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Lorazepam and diazepam effects on memory acquisition in priming tasks

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Abstract. Unlike diazepam, lorazepam has repeatedly been shown to impair perceptual priming as well as explicit memory. To determine whether this deleterious effect was due to an impairment in acquisition of information, 60 healthy volunteers were randomly assigned to five treatment groups (placebo, lorazepam 0.026 or 0.038 mg/kg, diazepam 0.2 or 0.3 mg/kg) and successively performed perceptual priming tasks and a free-recall task. Priming performance on information learned before or 2 h after drug administration, i.e. at the peak concentration of lorazepam, was assessed under the influence of the drugs, using a picture-fragment and a word-stem completion task. Free-recall performance was altered by both drugs. Lorazepam decreased priming performance when information was acquired after, but not before, drug administration, indicating that the drug alters the acquisition of information. Lorazepam also impaired the ability to identify fragmented pictures, but there was no evidence that this perceptual effect accounts for the priming impairment. Surprisingly, diazepam also decreased priming when information was acquired after drug administration, suggesting that, at least in certain circumstances, the two benzodiazepines may exert similar effects on priming measures.

Key words: Benzodiazepine – Diazepam – Human – Lorazepam – Memory – Perceptual priming

The anterograde amnesia caused by benzodiazepines has been well documented (reviews in Lister 1985, 1991; Taylor and Tinklenberg 1987; Ghoneim and Mewaldt 1990; Curran 1991;). It results from an impairment in the acquisition of new information rather than from defective storage or retrieval. This conclusion has been drawn from studies using the so-called pre-drug/post-drug technique (Clarke et al. 1970; Ghoneim and Mewaldt 1977; Brown et al. 1982; Ghoneim et al. 1984; Lister and File 1984). These studies compare memory performance on material learned before or after drug administration. They show that, when subjects are required to learn items prior to drug administration and then to recall them during the period of drug action, their recall is not impaired relative to that of placebo-treated subjects; this suggests that benzodiazepines do not impair retention or retrieval of information. In contrast, recall of items learned by subjects after drug administration is decreased, suggesting that benzodiazepines impair acquisition. Impairments are observed regardless of whether performance is measured by recall or recognition tasks, i.e. tasks in which subjects are explicitly asked to remember recently presented information (Clarke et al. 1970; Brown et al. 1982). The memory assessed by these tasks has been referred to as explicit memory (Graf and Schacter 1985).

In recent years, there has been a growing interest in tasks which do not make explicit reference to any particular experience. The memory assessed by these tasks has been referred to as implicit memory (Graf and Schacter 1985). The main form of implicit memory is perceptual priming, i.e. facilitation of performance via prior exposure to stimuli in tasks such as picture-fragment or word-stem completion (Tulving and Schacter 1990). In a picture-completion task, subjects are shown at study a series of line drawings of common objects. At test, they are presented with a series of increasingly more complete line drawings, including pictures presented at study (old pictures) and others that were not (new pictures), until they can identify them. Subjects perform better with old pictures than with new pictures. In a word-stem completion task, subjects are shown at study a list of words which includes, for instance, the word DEFENCE; at test, they are required to complete a list of word stems (DEF ...) with instruction to write the first word that comes to mind. Subjects show an enhanced tendency to complete stems by forming a word presented in the study list (DEFENCE rather than DEFECT, for instance).

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It has been repeatedly shown that lorazepam, a benzodiazepine, impairs explicit memory as well as perceptual priming, as assessed by a word-stem completion task (Brown et al. 1989; Knopman 1991; Danion et al. 1992). In contrast, diazepam, another benzodiazepine, impairs explicit memory but spares priming, therefore inducing a dissociation between the two forms of memory (Fang et al. 1987; Danion et al. 1989, 1990). These results, which have been obtained from independent studies of either lorazepam or diazepam, suggest that the two benzodiazepines have differential amnestic effect. However, they have only been partially replicated in a recent study which directly compared the effects of the two benzodiazepines on priming, using a word-stem and a picture-fragment completion task (Sellal et al. 1992). In this study, lorazepam, but not diazepam, decreased word-completion performance. Whereas lorazepam also decreased picture-completion performance, the effect of diazepam depended on whether pictures were presented complete or in fragmented form at study: no deleterious effect was observed in the complete condition, but performance was disrupted in the fragmented condition. Whatever the correct explanation for this complex pattern of results, this study indicates that whereas the two benzodiazepines seem to have differential amnestic effects, diazepam is not entirely devoid of effect on priming. In addition, by highlighting the role played by the conditions under which information is acquired for demonstrating a deleterious effect of benzodiazepines, this study suggests that impairment of priming induced by these drugs, like the impairment of explicit memory, might result from a disturbance in acquisition of information rather than from a disturbance in storage or retrieval.

