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DO LORAZEPAM-INDUCED DEFICITS IN LEARNING RESULT FROM IMPAIRED REHEARSAL, REDUCED MOTIVATION OR INCREASED SEDATION?

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1 The effects of 1.0 mg and 2.5 mg lorazepam on learning performance were examined in a double-blind cross-over study using student volunteers.

2 Test conditions were manipulated to prevent rehearsal and to vary the subjects' motivation to perform well. Self-ratings of alertness, motivation to perform well and state anxiety were obtained prior to each test.

3 Performance in arithmetic tasks of varying difficulty was also studied.

4 Lorazepam produced dose-related deficits in verbal and nonsense-syllable learning tasks. A greater proportion of errors in the number of problems attempted in the arithmetic tests reflected an impairment in cognitive function. Lorazepam reduced the number of arithmetic problems that were correctly solved as well as increasing the percentage of errors in the problems attempted.

5 Lorazepam did not significantly decrease motivation to perform well and the lorazepam impairment was found even when the test conditions were manipulated so as to prevent rehearsal. Therefore the learning deficits cannot be explained solely by changes in motivation or impairments in rehearsal.

6 Performance in the learning tasks correlated with ratings of alertness and therefore the deficits observed after administration of lorazepam seem likely to result from the non-specific sedative effect of the drug.

Introduction

Benzodiazepines are known to impair performance in a variety of learning tasks (Brown *et al.*, 1978; File & Bond, 1979; Liljequist *et al.*, 1979) although the reason for this is unclear. The purpose of the present study was to explore some of the factors that might contribute to this impairment. One possibility is that the deficit results from the subjects failing to rehearse or adopting an inefficient rehearsal strategy in the drugged state. If this is so, then the benzodiazepine impairment should not be found under test conditions in which rehearsal is prevented. Rehearsal might be indirectly impaired by a drug-induced reduction in motivation. In order to explore this possibility, motivation was measured before each learning test and the effects of both financial reward and financial penalty on motivation and performance were measured. Thirdly, performance in learning tasks might be impaired as part of the non-specific effects of benzodiazepine-induced sedation. In this case, subjects would be processing and rehearsing material in the same way whether or not they had received a benzodiazepine, but would be doing so more slowly when in the drugged state. They should show a uniform deficit, relative to their various undrugged levels of performance, whether rehearsal was allowed or not and across the different motivational conditions.

Since previous studies have shown that the effect of anxiety on task performance depends on the difficulty of the task (Korchin & Levine, 1957; Harleston, 1962) the effects on performance in a variety of arithmetic tests, graded in difficulty, were also studied.

Lorazepam (1.0 mg and 2.5 mg) was chosen as the benzodiazepine and its effects examined 4 h after administration, since these doses have been shown to have profound actions at this time (File & Bond, 1979).

Methods

Subjects

The subjects were 12 students (8 females and 4 males, mean age 21 years) from the School of Pharmacy who were medically fit. Four females were taking oral contraceptives, but subjects were receiving no other drug treatment at the time of the experiment.

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Medical attention was available at all times during the experimental days. Before the start of the experimental series subjects were given a Taylor Trait-anxiety questionnaire to complete (Taylor, 1953).

The subjects were divided into two groups, each containing four females and two males. The groups were balanced for Trait-anxiety scores and each contained two subjects taking oral contraceptives since benzodiazepine pharmacokinetics are known to be affected by these compounds (Jochemsen *et al.*, 1982). Group A received 1.0 mg lorazepam and Group B 2.5 mg lorazepam. Within each group each subject served as his own control. The experiment took place on the Monday of two successive weeks. Half of each group received the drug and half received placebo tablets on each day. Subjects abstained from alcoholic beverages on the Sunday and Monday of each experimental week. They were allowed their normal intake of caffeine containing beverages until 10.30 h on the test day, but none thereafter until testing was complete, as caffeine interacts with lorazepam in some tests of performance (File *et al.*, 1982).

Drug

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 tablets and who took no further part in the experiment. Group A received 1.0 mg (blue tablets) and Group B 2.5 mg (yellow tablets); subjects were asked to close their eyes when they took the tablets so they could not see the colour. The experiment was double-blind in that neither subjects nor experimenters were aware of the subjects' drug states.

