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Time course of the effects of diazepam and lorazepam on perceptual priming and explicit memory [1]

François Legrand[a], Pierre Vidailhet[a], Jean-Marie Danion[a], Danielle Grangé[a], Anne Giersch[b], Martial Van Der Linden[c], Jean-Louis Imbs[d]

[a]*INSERM Unité 405, Département de Psychiatrie, Hôpitaux Universitaires, Strasbourg Cedex, F-67091, France*

[b]*CNUSC, 950 rue de Saint Priest, Montpellier Cedex 4, F-34184, France*

[c]*Faculté de Psychologie, Université de Liège, Service de Neuropsychologie, B. 18 Sart Tilman, Allée du 6 Août, Liège, B-4000, Belgium*

[d]*Faculté de Médecine, Institut de Pharmacologie, Unité de Pharmacologie Clinique, 11 rue Humann, Strasbourg, F-67000, France*

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ABSTRACT

The effects of diazepam and lorazepam on explicit memory and perceptual priming were studied 50, 130 and 300 min after drug administration. Sixty healthy volunteers were randomly assigned to one of five parallel groups (placebo, diazepam 0.2 or 0.3 mg/kg, lorazepam 0.026 or 0.038 mg/kg). The corresponding doses of benzodiazepines exerted a similar negative effect on explicit performance. Lorazepam markedly impaired priming performance, whereas the effect of diazepam was intermediate between that of placebo and that of lorazepam 0.038 mg/kg. The impairment was maximal at the theoretical peak plasma concentration. Contamination by explicit memory could account for the decrease in priming performance observed in the diazepam groups.

Introduction

The vast majority of studies concerning the amnestic effects of benzodiazepines have used recognition and free-recall tasks. These tasks, in which subjects are explicitly asked to remember previously presented information, assess explicit memory. Recently, attention has focused on the effect of benzodiazepines on perceptual priming, the most extensively investigated type of implicit memory. Perceptual priming is involved in tasks such as picture completion or word completion, during which exposure to a stimulus facilitates its subsequent perceptual identification when degraded cues are provided (Tulving and Schacter 1990). It has been repeatedly shown that lorazepam impairs priming (Brown et al. 1989; Knopman 1991; Danion et al. 1992; Sellai et al. 1992; Curran and Gorenstein 1993; Vidailhet et al. 1994). The data concerning diazepam are more contradictory. Some studies have shown that diazepam spared priming (Fang et al. 1987; Danion et al. 1989, 1990), while two others have recently reported a deleterious effect (Sellai et al. 1992; Vidailhet et al. 1994). One of them (Vidailhet et al. 1994) differed from previous ones in that the effect of diazepam was assessed 2 h after drug intake instead of 1 h, at the peak plasma concentration. Two different hypotheses could explain this discrepancy:

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contamination of implicit tasks by explicit memory, or the need for a period of at least 2 h between drug[2] intake and tasks to demonstrate a deleterious effect of diazepam. In order to discriminate between these two hypotheses, we explored the effects of diazepam on explicit memory and perceptual priming 50, 130 and 300 min after drug intake and compared them to those of lorazepam.

Materials and methods

SUBJECTS

Sixty healthy volunteers of both sexes, 20-30 years of age (mean 23 years), weighing 44-93 kg (mean 68 kg) were recruited from the University of Strasbourg. They had no medical illness or history of alcoholism, drug abuse or tobacco consumption of more than ten cigarettes/day. They were not chronic users of benzodiazepines and had not taken any concomitant medication for at least 21 days. The subjects were instructed to abstain from beverages containing caffeine or alcohol for the 24 h prior to the study. Informed written consent was obtained from all volunteers before they entered the study, which was approved by the Faculty Ethics Committee.

EXPERIMENTAL DESIGN AND DRUGS

Subjects were randomly assigned to one of five parallel groups, each of 12 subjects: a placebo group, a diazepam 0.2 mg/kg group, a diazepam 0.3 mg/kg group, a lorazepam 0.026 mg/kg group and a lorazepam 0.038 mg/kg group. The drug tablet was given orally following a double-blind procedure.