The aim of the present study was to test the hypothesis that the deleterious effect of lorazepam on priming is due to an impairment in acquisition of information. A pre-drug/post-drug technique was used. The hypothesis predicted that priming would be impaired when material was studied after drug administration; when material was studied before drug administration, priming would be normal. The effects of lorazepam were compared to those of diazepam.

Materials and methods

Subjects

Sixty paid healthy volunteers of both sexes (33 women, 27 men) whose native language was French were recruited from the University of Strasbourg. They ranged in age from 20 to 28 (mean age: 23.1) and ranged in weight from 50 to 95 kg (mean weight: 66.5).

The subjects 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 15 days. They were instructed to abstain from beverages containing caffeine or alcohol for the 24 h prior to the study. All subjects were tested in the morning, after an overnight fast. The protocol was approved by the Faculty Ethics Committee. All the volunteers gave their written informed consent.

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. Thus, for each drug a low and a high amnesia-inducing dose were selected on the basis of an equipotential effect on explicit memory (Dundee et al. 1979; Kothary et al. 1981; Sellal et al. 1992). The drug tablet was given orally following a double-blind procedure. A sample of blood (10 ml) was collected 1 h 45 min after the ingestion of the drug. Drug plasma concentrations were measured at the end of the study following a double-blind procedure. The capillary gas chromatographic-mass spectrometric method and fluorescence polarization immunoassay were used to quantify plasma concentrations of diazepam and lorazepam, respectively (Jolley 1981; Drouet-Coassolo et al. 1989).

Tests

A series of memory and cognition tests were administered to each subject individually. Perceptual priming was assessed by a word-stem completion task and a picture-fragment completion task and explicit memory by a free-recall task. Subjects assessed their subjective state of sedation with visual analogue scales, and performed digit symbol substitution and symbol cancellation tasks. The order of the tests and their respective times of administration are summarized in Table 1.

Perceptual priming. For each of the picture and word-completion tasks, two study-phases were used, a pre-drug (tasks 1) and a post-drug (tasks 2) one. Tasks 1 comprised two test-phases, one before drug administration (pre-drug test-phase), to measure baseline performance, the other after drug administration (post-drug test-phase), to measure performance when material was retrieved under the effect of the drugs. In tasks 2, both the study and test-phases took place after drug administration, making it possible to measure performance when material was acquired and retrieved during the period of drug action. Since the primary aim of the study was to test the hypothesis that lorazepam impairs the acquisition of information, the study-phase of tasks 2 took place 2 h after drug intake, i.e. at the peak concentration of this drug (Greenblatt 1981). Conse-

Table 1. Schedule of testing

0720	Picture-fragment and word-stem completion tasks 1: pre-drug study-phase Visual analogue scales
0750	Picture-fragment and word-stem completion tasks 1: pre-drug test-phase
0815	Ingestion of lorazepam or diazepam or placebo
0920	Digit symbol substitution task Symbol cancellation task Visual analogue scales
0935	Picture-fragment and word-stem completion tasks 1: post-drug test-phase
1000	Sample of blood
1005	Digit symbol substitution task Picture-fragment and word-stem completion tasks 2: post-drug study-phase Symbol cancellation task
1040	Visual analogue scales Picture-fragment and word-stem completion tasks 2: post-drug test-phase
1105	Free-recall task

quently, the effect of diazepam was assessed slightly after its peak concentration, which occurs 1 h after drug intake (Mandelli et al. 1978). For a given subject, the picture and word-completion tasks were always given in the same order at study and at test. This order was counterbalanced within each group, so that throughout the study, in each group, half the subjects performed the word-stem completion task first, the other half the picture-fragment completion task first.

Picture-fragment completion task. Six sets of 15 pictures of common objects (sets A_1, A_2, B_1, B_2, C_1, C_2) were drawn from the eight sets of pictures constructed by Snodgrass and Corwin (1988). For each picture, a series of fragmented images was obtained, using an algorithm which randomly and cumulatively deleted equal blocks from the picture to produce eight levels of fragmentation per stimulus (Snodgrass et al. 1987). Level 1 corresponded to the most fragmented picture and level 8 to the complete picture. The six sets of 15 pictures were paired: A_1 A_2, B_1 B_2, C_1 C_2, to form supersets A, B, C.