Procedure

Subjects received their tablets at 12.00 h and were then given a standard lunch. Testing started at 16.00 h and lasted about 75 min. The week before the start of the experiment the subjects were practised in all the tests. The order of the learning tasks and of the different test conditions were randomized among subjects and test days. The arithmetic tests were performed after completion of the learning tests.

Verbal learning

In the verbal learning task, four tests were given to each subject on both days. In each test 16 words were shown, one word at a time for 5 s at 1 s intervals. A 2 min period elapsed after presentation of the final word after which subjects were given 90 s to recall the 16 words in any order. The four test conditions differed as follows:

Test A Subjects were informed that they would receive 5p for each word after the tenth that they recalled and a total of 50p if they remembered all 16 words. Subjects were free to rehearse in the 2 min period prior to recall.

Test B Subjects were informed that they would be fined 10p for each word that they failed to recall. Subjects were free to rehearse during the period prior to recall.

Test C No financial incentive was offered for recalling the words. Subjects were free to rehearse during the period prior to recall.

Test D During the presentation of the words subjects were asked to count backwards in threes from a given 3 figure number. After each word had been presented the subject had to write down the number he had reached. Subjects had to continue counting backwards after presentation of the final word until they were asked to recall. This was designed to prevent rehearsal of the verbal material.

Each subject was given an 8-page booklet containing test instructions, analogue rating scales and answer sheets. Page 1 contained details of the first test and 7 analogue rating scales that the subject was required to complete before the first word was presented. Each subject was asked to mark the point along a 120 mm line that corresponded to how he felt at that time. Each line was equally divided into 4 sections labelled 'Not at all', 'Somewhat', 'Moderately so', and 'Very much so'. Five of the ratings were taken from a modified version of the Spielberger State-anxiety questionnaire (Spielberger *et al.*, 1970; Leherissey *et al.*, 1973). A score for each subject's state anxiety was obtained by measuring the distances marked from the no anxiety end of each of the five lines. The 6th item was 'I feel alert' (an index of sedation) and the final measure was that of motivation to do well in the task.

Page 2 was used to recall the words from the first test. Pages 3, 5 and 7 contained details of and analogue ratings for the second, third and fourth tests and pages 4, 6 and 8 were used to recall the words from these tests.

In each test condition the number of words correctly recalled was scored.

Nonsense-syllable learning

Each subject performed two nonsense-syllable learning tests. These were identical to verbal learning tests C and D except CVC (consonant-vowel-consonant) nonsense-syllables replaced the words. A booklet was given to each subject as in the verbal learning tests. The test order was randomised between subjects and test days.

Arithmetic tests

Subjects were required to complete four arithmetic tests. In each test the subjects received a list of 40

three-figure numbers. They were given 5 min to perform one of the following operations on as many of these numbers as possible:

(i) multiply by 3 and divide by 2 with written calculation allowed
(ii) multiply by 7 and divide by 11 with written calculation allowed
(iii) multiply by 3 and divide by 2 mentally
(iv) multiply by 7 and divide by 11 mentally.

The test order was randomised between subjects and test days and the number of correct answers on each sheet was scored. The proportion of problems attempted that were correct was also noted.

Statistics

Data were analysed by 2 way split plot analyses of variance with the dose of lorazepam as the independent factor. For the learning tasks the test conditions provided the related factor and for the arithmetic tasks the task difficulty was the related factor. Comparisons between individual groups were made using Dunnett's test.

Results

Half the subjects were tested first with the drug and the other half received placebo first; the drug effects on performance and self-ratings were not significantly affected by the test order. In none of the performance tests or self-ratings did a difference in the placebo scores of groups A and B reach significance.

Verbal learning

Self-ratings Lorazepam significantly reduced subjects' ratings of alertness in all the tests ($F(1,10) = 18.16$, $P < 0.005$). There were no significant effects in subjects' self-ratings of anxiety. Both the penalty and reward incentives increased subjects' ratings of motivation to perform well ($P < 0.05$), and this effect was independent of drug condition, i.e. there was no lorazepam × incentive interaction. Lorazepam did not significantly alter subjects' ratings of motivation to perform well ($F(1,10) = 2.48$, $P < 0.1$) (Table 1).