TASKS

Perceptual priming was assessed using a picture-completion task and a word-fragment completion task. In the picture-completion task, eight sets of 15 pictures of common objects were used (Snodgrass and Corwin 1988). A series of fragmented images was obtained with eight levels of fragmentation for each picture. Level 1 corresponded to the most fragmented picture and level 8 to the complete picture (Snodgrass et al. 1987). The eight sets of 15 pictures were paired to form four supersets. The pictures were presented on a computer screen. During the study-phase, subjects were shown a list of 19 pictures: the 15 target pictures of a set, with two buffer pictures each at the beginning and end of the list to control primacy and recency effects. Pictures were shown complete, one at time, for 10 s each. Subjects were asked to name each picture aloud and to remember it. In the test-phase, subjects were shown 30 pictures, comprising 15 study pictures or "old" pictures, randomly mixed with 15 non-study pictures or "new" pictures of the paired set. Pictures were shown one at a time, using the ascending method of limits: each picture was shown at level 1, and subjects were asked to identify the fragmented picture within 5 s, taking as many guesses as they liked; if they failed, the next level of fragmentation was shown in the same way until the picture was identified. The perceptual identification threshold (IT) was the level of fragmentation at which the picture was identified. Absolute savings was calculated by subtracting the mean IT of the old pictures from that of the new pictures. Relative savings, which was taken as the primary measure of priming performance, was calculated by dividing absolute savings by the mean IT of the new pictures. In each group, the order of presentation of supersets was counterbalanced between subjects, and pictures of paired sets were presented the same number of times as "old" and as "new".

In the word-fragment completion task, a pool of 160 words, five letters in length, was used. The words

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were nouns, without accent, with frequencies less than 30 occurrences per million. Two letters were[3] deleted at random in order to obtain a three-letter word fragment with a single solution. The pool of target words was then randomly divided into eight sets of 20 words which were paired to form four supersets of 40 words. The words and the word fragments were presented in a booklet. At study, subjects were shown a list of 26 words: the 20 target words of a set, with three buffer words at the beginning and at the end of the list. Words were presented one at a time for 5 s each and subjects were asked to *read them* aloud and to remember them. At test, subjects were shown 40 word fragments, including 20 word fragments corresponding to the set of 20 words presented in the study-phase ("old" words), randomly mixed with 20 word fragments corresponding to a set of non-study words ("new" words). Word fragments were shown one at a time for 10 s each and subjects were asked to complete them by a noun. Priming was assessed by subtracting the number of "new" word fragments successfully completed from that of "old" word fragments successfully completed. In each group, the order of presentation of supersets was counterbalanced, words of paired sets being presented the same number of times as "old" and as "new".

Subjects performed a symbol cancellation task between each study and test-phase of the priming tasks. Explicit memory was assessed with a free-recall task, which followed the priming tasks; subjects were asked to write down, in 3 min, as many of the pictures, and subsequently as many of the words, as they could remember from each last study list. Sedation was repeatedly assessed using visual analogue scales.

Memory tasks were administered 60 min before, and 50, 130 and 300 min after drug ingestion.

STATISTICAL ANALYSIS

Results were analysed using multivariate analyses of variance with repeated measures (MANOVAs), with the drug as a between-subjects factor and performance at 50, 130 and 300 min as a repeated factor. Whenever these analyses were significant, /-tests were used, comparing groups at each time. The *P* values were corrected according to the Bonferroni probabilities.

Results

At baseline, explicit and implicit memory performance did not vary significantly across groups (data not shown).

FREE RECALL TASKS

Lorazepam and diazepam induced an impairment of free recall of pictures (Fig. 1a), the extent of which was similar at corresponding doses and most marked at the highest dose. The deficit was maximal 50 min after ingestion of diazepam and 130 min after ingestion of lorazepam. Performance tended to return to control values at 300 min. A MANOVA carried out on the number of pictures recalled confirmed this analysis. There was a significant group [F (4, 55) = 14.44, $P < 0.0001$] and time effect [F (2, 54) = 33.22, $P < 0.0001$] and a significant interaction between groups and time [F (8, 108) = 2.15, $P < 0.05$]. Follow-up analyses showed that free recall of pictures was significantly decreased by drugs at 50 and 130 min. It remained significantly impaired at 300 min in the two high dose benzodiazepine groups. A similar pattern of performance was observed in free recall of words (data not shown).

