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DOES TOLERANCE TO LORAZEPAM DEVELOP WITH ONCE WEEKLY DOSING?

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1 The effect of once weekly administration of lorazepam (2.5 mg) to benzodiazepine-naive student volunteers was assessed in a number of performance tests and on self-ratings.

2 Tolerance developed to the effects of lorazepam on finger-tapping and on self-ratings of dizziness. No tolerance was observed to the drug-induced impairment in a nonsense-syllable paired associate learning test or to the effects on self-ratings of sedation or on heart rate. It is suggested that the reduced impairment in the digit-symbol substitution test observed in weeks 2 and 3 of lorazepam treatment was due to a 'masked' practice effect rather than to tolerance.

3 Test-retest correlation coefficients were calculated for all the tests used. The effect of lorazepam in each test was also correlated with its effect in the other tests. There were significant correlations in performance on placebo in the finger-tapping ($r = 0.66$), digit-symbol substitution ($r = 0.94$), symbol copying ($r = 0.96$) and nonsense-syllable learning ($r = 0.74$) tests.

4 It is suggested that benzodiazepine experience should be given to drug-naive subjects before they are used in cross-over experiments that involve this class of compound, since the major change in impairment occurred between the first and second exposure to lorazepam.

Keywords lorazepam tolerance psychomotor testing

Introduction

There are numerous studies demonstrating that psychomotor impairments result from a single dose of a benzodiazepine (Kleinknecht & Donaldson, 1975; Wittenborn, 1979; Hindmarch, 1980). With repeated daily dosing, tolerance develops to these impairments (Aranko *et al.*, 1983). The present experiment was designed to investigate whether tolerance could develop to lorazepam-induced impairments in a number of performance tests following once weekly dosing. Lorazepam was chosen as the benzodiazepine since it has a relatively short elimination half-life, has no active metabolites and its pharmacokinetics are not changed by repeated administration (Ameer & Greenblatt, 1981). Dispositional tolerance could not therefore account for any observed reductions in impairment following once weekly administration.

A considerable variability has been observed in subjects' responses to a benzodiazepine (Bond & Lader, 1983; Cochrane *et al.*, 1983). It is not clear, however, whether a subject who responds strongly to one action of the drug (e.g. the sedative effect) will also be a strong responder to another of the drug's actions (e.g. the amnesic effect). Of further interest is the stability of an individual's response. Will a subject who responds weakly to the sedative action of a benzodiazepine on one occasion be a strong responder on a subsequent occasion? The present study also aimed to investigate these questions.

Methods

Subjects

The subjects were 17 students (11 females and six males, mean age 22 years) from the School of Pharmacy who were medically fit. No subject had previously had experience of a benzodiazepine. The subjects were divided into two groups. Group 1 (six females, three males) received placebo on three consecutive Mondays and on the fourth Monday received 2.5 mg lorazepam. Group 2 received placebo on the first Monday of the experiment and lorazepam (2.5 mg) on the following three Mondays. Subjects abstained from alcoholic beverages on the Sunday and Monday of each experimental week.

Lorazepam (Ativan, Wyeth) and matching placebo

tablets were administered orally by the same person who did not know which were active and which were placebo and who took no further part in the experiment. The experiment was double-blind in that neither experimenters nor subjects were told of the subjects' drug treatment, and they were not aware of the aim or the design of the experiment.

Practice

The week before the start of the experiment subjects were practised in the tests. The digit-symbol substitution and symbol copying tests were administered three times at 2 h intervals. The finger-tapping test was also performed three times. Subjects were not practised in the nonsense-syllable learning test but they were experienced in other learning tests.

Procedure

On each day subjects received their tablets at 11.30 h and were given a standard lunch at 12.30 h. If subjects normally drank a caffeine-containing beverage at lunchtime they were given a cup of coffee to prevent the possibility of caffeine withdrawal. Subjects were allowed no further caffeine-containing beverages until after the end of each test day since caffeine is known to interact with lorazepam in some tests of performance (File *et al.*, 1982; Mattila *et al.*, 1982). Testing started at 14.30 h and lasted approximately 2 h.