In task 1, subjects were shown a list of 34 pictures at study: the 30 target pictures belonging to two different sets (e.g. set A_1 and set B_1) with two buffer pictures at the beginning and at the end of the list to control primacy and recency effects. Pictures were shown complete (level 8), one at a time in a booklet, for 10 s each. Subjects were asked to name each picture aloud. The pre-drug test-phase was given 30 min later. Subjects were shown 30 pictures, including 15 study pictures or old pictures (e.g. set A_1) randomly mixed with 15 non-study pictures or new pictures belonging to the paired set (e.g. set A_2). Pictures were shown one at a time with 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; to prevent any contamination of this implicit task by explicit memory, subjects were informed that some of the fragmented pictures could be completed with pictures from the previously studied list, but they were instructed to indicate what they actually saw. The perceptual identification threshold was the level of fragmentation (levels 1–8) at which the picture was identified. Savings was calculated by subtracting identification thresholds of old pictures from those of new pictures. The post-drug test-phase was given 135 min after the study-phase. It followed exactly the same procedure, except that the 15 old pictures belonged to the other study set (e.g. set B_1) and the 15 new pictures belonged to its paired set (e.g. set B_2).

Task 2 followed the same procedure as task 1, except that subjects were shown only one set at study and there was only one test-phase. At study, subjects were shown a list of 19 pictures: the 15 target pictures (e.g. set C_1) with two buffer pictures at the beginning and at the end of the list. At test, subjects were presented with 30 pictures, including the 15 pictures showed in the study-phase (e.g. set C_1) randomly mixed with the 15 pictures of its paired set (e.g. set C_2).

In each group, the order of presentation of supersets A, B, C, in tasks 1 and 2 was counterbalanced between subjects, and pictures from paired sets were presented the same number of times as old and as new.

Word-stem completion task. A pool of 90 target words, comprising common words, was selected according to the following criteria: the initial three letters – the stem – of each word had to be unique in the whole set of words; for each three-letter target stem, a French pocket dictionary had to list at least ten common words; none of the stems could be completed by the name of a picture showed in the picture-fragment completion task; the target words had to have at least five letters and their frequencies ranged from 1.2 to 98.1 per million according to the Brulex (Content et al. 1990). The pool of target words was then randomly divided into six sets of 15 words (set X_1, X_2, Y_1, Y_2, Z_1, Z_2). The sets were paired: X_1 X_2, Y_1 Y_2, Z_1 Z_2, to form supersets X, Y, Z. At study, subjects were shown a list of words typed in block capitals; each word was presented in a booklet for 5 s and subjects were asked to read it aloud and to remember it. At test, subjects were presented with a completion test form which listed the stems of the words presented in the study-phase (primed words or "old words") randomly mixed with the stems of non-presented words (non-primed words or "new words"). Thus, half the test items measured completion on previously presented words and the other half provided a measure of chance performance. Subjects were instructed to complete the stems with the first word that came to mind, working quickly; they were asked for an alternative completion if proper nouns were given.

The sets of words used in task 1 and in task 2 were manipulated at study and at test exactly in the same way as the sets of pictures in the picture-completion task, except that five buffer words, instead of two pictures, were added at the beginning and at the end of each study list.

Explicit Memory. At the end of the last priming task, subjects were asked to write, in any order, as many of the pictures as they could remember from the post-drug study list. Three minutes were allowed for recall. The same procedure was followed for recall of the words from the post-drug study list.

Digit symbol substitution task (DSST). The DSST, a 90-s recording task from the Wechsler Adult Intelligence Scale-Revised (1981) was administered just before the post-drug test-phase of priming tasks 1 and just before the study-phase of priming tasks 2. Psychomotor, perception and learning factors play significant roles in the DSST performance (Delaney et al. 1981).

Symbol cancellation task. Subjects performed a symbol cancellation task just before the post-drug test-phase of priming tasks 1 and just after the study-phase of priming tasks 2. This task involves a single page filled with rows of eight different symbols. Subjects were instructed to cross out every instance of the three target symbols which were indicated at the top of the page. The total number of symbols processed in 3 min was taken as a measure of sustained attention.

Analogue self-ratings of sedation. Subjects repeatedly used a set of 15 visual analogue scales derived from Bond and Lader (1974) to assess their subjective feelings in the course of the study. Each scale consisted of a 100-mm horizontal line without gradation, anchored by contrasting states of mind. Subjects were asked to regard each line as a continuum and to rate their feelings at that moment by placing a mark perpendicularly across each line. The scales were scored by measuring in mm from the positive end of each line to the subject's mark. Five of these scales assessed complementary aspects of sedation (alert-drowsy, excited-calm, clear headed-muzzy, energic-lethargic, quick-slow); the mean scores of these five scales was calculated for each subject and was taken as a measure of sedation.