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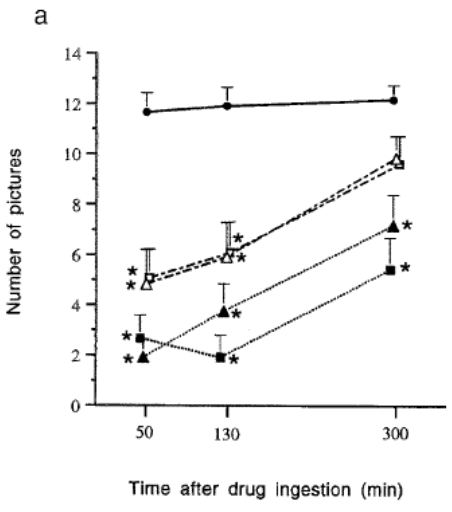
PICTURE- AND WORD-FRAGMENT COMPLETION TASKS

In the picture-completion task, lorazepam increased the IT of new pictures at each time by a mean amount of 0.8 level; this indicates that the drug impaired the basal ability to identify fragmented pictures. The IT of old pictures were also higher at each time. Lorazepam profoundly impaired relative savings (Fig. 1b). The decrease in performance was most pronounced with the highest dose of the drug. It was maximal at 130 min, where there was virtually no savings. The profile of results in the diazepam groups was roughly similar to that in the lorazepam groups, but performance was intermediate between those in the lorazepam 0.038 mg/kg and placebo groups. The maximum effects of diazepam were observed at 50 min, and performance tended to return to control values at 300 min. This interpretation of the results was confirmed by statistical analyses. A MANOVA carried out on IT of new pictures revealed a significant group [F (4, 55) = 5.86, $P < 0.0005$] and time effect [F (2, 54) = 4.65, $P < 0.02$] and no interaction between groups and time. Compared to the placebo, the decrease in the ability to identify new pictures was significant at 50 min in the lorazepam 0.026 mg/kg group and at each time in the lorazepam 0.038 mg/kg group, but not in the diazepam groups.

Fig. 1a–c Effects of diazepam, lorazepam and placebo on free-recall and picture-completion performance. **a** Number of pictures recalled. **b** Relative savings = difference between the identification thresholds of new and old pictures divided by the identification threshold of new pictures. **c** Identification thresholds of recalled and non-recalled old pictures at 50 min. –●– placebo, – – –△– – – diazepam 0.2 mg/kg, ···▲··· diazepam 0.3 mg/kg, – – –□– – – lorazepam 0.026 mg/kg, ····■···· Lorazepam 0.038 mg/kg. ⊡Recalled old pictures, ▩ non-recalled old pictures. Scores are means ± SEM. * Performance significantly different from that of the placebo group ($P < 0.05$); (t-tests, P values corrected according to the Bonferroni probabilities)



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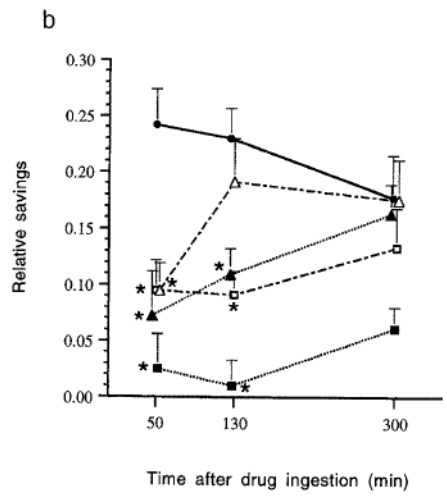

