment (Table 4). The side-effects due to D15 on Day 8 after the pretreatment with lorazepam did not differ from those obtained after D15 on Day 1, or from those caused by L3 after pretreatment with lorazepam.

Table 4 The number of side-effects reported counted per one subject.

Treatment	*0*	*1 h*	*2.5 h*	*4 h*
Placebo	1.9	2.6	2.5	2.8
Diazepam 15 mg (D15)	2.4	9.9[a]	5.9	3.3
Lorazepam 3 mg (L3)	1.8	6.8[a]	6.3[a]	5.7[a]
L3 after placebo	1.1	7.6	7.1	5.9
L3 after diazepam 5 mg twice daily	3.1	8.5	8.3	6.4
L3 after lorazepam 1 mg twice daily	1.1	4.9[b]	6.8	3.9
D15 after lorazepam 1 mg twice daily	1.8	5.8	3.6	2.3

a = significantly different from placebo
b = significantly different from L3 after diazepam 5 mg twice daily

Discussion

The data presented indicate that pretreatment with lorazepam for 7 days led to the development of tolerance to the lorazepam-induced impairment of most psychomotor functions measured (reaction errors, attention, body balance) except flicker fusion. The results also reveal a partial cross-tolerance between lorazepam and diazepam on attentive monitoring, flicker fusion, and body balance. Diazepam 15 mg had relative mild effects on performance thus impeding definite conclusions about the development of cross-tolerance.

In spite of criticism towards cross-over designs (Hill & Armitage, 1979) we chose such an approach mainly to minimize the number of volunteers challenged to subacute treatments with benzodiazepines. Our eight subjects represent a small but homogenous population, and we consider it acceptable both ethically and scientifically. The subjects were well motivated and co-operative, and there was no reason to doubt their compliance yet we were unable to document it.

The intensity and duration of action of single doses of benzodiazepines depend on the doses used (Nicholson, 1981), and on their distribution half-life (Curry, 1979) more than on their elimination half-lives. Our comparative doses were based on clinical recommendations which might underestimate a fairly long duration of action of lorazepam (Seppälä *et al.*, 1976), misled by its elimination half-life which is shorter than the respective half-life of diazepam. But the elimination half-life derives from the drug clearance as well as from its volume of distribution; since lorazepam is less lipophilic than diazepam and has a smaller distribution volume (Arendt *et al.*, 1982) it may be that the ratios of their brain to plasma concentrations are different. We consider that the strong effect of lorazepam on flicker fusion on Day 8, after 1 weeks' pretreatment with lorazepam, was a cumulative effect that fully compensated eventual development of tolerance. It seems as if the doses used for acute challenges were not really equipotent although they were chosen to meet with the clinical recommendations. Since young subjects are usually leaner than middle-aged subjects and have shorter half-lives for diazepam, our dose of diazepam was probably too low. The metabolites of benzodiazepines may interfere with the effects of parent drugs. For instance, during prolonged treatment with diazepam more nordiazepam than diazepam is accumulated in tissues, and a shift of the profile of action of diazepam towards that of nordiazepam is predicted in overall drug responses (Elsass *et al.*, 1980). Nordiazepam has repeatedly proved less potent on the psychomotor tests and less

Table 5 The absolute values in predrug tests on Day 1 and Day 8

Test	*Day 1*	*Placebo*	*Day 8 after D 5 mg twice daily*	*L 1 mg twice daily*
Reaction mistakes	5.42	5.13	4.63	4.19
CFF (Hz)	26.3	25.4	24.9	25.9
Correct counts in attention test	523.0	552.5	536.8	546.3
Tracking mistakes	12.0	12.4	10.4	10.7
Tracking mistakes (%)	26.8	24.9	21.5	21.7
Body sway	88.0	87.8	81.8	87.5
Tapping speed	132.1	129.5	132.9	134.2
Maddox wing	2.1	1.5	2.8	2.9

sedative at anxiolytic doses than diazepam (Palva & Linnoila, 1978; Hendel *et al.*, 1980). If tolerance phenomenon resulted from the concurrence of agents of different efficacy and different affinities at receptor sites, we would have found tolerance to lorazepam after pretreatment with diazepam only. But tolerance to lorazepam was induced by lorazepam itself as well. This and the partial cross-tolerance found between lorazepam and diazepam tallies with the interpretation of Rosenberg & Chiu (1981) who proposed, on the grounds of animal experiments, that tolerance to benzodiazepines is associated with a decrease of the amount of functional benzodiazepine receptors during long-term treatment. The importance of the receptors in the mechanism of tolerance was further supported by studies with benzodiazepine antagonist Ro 15-1788. File (1982) has shown in rats that a long lasting receptor blockade by Ro 15-1788 during subacute treatment with lorazepam attenuated the development of tolerance. Alternatively tolerance might reflect a non-specific ability of adaptation to the drowsiness and impaired psychomotor functions. We cannot exclude this possibility when interpreting 'normal' baseline values on Day 8 when benzodiazepines still must have existed on receptors.

The present results confirmed our previous observations (Mattila *et al.*, 1977; Seppälä *et al.*, 1980) that tolerance did not develop similarly to various psychomotor functions. In those experiments diazepam 10 mg given to healthy subjects on two consecutive days impaired coordination and attention on Day 2 less than on Day 1 whilst the impairment of flicker fusion was even enhanced on Day 2. In another human trial Liljequist & Mattila (1979) showed that in a cross-over acute study at 1 week intervals a sequence effect appeared, indicating an adaptation of the subjects to the test situation or/and to the benzodiazepines (temazepam, nitrazepam) used. This sequence effect was highly significant on reactive and coordinative skills but not on flicker fusion. Such an apparent sequence effect was not seen in the present experiments when the results on Day 1 were analyzed. This difference might result from a longer wash-out period between treatments as well as from differences in experimental set-up. One may expect that tolerance develops to multisynaptic complex functions more easily than to simpler functions, but the role of different types of benzodiazepine receptors as a cause of varying tolerance cannot be excluded.

In the present study a significant cross-tolerance, though no actual tolerance developed to benzodiazepines on the flicker fusion test. The opposite result was found with lorazepam when reaction errors were measured. Even though a cumulative effect of lorazepam can explain the situation on flicker fusion, it does not explain the results obtained with the same plasma concentrations of lorazepam 10 min earlier on reactive skills. We believe that the difference lies mainly in the test procedures. It is possible that different types of benzodiazepine receptors (e.g. cerebral *vs* retinal receptors; Young & Kuhar, 1980) in varying combinations are involved in various psychomotor tests. We found recently that caffeine 250 mg counteracted the calming effect, muscle relaxation, and impairment of digit symbol substitution after diazepam 10 mg more clearly than the diazepam effect on flicker fusion (Mattila *et al.*, 1982). File *et al.* (1982) found that caffeine counteracted the anxiolytic effect of lorazepam as well as lorazepam-induced impairment of mental skills while flicker fusion was not affected by either agent. These discrepancies on flicker fusion await further analysis.

In conclusion, tolerance developing to benzodiazepine actions is to some extent task-related, which can result from effects on different receptors. The current doses used may not necessarily be equipotent and this probably modifies the results. However, an easy statement about cross-tolerance between benzodiazepines should be defined more accurately and taken with reservation.

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