Statistical analysis. Picture and word-completion performances were analysed with ANOVAs on repeated measures, with drugs as a between-subject factor, and priming (old versus new items) as a within-subject factor. Performance in the other tasks was analysed with one-way ANOVAs. Whenever the analysis was significant, *t*-tests were used, comparing each active group with the placebo group, and lorazepam groups with diazepam groups. The *P* values were corrected according to the Bonferroni probabilities. Analyses of covariance (ANCOVAs) were carried out on picture and word-completion performance using self-ratings of sedation, DSST performance and symbol cancellation scores as covariates, according to Cochran and Cox (1957).

Results

The five groups did not significantly differ in terms of mean age, mean weight and mean score on the Wechsler Memory Scale, measured during a pre-study session.

The mean serum levels of lorazepam were 10.08 ± 1.19 (SEM) and 13.25 ± 1.15 ng/ml in the lorazepam 0.026 and 0.038 mg/kg groups, respectively. The mean serum levels of diazepam were 0.47 ± 0.07 and 1.08 ± 0.14 µg/ml in the diazepam 0.2 and 0.3 mg/kg groups, respectively.

Picture-fragment completion task

The mean performance in picture-fragment completion tasks 1 and 2 is shown in Fig. 1.

Task 1. An ANOVA carried out on performance measured during the pre-drug test-phase revealed a significant priming effect [F (1, 55) = 302, P <0.0001], no group effect [F (4, 55) = 0.39] and no interaction between priming and groups [F (4, 55) = 0.97]. Follow-up analyses indicated that the identification thresholds of old pictures were significantly lower than those of new pictures, providing evidence of savings, and that the identification thresholds were similar across groups. The picture-completion performance of the five groups did not therefore differ before drug administration.

An ANOVA carried out on performance measured during the post-drug test-phase revealed a significant priming effect [F (1, 55) = 168, P < 0.0001], a significant drug effect [F (4, 55) = 4.64, P < 0.005] and no interaction between priming and drugs [F (4, 55) = 0.37]. Follow-up analyses showed that the drug effect was due to higher identification thresholds of both new and old pictures in the lorazepam groups than in the placebo group; the difference was significant with the highest dose of the drug. However, as indicated by the absence of a significant interaction between priming and drugs, the amount of savings did not differ significantly between the five groups. This suggests that the lorazepam-treated subjects have a globally impaired ability to identify the fragmented pictures; in contrast, savings, i.e. the benefit in performance induced by the previous presentation of pictures, was spared. Performance in the diazepam and in the placebo groups did not differ significantly.

Task 2. An ANOVA carried out on performance in task 2 yielded a significant priming effect [F (1, 55) = 197, P < 0.0001], a significant drug effect [F (4, 55) = 9.32, P < 0.0001] and a significant interaction between priming and drugs [F (4, 55) = 3.19, P = 0.02]. Follow-up analyses indicated that the identification thresholds of new pictures were higher in the lorazepam than in the placebo and diazepam groups, the difference being significant at the highest dose of the drug. The identification thresholds of old pictures were significantly higher in the two lorazepam groups than in the placebo group. The highest dose induced the most pronounced deficit, the identification thresholds of old pictures also being significantly higher than those of the diazepam-treated subjects. In the diazepam groups, there was also an increase in the identification thresholds of old pictures, but not of new ones, the difference compared with the placebo group being significant at the 0.3 mg/kg dose. When expressed as savings, performance was lower in the four active groups than in the placebo group, the deficit being significant at the highest dose of lorazepam and diazepam. Lorazepam induced a slightly more pronounced deficit than diazepam but this was not significant. These results therefore show that lorazepam provoked a dose-dependent decrease in priming in task 2, as well as a dose-dependent decrease in the identification of fragmented pictures, whether or not the pictures were previously presented. Unexpectedly, a dose-dependent decrease in priming was also observed in the diazepam groups, while the identification of fragmented pictures was spared.

To take account of the fact that groups differed in their basal ability to identify fragmented pictures, complementary ANOVAs were carried out on relative savings, rather than absolute savings, as suggested by Snodgrass and Surprenant (1989). Absolute savings is the difference between the identification thresholds of new and old pictures, whereas relative savings is the absolute savings divided by the thresholds of the new pictures. These analysis yielded similar results (data not shown).