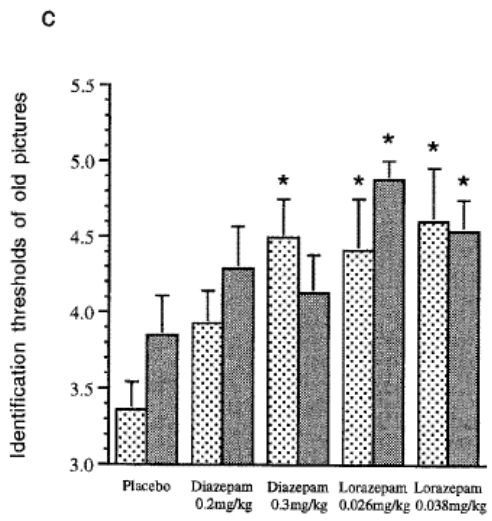

C

A MANOVA carried out on the IT of old pictures revealed a significant group [F (4, 55) - 15.25, $P < 0.0001$] and time effect [F (2, 54) - 13.10, $P < 0.0001$], and a significant interaction between groups and time [F (8, 108) = 5.06, $P < 0.0001$]. A MANOVA carried out on relative savings revealed a significant group effect [F (4, 55) = 10.84, $P < 0.0001$], no time effect and no interaction between groups and time. When compared with the placebo, there was a significant decrease in relative savings in the four benzodiazepine groups at the two early stages (except for the diazepam 0.026 mg/kg group at 130 min); at 300 min, there was no significant difference in savings between the five groups. In order to reveal differences between the corresponding doses of drugs, exploratory analyses were carried out using *t*-tests without Bonferroni correction. There was a statistically significant difference in relative savings at 130 min between the diazepam 0.3 mg/kg group and the lorazepam 0.038 mg/kg group. The difference between the low dose groups was also significant at 130 min. These differences were not significant when a Bonferroni correction was used. At each point in time and in each group, the mean absolute savings was compared to zero using /-tests in order to reveal a significant priming effect. Significant differences were found (all

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Ps < 0.01), other than in the lorazepam 0.038 mg/kg group at 50 and 130 min, indicating that there was[6] no priming effect in this group; the difference was marginally significant in the diazepam 0.3 mg/kg group at 50 min ($P = 0.08$).

The profile of word-completion performance observed in the five groups was strictly similar to the profile of picture-completion performance, with one exception: there was no significant difference in completion of new items (data not shown). The mean difference between the number of old and new words successfully completed, i.e. the priming effect, was compared to zero. A significant difference was only absent in the lorazepam groups at 130 min, indicating that there was no longer any priming effect under the influence of lorazepam but still a priming effect under the influence of diazepam.

An analysis also examined in the picture-completion task the relationship between recall and savings, in order to assess any potential influence of explicit memory on picture-completion performance (Parkin and Russo 1990). Mean IT of recalled and non-recalled old pictures were calculated for each subject. When the five groups were combined, the mean IT of recalled old pictures (for example, 3.33 ± 0.06 before treatment, 3.86 ± 0.10 at 50 min) was significantly lower *(Fs* ≥ 1.28, *Ps* < 0.05) than that of non-recalled old pictures (3.73 ± 0.08 before treatment, 4.63 ± 0.06 at 50 min), suggesting contamination of the implicit task by explicit memory, which had been present since the first administration of the task. Performance at 50 min in the placebo group concerning recalled (3.36 ± 0.19) and non-recalled (3.85 ± 0.26) old pictures strongly suggests that the contamination was not increased by the repetition of the task. To determine whether such contamination can account for the decrease in implicit performance observed in the diazepam groups at 50 min, mean ITs of recalled and non-recalled old pictures at 50 min were calculated for each benzodiazepine group. As shown in Fig. 1c, the mean IT of recalled old pictures was lower than that of non-recalled old pictures in the placebo group and in the low dose benzodiazepine groups. A different pattern of results was found in the high dose benzodiazepine groups, where the mean IT of non-recalled old pictures did not exceed that of pictures that were recalled. There was thus evidence of explicit contamination in the placebo and low dose benzodiazepine groups, but not in the high dose benzodiazepine groups, probably because explicit memory was profoundly impaired in the latter groups. An ANOVA carried out on the IT of recalled old pictures at 50 min revealed a significant drug effect [F (4, 39) = 4.74, $P < 0.005$], due to a significant increase in the IT in the two lorazepam groups and in the diazepam 0.3 mg/kg group, in comparison to the placebo group. When the IT of non-recalled old pictures were considered alone, there was a significant drug effect [F (4, 52) = 3.42, $P < 0.02$], but follow-up analysis indicated that lorazepam (at both doses), but not diazepam, induced a significant impairment, when compared to the placebo. To take account of both explicit contamination and basal ability to identify fragmented pictures, savings was calculated by dividing the difference between the IT of new pictures and of the non-recalled old pictures by the IT of the new pictures; no further significant drug effect was observed at 50 min, whereas the impairment of savings remained significant in the two lorazepam groups at 130 min (data not shown).