Finger-tapping

Subjects were asked to tap on a key as many times as they could in 15 s with their writing hand. The number of finger-taps made was counted by an electronic counter. The procedure was repeated until at least two scores were obtained that did not differ by more than 5. The mean of these scores was taken as the subject's finger tapping rate.

Digit-symbol substitution

Subjects were given 90 s to perform a digit-symbol substitution task taken from the manual of the Wechsler Adult Intelligence Scale (Wechsler, 1955). The number of digits correctly substituted was scored.

Symbol copying

Subjects were given a sheet of symbols taken from the digit symbol substitution test. Below each symbol was a box and subjects were asked to copy as many symbols as possible in 90 s. The number of symbols correctly copied was scored.

Pulse

The pulse of each subject was taken.

Nonsense-syllable learning

Subjects were shown 10 consonant-vowel-consonant (CVC) nonsense-syllables, each preceded by a number from 0 to 9 (no number being used twice). The number-CVC pairs were shown in numerical order for 2 s each, one pair at a time. After the end of presentation the subjects were given an answer sheet with the numbers written in a random order and allowed 1 min to recall the nonsense-syllables. This procedure was repeated for a further 5 trials. The nonsense-syllables used were different each week and were balanced for scaled meaningfulness (Noble, 1961). The number of nonsense-syllables correctly recalled in each trial was scored. The number of trials needed to recall 8/10 of the syllables was also calculated (not all subjects attained a 10/10 within the six trials when they had received lorazepam).

Self rating scales

Subjects were given a mood-rating scale of 16 items (Bond & Lader, 1974). For each item the subject had to mark the point along a 100 mm line that represented how he felt at the time of testing. Using the same method subjects were asked to give a rating of 15 bodily symptoms (anxiety, sweating, trembling, palpitations, nausea, loss of appetite, restlessness, dryness of mouth, muscular tension, irritability, physical tiredness, headache, dizziness, indigestion, hiccoughs) that have been noted in patients taking benzodiazepines.

Statistics

Data were analysed using analysis of variance. Two ANOVAS were performed on the data from each test. One compared the effect of three once weekly treatments with placebo, with three once weekly treatments of lorazepam. Lorazepam was the independent factor and the weeks of treatment provided the related measure. In this first ANOVA:
(i) a lorazepam effect would indicate that the performance of the lorazepam-treated group was different from that of the placebo-treated group;
(ii) a 'weeks' effect would indicate that both the lorazepam and the placebo-treated groups' performance changed over the duration of the experiment. Thus a practice effect in which the overall level of performance improved from week to week would give rise to a 'weeks' effect;
(iii) a lorazepam × weeks interaction would indicate that the performance of one group changed from week to week in a manner significantly different from

the other group, e.g. lorazepam-treated subjects might perform worse than controls the first time the drug was given, and might improve from week to week if tolerance developed to the drug's effect. If the placebo-treated subjects performed equally well each week then a lorazepam × weeks interaction would be observed, reflecting the development of tolerance.

A second ANOVA was performed on the data from the first and fourth weeks of the experiment in order to gain a second measure of tolerance. In this second ANOVA tolerance would be shown by a significant lorazepam × group interaction (i.e. lorazepam affecting Group 1 subjects more than those in Group 2).

Correlations

For each subject the drug effect in each task was taken as his placebo score minus his drug treatment score. The effect of lorazepam in each test was correlated with its effect in the other tests by calculating Spearman rank correlation coefficients. The week to week variation in performance was also calculated for each test using this method.

Results

Finger-tapping

The criterion was reached in two or three trials. Lorazepam caused a reduction in finger-tapping the first time that it was administered, but tolerance developed to this on subsequent administrations (see Figure 1). This produced a significant lorazepam × weeks interaction ($F(2,28) = 10.7$, $P < 0.001$) in the first ANOVA. There was no practice effect observed in Group 1 subjects. This interpretation was confirmed in the results from the second ANOVA in which there was a significant lorazepam × group interaction ($F(1,14) = 9.1$, $P < 0.01$), lorazepam impairing the performance of the Group 1 subjects (who had not had the drug before) and leaving the performance of the Group 2 subjects (who were familiar with the drug) unaltered. Analysis of subjects' performance in the first trial only produced an identical pattern of results.

Digit-symbol substitution

The performance of subjects in week 1 did not differ from their performance in the final two trials of the practice session.