An inspection of the results in Fig. 1 suggested that placebo-treated subjects increased their ability to iden-

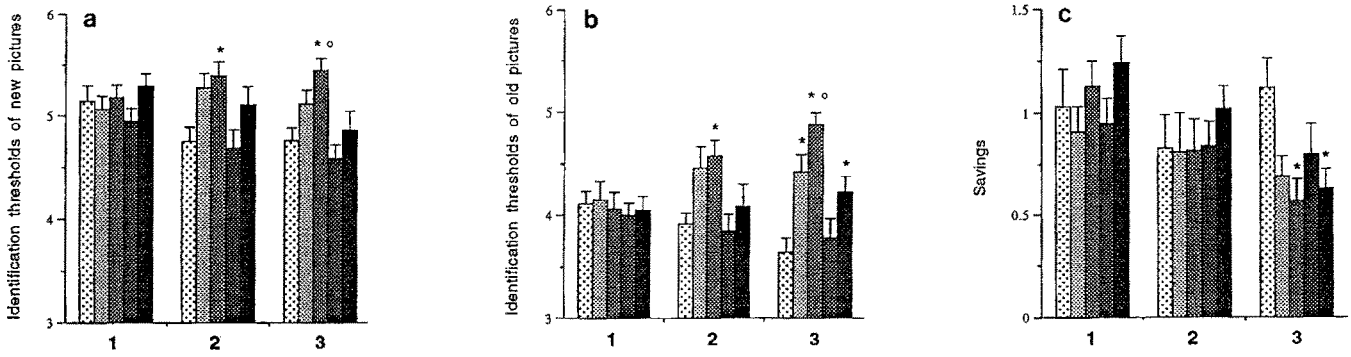

Fig. 1a–c. Picture-completion performance. **a** Identification thresholds of new pictures, **b** identification thresholds of old pictures, **c** savings = difference between the identification thresholds of new and old pictures. Placebo group ▨, lorazepam 0.026 mg/kg group ▨, lorazepam 0.038 mg/kg group ▩ diazepam 0.2 mg/kg group ■ and diazepam 0.3 mg/kg group ■. **1**: baseline performance (pre-drug test-phase of task 1); **2**: performance on items acquired before drug administration (post-drug test-phase of task 1); **3**: performance on items acquired after drug administration (post-drug test-phase of task 2). Scores are means ±SEM. * Performance significantly different from that of the placebo group (P < 0.05). ° Performance significantly different from that of the diazepam groups (P < 0.05) (t-tests, P values corrected according to the Bonferroni probabilities)

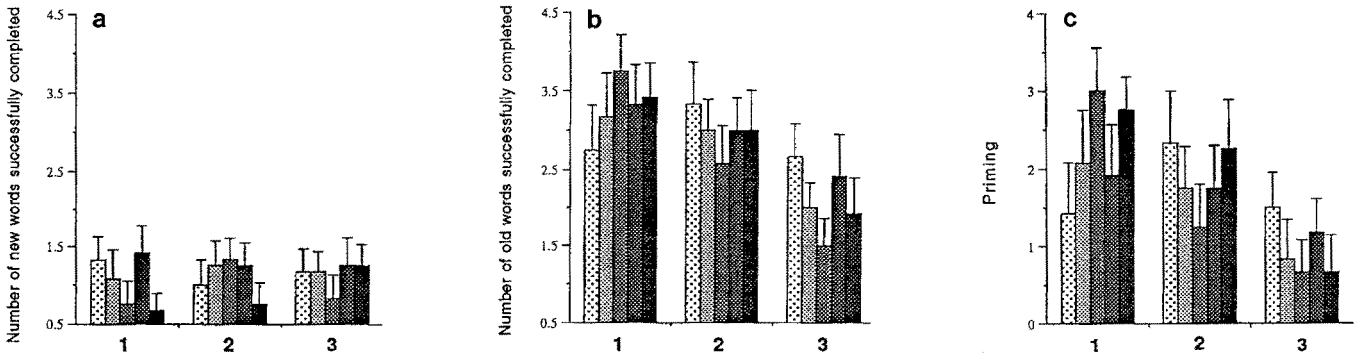

Fig. 2a–c. Word-completion performance. **a** Number of new words successfully completed, **b** number of old words successfully completed. **c** priming = difference between the number of old and new words successfully completed. Placebo group ▤, lorazepam 0.026 mg/kg group ▨, lorazepam 0.038 mg/kg group ▨, diazepam 0.2 mg/kg group ▩ and diazepam 0.3 mg/kg groups ■. **1**: baseline performance (pre-drug test-phase of task 1); **2**: performance on items acquired before drug administration (post-drug test-phase of task 1); **3**: performance on items acquired after drug administration (post-drug test-phase of task 2). Scores are means ±SEM

tify fragmented pictures over repeated tasks. To test whether these subjects exhibited a learning effect resulting from practice with the task, an ANOVA was carried out in this group, comparing the identification thresholds of new pictures in the three successive test-phases. Difference in performance failed to reach significance [F (2, 36) = 2.74, P = 0.08]. An ANOVA carried out on savings yielded no significant effect [F (2, 36) = 0.86].