Performance There was a significant overall lorazepam effect ($F(1,10) = 87.5$, $P < 0.0001$) and a significant lorazepam × dose interaction ($F(1,10) = 19.20$, $P < 0.005$), the low dose causing a slight and the higher dose a considerable impairment. This impairment was independent of the test condition, i.e. there was no lorazepam × dose × test condition interaction ($F(3,30) = 0.5$). Preventing rehearsal also significantly impaired performance ($P < 0.01$) and this effect was independent of drug condition and dose, i.e. there was no lorazepam × test condition interaction (Table 1).

Table 1 Self-ratings and performance in the verbal learning tests when rehearsal is allowed (with three incentive conditions) and when rehearsal is prevented, for subjects tested both after placebo and after either 1.0 mg or 2.5 mg lorazepam (Scores are means ± s.e. mean).

	Rehearsal allowed			*Rehearsal prevented*
	No incentive	*Penalty*	*Reward*	
Group A				
Placebo				
Motivation	88 ± 9	105 ± 5	102 ± 5	90 ± 6
Alertness	92 ± 8	90 ± 10	87 ± 10	92 ± 9
Performance	10.0 ± 1.3	10.8 ± 1.5	10.8 ± 1.0	4.0 ± 0.8
Lorazepam 1.0 mg				
Motivation	73 ± 13	99 ± 11	99 ± 4	80 ± 10
Alertness	52 ± 9	61 ± 11	62 ± 9	56 ± 10
Performance	7.7 ± 1.3	9.2 ± 1.5	9.2 ± 0.9	3.3 ± 0.7
Group B				
Placebo				
Motivation	70 ± 11	83 ± 8	80 ± 8	73 ± 10
Alertness	62 ± 8	65 ± 7	64 ± 7	61 ± 7
Performance	9.2 ± 0.7	8.3 ± 1.0	9.7 ± 0.7	4.3 ± 0.8
Lorazepam 2.5 mg				
Motivation	52 ± 19	61 ± 18	70 ± 16	65 ± 15
Alertness	33 ± 14	32 ± 15	32 ± 14	37 ± 15
Performance	4.8 ± 1.3	3.7 ± 0.4	4.0 ± 0.5	1.5 ± 0.2

Nonsense-syllable learning

Self-ratings Lorazepam significantly decreased subjects' ratings of alertness ($F(1,10) = 15.29$, $P < 0.005$). Neither the drug treatment nor the test conditions significantly affected subjects' ratings of anxiety or motivation to perform well.

Performance

Prevention of rehearsal significantly reduced the number of nonsense-syllables recalled ($F(1,10) = 13.85$, $P < 0.005$) and this effect was independent of drug treatment, i.e. there was no lorazepam × test condition interaction ($F(1,10) = 1.36$). Lorazepam significantly reduced nonsense-syllable learning ($F(1,10) = 6.04$, $P < 0.05$) due to the effects of the 2.5 mg dose (Table 2).

Arithmetic tests

Lorazepam significantly reduced the number ($F(1,10) = 51.7$, $P < 0.0001$) and the proportion ($F(1,10) = 16.3$, $P < 0.005$) of correct answers. There was a significant lorazepam × dose interaction, the higher dose reducing both the number ($F(1,10) = 35.3$, $P < 0.0005$) and proportion ($F(1,10) = 6.39$, $P < 0.05$) of correct answers to a greater extent than the lower dose. As expected, as the difficulty of the task increased, both the number ($F(3,30) = 67.6$, $P < 0.0001$) and proportion ($F(3,30) = 22.0$, $P < 0.0001$) of correct answers was reduced. There was no drug × test difficulty interaction (Table 3).

Table 2 Self-ratings and performance in the nonsense-syllable learning tests when rehearsal is allowed or prevented for subjects tested both after placebo and after either 1.0 mg or 2.5 mg lorazepam (Scores are means ± s.e. mean).

	Rehearsal allowed	*Rehearsal prevented*
Group A		
Placebo		
Alertness	90 ± 9	82 ± 12
Performance	5.7 ± 0.8	2.8 ± 0.7
Lorazepam 1.0 mg		
Alertness	60 ± 12	62 ± 11
Performance	5.3 ± 1.2	2.8 ± 0.9
Group B		
Placebo		
Alertness	59 ± 8	67 ± 9
Performance	5.3 ± 0.9	2.5 ± 0.5
Lorazepam 2.5 mg		
Alertness	31 ± 14	33 ± 13
Performance	2.8 ± 0.6	1.0 ± 0.3

Discussion

The lorazepam impairments observed in the verbal learning tests in both 1 mg and 2.5 mg groups confirms the results of previous work (File & Bond, 1979). On the basis of other experiments it seems unlikely that these deficits are due solely to a drug-induced impairment of retrieval (Brown *et al.*, 1979; Lister & File, 1982).