In this test there was also a significant lorazepam × weeks interaction ($F(2,28) = 6.2$, $P < 0.01$) in the first ANOVA; the impairment caused by lorazepam being less marked the second and third time that it was administered than it was after its first administration

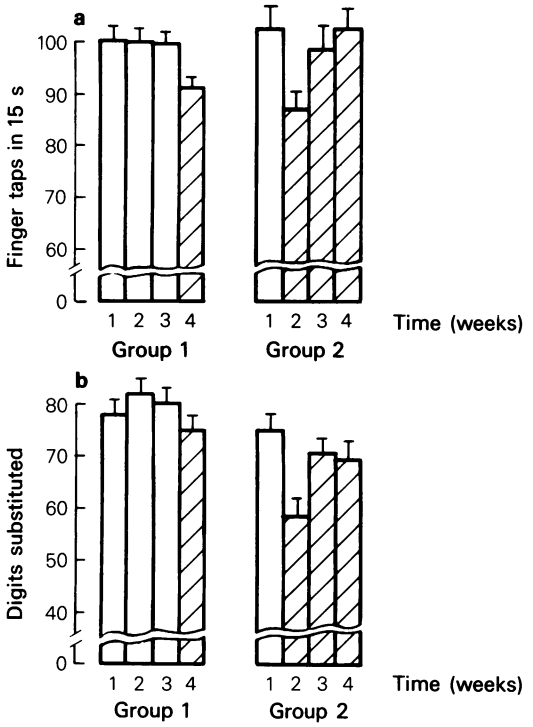

Figure 1 The number of finger-taps made in a 15 s trial (a) and the number of digits substituted in a 90 s trial (b) by subjects in each week of the experiment. Scores are means ± s.e. mean. □ placebo, ▨ lorazepam 2.5 mg.

(see Figure 1). Again the performance of subjects that received placebo was steady, i.e. there was no observable practice effect. Interestingly there was no lorazepam × group interaction in the second ANOVA. There was a significant lorazepam effect ($F(1,14) = 13.3$, $P < 0.01$) indicating that both groups were affected by the drug to an equal extent in spite of the apparent 'tolerance' that had developed in the group 2 subjects. This has important implications concerning the interpretation of a practice effect which are raised in the discussion.

Symbol copying

The overwhelming effect in this test was due to practice improvement over the weeks of the experiment (significant weeks effect ($F(2,28) = 43.5$, $P < 0.0001$). This occurred to an equal extent in both groups, i.e. there was no lorazepam × weeks interaction (see Figure 2).

Pulse

Lorazepam increased the heart rate ($F(1,14) = 28.2$, $P < 0.001$) to an equal extent each week, i.e. there

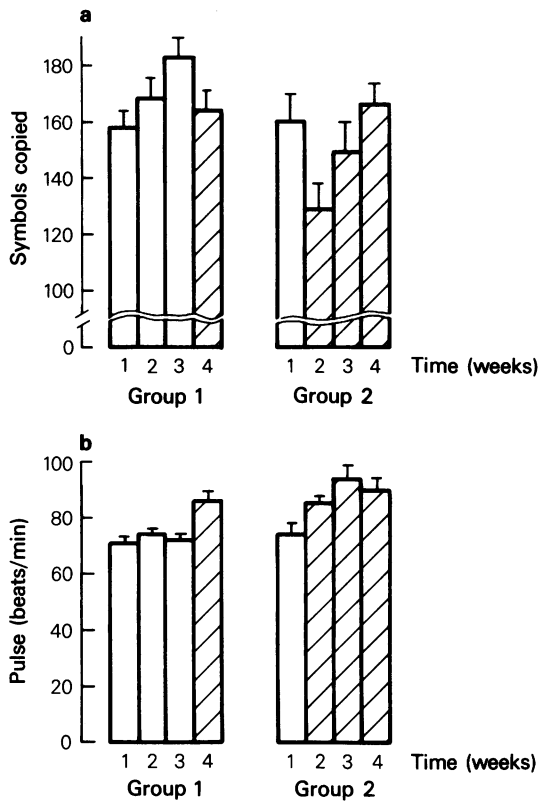

Figure 2 The number of symbols copied in a 90 s trial (a) and the pulse rate in a 60 s period (b) of subjects in each week of the experiment. Scores are means ± s.e. mean. □ placebo, ▨ lorazepam 2.5 mg.

was no lorazepam × weeks interaction in the first ANOVA. The results from the second ANOVA produced an overall lorazepam effect ($F(1,14) = 34.8$, $P < 0.0001$) and no lorazepam × group interaction ($F(1,14) = 0.0$). There was therefore no indication of tolerance developing to the tachycardia caused by lorazepam (see Figure 2).