Word-fragment completion task

The mean performance in word-fragment completion tasks is shown in Fig. 2.

Task 1. An ANOVA carried out on performance in the pre-drug test-phase revealed a significant priming effect [F (1, 55) = 69.4, $P < 0.0001$], no significant group effect [F (4, 55) = 0.24] and no significant interaction between priming and groups [F (4, 55) = 1.14]. Therefore, there was no significant difference in the performance of groups before drug administration. In the post-drug test-phase, there was a significant priming effect [F (1, 55) = 50.5, $P < 0.0001$], no significant drug effect [F (4, 55) = 0.23] and no significant interaction between priming and drugs [F (4, 55) = 0.56]. The number of old and new words successfully completed was similar in the five groups.

Task 2. Inspection of the results indicates that, whereas the number of new words successfully completed was similar in the five groups, the number of old words successfully completed was lower in the four active groups than in the placebo group, the decrease being the more pronounced at the highest drug doses. The pattern of priming impairment observed in the word-completion task was therefore similar to that observed in the picture-completion task. However, an ANOVA carried out on word-completion performance, while yielding a significant priming effect [F (1, 55) = 22.4, $P < 0.0001$], showed neither a significant drug effect [F (4, 55) = 0.99], nor a significant interaction between priming and drugs [F (4, 55) = 0.63]. This was probably due to a floor effect.

Free-recall task

As expected, free recall of pictures and free recall of words were decreased by drugs [F (4, 55) = 11.1, $P <$ 0.0001 and F (4, 55) = 6.64, $P < 0.0005$, respectively]. The deficit was significant in the four active groups except for the recall of words in the diazepam 0.2 mg/kg group (Table 2).

Digit symbol substitution task

DSST performance measured just before the post-drug test-phase of priming tasks 1 was decreased in the four active groups but the difference compared with the placebo group did not reach significance [F (4, 55) = 1.92]. DSST performance measured just before the study-phase of priming tasks 2 was significantly reduced in the four active groups [F (4, 55) = 6.42, $P < 0.0005$], the difference from the placebo group being significant for the lorazepam groups and for the diazepam 0.3 mg/kg group (Table 2).

Symbol cancellation task

Symbol cancellation scores measured just before the post-drug test-phase of priming tasks 1 were significantly lower in the four active groups than in the placebo group [F (4, 55) = 9.11, $P < 0.0001$]. There was also a significant drug effect when the performance was measured just after the study-phase of priming tasks 2 [F (4, 55) = 5.13, $P < 0.005$], the difference with the placebo group being significant for the lorazepam groups (Table 2).

Table 2. Effects of diazepam, lorazepam and placebo on digit symbol substitution, symbol cancellations and free-recall tasks

n = 5×12	Placebo	Lorazepam 0.026 mg/kg	Lorazepam 0.038 mg/kg	Diazepam 0.2 mg/kg	Diazepam 0.3 mg/kg
Free-recall task					
N° of pictures	7.4 ± 0.5	4.3* ± 0.7	1.8* ± 0.6	3.0* ± 0.8	2.6* ± 0.7
N° of words	1.4 ± 0.4	0.2* ± 0.1	0.2* ± 0.2	0.3 ± 0.1	0.2* ± 0.1
Digit symbol substitution task (Standard score)					
Before post-drug test-phase of priming tasks 1	13.0 ± 0.5	11.3 ± 0.5	10.3 ± 0.7	11.5 ± 0.8	11.3 ± 0.8
Before study-phase of priming tasks 2	15.4 ± 0.5	13.1* ± 0.6	11.0* ± 0.8	14.1 ± 0.6	13.2* ± 0.7
Symbol cancellation task (Total number of symbols processed)					
Before post-drug test-phase of priming tasks 1	270 ± 11	195* ± 15	165* ± 12	204* ± 12	199* ± 13
After study-phase of priming tasks 2	286 ± 11	221* ± 11	194* ± 13	250 ± 13	227 ± 23

Values 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)