Table 3 Performance in the arithmetic tests in which subjects were asked to multiply a series of numbers by 3/2 or 7/11 either with written calculation allowed (W) or prevented (NW). Subjects were tested both after placebo and after either 1.0 mg or 2.5 mg lorazepam. (Scores are means ± s.e. mean).

Number correct

	Group A		*Group B*	
	Placebo	*Lorazepam 1.0 mg*	*Placebo*	*Lorazepam 2.5 mg*
× 3/2 W	17.8 ± 0.8	16.7 ± 1.4	16.5 ± 3.4	8.0 ± 2.1
× 7/11 W	8.8 ± 1.6	7.7 ± 1.4	8.2 ± 1.9	4.5 ± 1.4
× 3/2 NW	6.3 ± 1.2	6.8 ± 1.4	8.8 ± 1.4	4.2 ± 1.9
× 7/11 NW	2.8 ± 0.8	2.8 ± 0.6	2.7 ± 0.7	0.8 ± 0.5

Percentage of problems attempted that were correct

	Group A		*Group B*	
	Placebo	*Lorazepam 1.0 mg*	*Placebo*	*Lorazepam 2.5 mg*
× 3/2 W	94 ± 2	92 ± 3	83 ± 8	71 ± 11
× 7/11 W	81 ± 9	78 ± 5	79 ± 8	69 ± 12
× 3/2 NW	73 ± 10	67 ± 10	81 ± 5	54 ± 14
× 7/11 NW	66 ± 17	59 ± 12	50 ± 12	21 ± 10

In both the verbal and nonsense-syllable learning tasks prevention of rehearsal significantly impaired performance. This was found to an equal extent whether the subjects were drugged or not (e.g. in the verbal learning test preventing rehearsal reduced Group B subjects scores by 54% when tested after placebo and by 56% after lorazepam). It can therefore be concluded that the lorazepam impairments are not due solely to interference with the rehearsal process.

Although both the financial incentives increased subjects' motivation to do well there were no significant effects on performance. Lorazepam did not significantly reduce the subjects' motivation to do well and lorazepam treated subjects responded to both incentives with increases in their ratings of motivation. In Test A (in which a financial reward was offered), lorazepam treated subjects performed worse than they did on placebo in Test C (in which no incentive was offered). In contrast the ratings of motivation in Test A were higher in the group receiving the 1 mg dose of lorazepam (and the same in the high dose group) than the motivation ratings when the subjects were on placebo. It can therefore be concluded that the lorazepam impairments cannot be attributed to a drug induced drop in motivation.

Both doses of lorazepam significantly decreased self-ratings of alertness. Spearman rank correlation coefficients between performance scores and the ratings of alertness were calculated for each test. In the verbal learning tests there were significant correlations between performance and alertness in all three tests in which rehearsal was allowed ($P < 0.01$), the more alert the subject the better his performance. The correlation was not significant in the test where rehearsal was prevented ($r = 0.17$). In the nonsense-syllable learning tests, the correlation was significant irrespective of whether rehearsal was allowed or not ($P < 0.01$). It therefore appears that the lorazepam deficits in learning are closely related to self-ratings of the sedative action of the drug. Deficits in performance in learning tasks have been found to parallel ratings of sedation after administration of other CNS depressants (Hart *et al.*, 1976).

The reduction in the number of correct answers in the arithmetic tests after subjects had received lorazepam is not surprising in view of the previously reported effects of this drug on performance in tests of speed (File & Bond, 1979). Of greater interest is the observed fall in the proportion of attempted questions that were correctly completed and this reflects a clear impairment of cognitive function.

The results of this experiment suggest that learning impairments observed after the acute administration of 1 mg and 2.5 mg of lorazepam result from the non-specific sedative effect of the drug. The impairments do not result from a drop in motivation to perform well or from interference with rehearsal. Whether these impairments remain after chronic treatment, when tolerance develops to the sedative effects of the benzodiazepines (Greenblatt & Shader, 1978) is worthy of further investigation.

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