Nonsense-syllable learning

Lorazepam impaired the recall of the nonsense-syllables irrespective of whether performance in the first two trials was considered ($F(1,14) = 13.5$, $P < 0.01$) or the number of trials needed to reach criterion ($F(1,14) = 8.9$, $P < 0.02$). There was no week, or lorazepam × week effects. In the second ANOVA significant lorazepam effects were observed both in performance in trials 1 and 2 ($F(1,14) = 16.1$, $P < 0.002$) and in the trials needed to reach criterion ($F(1,14) = 25.8$, $P < 0.001$). There were no lorazepam × group interactions in either measure. Thus no tolerance developed to the amnesic action of the drug (see Figure 3).

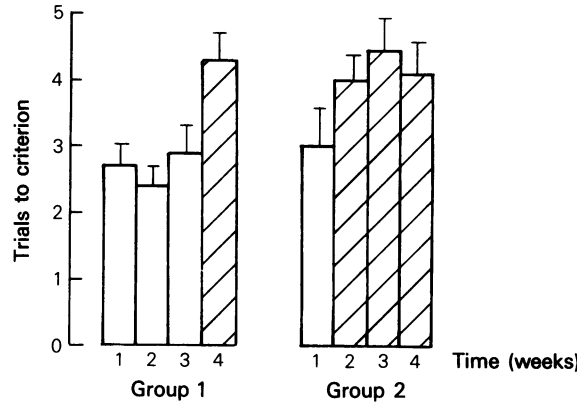

Figure 3 The number of trials required to recall 8/10 nonsense-syllables in a paired-associate learning test by subjects in each week of the experiment. Scores are means ± s.e. mean. □ placebo, ▨ lorazepam 2.5 mg.

Self-rating scales

Group 2 subjects felt significantly more dizzy after receiving lorazepam than after placebo. Tolerance to this effect just reached significance ($F(2,12) = 3.8$, $P = 0.05$). Lorazepam also caused a significant increase in subjects' self-ratings of sedation ($F(1,14) = 22.1$, $P < 0.001$) as measured by factor 1 (Bond & Lader, 1974). No tolerance developed to this effect, i.e. there was no lorazepam × weeks interaction. The second ANOVA confirmed this conclusion, i.e. there was a significant increase in ratings of sedation following lorazepam ($F(1,14) = 57.1$, $P < 0.001$) and there was no lorazepam × group interaction.

Correlations

In all the tests used in this experiment there were good correlations from week to week in the level of subjects' performance. Table 1 illustrates this, correlating performance in weeks 2 and 3 for each group of subjects. There are good correlations in the placebo treated subjects in all of the tests used, demonstrating the reliability of the various measures employed. These tests are therefore suitable for use in experiments taking place over several weeks. Table 1 also shows the week to week correlation in the *response* to lorazepam (i.e. the placebo minus drug treatment scores) in the various measures. In the measures in which lorazepam produced consistent effects (the digit-symbol substitution, nonsense-syllable learning, pulse, dizziness) the correlation coefficients ranged from 0.41 to 0.92 (see Table 1), but because of the small number contributing to the correlations ($n = 7$) only the highest reached significance. When lorazepam-induced deficits were not consistent (in the finger-tapping and symbol-copying tests) the correlations were not good.