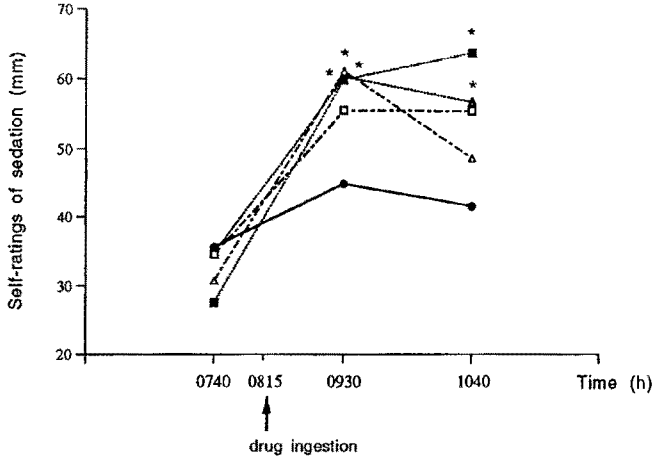

Fig. 3. Analogue self-ratings of sedation measured in mm at various intervals before and after ingestion of the drug in the five treatment groups. * Sedation significantly different from that of the placebo group ($P < 0.05$) (t-tests, P values corrected according to the Bonferroni probabilities). (–●–) PCB; (□—□) lorazepam 0.026 mg-kg; (···■···) lorazepam 0.038 mg/kg; (△—△) diazepam 0.2 mg/kg; (···▲···) diazepam 0.3 mg/kg

Analogue self-ratings of sedation

While sedation did not significantly differ among groups before drug administration [F (4, 55) = 1.55], a significant drug effect was found when sedation was measured just before the post-drug test-phase of priming tasks 1 [F (4, 55) = 4.09, $P = 0.01$] and just before the test-phase of priming tasks 2 [F (4, 55) = 3.62, $P < 0.02$]. Sedation was significantly increased by the two drugs, particularly by the highest doses (Fig. 3).

ANCOVAs

ANCOVAs were carried out on picture and word-completion performance with self-rated sedation, DSST performance and symbol cancellation scores as covariates. DSST performance, but not sedation or symbol cancellation scores, was significantly correlated with the identification thresholds of new and old pictures measured during the post-drug test-phase of task 1 and during task 2 [$Fs \geq 6.27$, $Ps < 0.02$]. Covarying DSST performance reduced the level of significance of the difference between lorazepam and placebo on these parameters, but it still remained significant [$Fs \geq 2.65$, $Ps < 0.05$]. DSST performance was not significantly correlated with savings [$Fs \leq 0.24$]. No other significant correlation was found.

Discussion

The results confirm the hypothesis that the lorazepam-induced deficit of perceptual priming results from an impairment in the acquisition of information, rather than from defective storage or retrieval. As predicted, savings in the picture-completion task were lower when information was acquired after, but not before, lorazepam administration; the reduction was observed at the 0.026 mg/kg dose, and was reliable at the 0.038 mg/kg dose, in comparison to performance in the placebo group. The same pattern of results was obtained in the word-completion task: the decrease in priming observed in task 2, with the highest dose of lorazepam inducing the most important decrease in performance, in conjunction with the absence of drug changes in task 1, all suggest that lorazepam exerted the same deleterious effect on word completion as on picture completion. The absence in the word-completion task of statistically significant lorazepam-induced changes was probably due to a floor effect, which could be explained by the relatively low number of words per set. It could be argued that the most impressive pattern of results, obtained in the picture-completion task, was artefactual, i.e. simply reflected the reduction of the ability to identify fragmented pictures, as indicated by the increase in the identification thresholds of both old and new pictures. This seems unlikely for two reasons. First-

ly, performance in task 1 showed that an increase in the identification thresholds of pictures does not necessarily lead to a decrease in savings. Secondly, the same conclusions were obtained when calculations were carried out on relative savings, instead of absolute savings, a measure which takes into account the basal ability to identify fragmented pictures (Snodgrass and Surprenant 1989).