VISUAL ANALOGUE SCALES

Subjects experienced a sedative effect in the four active groups. A MANOVA carried out on the analogue selfratings of sedation revealed a significant group effect [F (4, 55) = 3.18, $P < 0.05$], a significant time effect [F (2, 54) = 40.84, $P < 0.0001$] and no interaction between groups and time. Sedation was significantly increased by the highest dose of diazepam at 50 and 130 min (data not shown).

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Analyses of covariance were carried out on picture and word-completion performance using self-ratings[7] of sedation as covariate. The pattern of results remained unchanged (data not shown).

Discussion

The main findings of the study are as follows, i) Lorazepam exhibited a marked deleterious effect on performance in both implicit tasks, virtually no priming being observed at 130 min. ii) The effect of diazepam on that performance was intermediate between that of lorazepam and the placebo: performance was lower as compared to the placebo, but there was still a significant priming effect. iii) The two benzodiazepines exhibited different effects on implicit tasks while the corresponding doses of benzodiazepines showed a similar deleterious effect on explicit memory.

This study confirmed that lorazepam decreases or, at highest doses, suppresses perceptual priming. This deleterious effect was maximal at the theoretical peak plasma concentration (2 h after ingestion). As previously reported (Vidailhet et al. 1994), lorazepam also increased the IT of new pictures in the picture-completion task. The mechanism of this perceptive impairment is unknown. It could not be argued that the influence of lorazepam on priming as assessed by the picture-completion task was artefactual, i.e. simply reflected a reduced ability to identify fragmented pictures, since lorazepam impaired the IT of old pictures more than those of new pictures, as shown by the deleterious effect of the drug on savings. In contrast to lorazepam, diazepam did not suppress priming, even though the magnitude of performance was decreased in the two implicit tasks, being intermediate between that of the lorazepam 0.038 mg/kg group and the placebo group. Diazepam exerted its maximum deleterious effect on implicit performance at its theoretical peak plasma concentration (1 h after ingestion). Performance in diazepam and in lorazepam groups tended to return to control values at 300 min. This time course paralleled that of the effect of these drugs on explicit memory. Therefore, the hypothesis that a deleterious effect of diazepam on implicit memory would occur later than its effect on explicit memory was invalidated. The present results show that the time course of the effect of diazepam on implicit performance cannot explain the previously reported discrepancies concerning the deleterious effect of this drug on priming.

To assess whether an explicit contamination in the placebo group might account for the difference in implicit performance observed between the diazepam and the placebo groups, an additional analysis of the picture-completion performance was carried out separately for recalled and non-recalled old pictures. The pattern of performance, in which IT of recalled old pictures are lower than those of non-recalled old pictures only in the groups where explicit memory is not impaired, strongly suggests explicit contamination. Taken in conjunction with the persistence of a significant priming effect in the diazepam groups and with the absence of statistically significant diazepam-induced impairment of relative savings for non-recalled old pictures, it suggests that the difference in performance between the diazepam and placebo groups might have resulted from an explicit contamination in the placebo group. Future studies will therefore have to take into consideration the part played by the different processes involved in each memory task. Our study clearly shows that the performance measured in a picture-completion task reflects not only implicit memory, but also explicit memory as well as perceptual ability. Moreover, the role of each process may vary from one task or experimental protocol to another and could possibly depend on the drugs used. Briefly stated, implicit and explicit tasks are not process-pure (Jacoby and Kelley 1991).

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