Table 1 Test–retest reliability. Correlations between scores in weeks 2 and 3 of the experiment. Group 1 received placebo each week and Group 2 received lorazepam (2.5 mg). The final column gives the correlation in the responses of the Group 2 subjects to lorazepam in weeks 2 and 3 (i.e. placebo score–lorazepam score)

	Correlation coefficients		
	Group 1 (placebo)	*Group 2 (lorazepam)*	
	Totals	*Totals*	*Drug response*
Finger tapping (FT)	0.66*	0.69	0.28
Digit-symbol substitution (DSS)	0.94**	0.82*	0.53
Symbol copying (SC)	0.96**	0.61	0.01
Nonsense-syllable (NS) learning	0.74*	0.88*	0.68
Pulse	0.59	0.68	0.41
Dizziness	—	0.46	0.92**

* $P < 0.05$, ** $P < 0.01$

The mean correlations (from the last 3 weeks of the experiment) between the responses to lorazepam in the various tests are shown in Table 2. The only correlation that was consistently high was between the impairments in the digit-symbol substitution and the nonsense-syllable paired associate learning tests.

Discussion

The results from the finger tapping test illustrate that a significant degree of tolerance developed to the effect of lorazepam. There was no practice effect in the group that received placebo for 3 weeks, and the group that received lorazepam was only impaired the first time it received the drug. Furthermore, lorazepam caused similar impairments in each group the first time it was administered. It is interesting that although tolerance developed to the impairments caused by lorazepam in this test of sedation, there was no sign of tolerance in subjects' self-ratings of sedation as measured by factor 1.

The impairment observed in the digit-symbol substitution test in the Group 2 subjects on their first exposure to lorazepam was of the same magnitude as that found in previous studies (File & Bond, 1979; File *et al.*, 1982). As in the finger-tapping test, there was a marked reduction in impairment following the second administration of lorazepam, although the performance of subjects on placebo remained at the same steady level they had reached in the final two trials of the practice week. However, when the Group 1 subjects finally received lorazepam, they were not impaired as greatly as the Group 2 subjects had been when they first received the drug. This raises the question of what constitutes a practice effect, and suggests that if subjects become used to performing at a certain level, it is harder to impair their performance. It is unlikely that subjects were performing at ceiling level since we have previously found caffeine to improve the performance of student volunteers that had been practised in this test (File *et al.*, 1982).

Table 2 Correlations between the effects of lorazepam in the tests studied (see Table 1 for abbreviations)

FT	−0.01	0.35	0.21	0.00	0.20
	DSS	0.37	0.68	0.46	−0.04
		SC	0.38	0.13	0.21
			NS	0.48	0.06
				Pulse	0.04
					Dizziness

In the symbol copying test it is not possible to attribute the improvement in performance of lorazepam treated subjects to a development of tolerance since placebo treated subjects also improved from week to week. However, either tolerance must have developed to the drug's effect or lorazepam did not impair the practice effect. We have recently shown that although lorazepam has a severe amnesic action, it does not impair the ability of subjects to learn a new task (Lister & File, submitted for publication).

Elliott *et al.* (1971) found that lorazepam increased heart rate in healthy adults. In the present study there was no indication of tolerance developing to this effect following once weekly dosing. Muzet *et al.* (1982) found that triazolam increased heart rate the first night that it was administered but that the increase was not significant following the third night-time administration. When flurazepam was used the increase in heart-rate was still significantly above baseline after five consecutive nights of treatment.

A subsequent effect that was not attributable to a simple learning effect was observed in a cross-over experiment using student volunteers to compare temazepam with nitrazepam (Liljequist & Mattila,

1979). The present study adds further evidence that caution should be exercised in using drug naive subjects in cross-over experiments. Since the greatest effects were observed between the first and second administrations it is possible that important sequence effects might be overcome by administering a related drug a week or so before the start of experiments using cross-over designs.

There was a good correlation in the week to week ratings of dizziness despite the tolerance that developed to lorazepam's effect on this measure. This suggests that tolerance develops to lorazepam-induced dizziness at a similar rate in all subjects.

Bond & Lader (1983) reported that benzodiazepine-induced impairments in closely related measures correlated well, but that other correlations were sparse. The data from the present experiment add further support to this idea, the only consistently observed correlation being between impairments observed in the digit-symbol substitution and nonsense-syllable paired associate learning tests. These two tests involve very similar cognitive processes. It is of interest that whilst other inter-test correlations were not significant they tended to be positive (see Table 2).

We conclude that tolerance can develop to some of the impairments caused by lorazepam in benzodiazepine-naive subjects following once weekly administration. When tolerance does develop, the greatest effect is seen between the first and second administrations. Such an effect should be taken into consideration in any study involving drug-naive subjects.

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