That lorazepam decreased the ability to identify fragmented pictures was quite unexpected. In fact, a reanalysis of a previous study carried out by the same group (Sellal et al. 1992) showed a similar trend towards higher identification thresholds of new fragmented pictures in lorazepam-treated subjects; that this increase did not reach statistical significance was probably due to the fact that the number of pictures per list was relatively low (7 instead of 15 in this study). The determinants of the decreased identification of fragmented pictures merit comment. Firstly, it could be argued that the reduced ability to identify fragmented pictures reflects a global, non specific, effect of lorazepam on baseline performance in priming tasks, for instance due to a sedative and/or an attentional drug effect. This seems unlikely, since lorazepam did not alter completion of new words in the word-completion task; in addition, the identification of fragmented pictures was not significantly correlated with self-rated sedation or symbol-cancellation performance, a measure of sustained attention. Secondly, it could be argued that the reduced ability to identify fragmented pictures reflects an impairment in any practice effect on the task, since in the placebo group there was a progressive, although not significant, decrease of the identification thresholds of pictures (but not of savings) over the successive test-phases. Indeed, the lower performance of lorazepam-treated subjects was observed in the last test-phases of the study, and not in the first one. However, Danion et al. have shown a significant deleterious effect of lorazepam on the identification of fragmented pictures in the absence of any previous presentation (unpublished data). Even though an impairment of a practice effect cannot be entirely ruled out, the reduced ability to identify fragmented pictures is more likely to result from a true lorazepam effect on perception: lorazepam-treated subjects need more contours, i.e. more perceptual information, to identify fragmented pictures. It is worth noting that a deleterious effect of benzodiazepines in perceptual tasks has already been reported. Sellal et al. (1992) have shown that an acute administration of lorazepam and of diazepam to healthy volunteers decreases performance in the Gottschaldt's task (Gottschaldt 1928), which assesses the ability to perceive visual information. Golombok et al. (1988) reported a reduction of visual-spatial ability in anxious patients chronically treated with various benzodiazepines. The interpretation of the present results in terms of perceptual impairment is further supported by the significant correlation observed in this study between DSST performance and the identification of fragmented pictures, inasmuch as it has been postulated that the ability to discriminate perceptually the symbolic stimuli is a critical factor in DSST performance (Royer 1971; Delaney et al. 1981). However, it cannot be excluded that the effect of lorazepam on the identification of fragmented pictures can be explained by other mechanisms, since covarying DSST performance still left a significant difference between the lorazepam and placebo groups in the identification of pictures. Taken together, these results indicate that lorazepam, as well as other benzodiazepines, exhibit negative effects on perception. But the mechanism of the deleterious effect of lorazepam on object identification still needs to be established. Three steps are classically considered to be necessary for object identification (Marr 1982; Bonnet 1989). The first concerns the extraction of primitives such as orientation, luminance or spatial frequencies. The second concerns the integration of the primitives and the perceptual structuration, which permits, for example, the perceptual closure or the segmentation of the form into parts. The third concerns the comparison of the form with the objects stored in memory. The results obtained with lorazepam are consistent with two hypotheses. Lorazepam could affect the computation of contours from discrete local form elements (Zucker and Davis 1988; Von der Heydt and Peterhans 1989; Boucart and Bonnet 1991; Dresp and Bonnet 1991). Alternatively, it could affect the use of local specific details for the denomination of the stimuli. This study does not enable us to choose between these two hypotheses. In addition, it cannot be excluded that the deficit is consecutive to a peripheral, and not central, impairment such as blurred vision. Since similar deficits of object identification have been reported in normal aging (Danziger and Salthouse 1978; Read 1988; Frazier and Hoyer 1992) and in Korsakoff's disease (Warrington and Weiskrantz 1968; Bonebakker and Wolters 1992; Van Der Linden et al. 1992), a major objective for further studies would be to determine whether or not these various deficits share common mechanisms. Finally, it still needs to be established whether the deleterious effect of lorazepam on the identification of fragmented pictures is shared by other benzodiazepines. In this study, diazepam seemed devoid of any effect on the identification of new fragmented pictures. In a previous study (Sellal et al. 1992), a trend towards a deleterious effect of diazepam was observed when sujects were tested at the peak plasma concentration of the drug. It cannot therefore be excluded that diazepam, like lorazepam, exhibits a deleterious effect on the ability to identify fragmented pictures, provided that it is assessed during the peak concentration of the drug.

This study showed clearly that diazepam induced a pattern of performance in priming tasks which was similar to that induced by lorazepam. In the picture-completion tasks, diazepam reduced savings when information was acquired after, but not before, the drug administration, the reduction being reliable at the highest dose. This held true in the word-completion task, although, like lorazepam, diazepam provoked changes which were not statistically significant. These results indicate that both benzodiazepines reduced priming by impairing the acquisition of information. The deleterious effect of diazepam was unexpected, since previous studies using similar, conventional, paradigms of word and picture completion were unable to demonstrate any negative effect

of diazepam on priming (Fang et al. 1987; Danion et al. 1989, 1990; Sellal et al. 1992). As noted above, the only previous study which revealed a deleterious effect of diazepam on priming used a modified paradigm of picture completion, characterized by the presentation at study of fragmented pictures (Sellal et al. 1992). The present results, obtained with conventional priming tasks, were therefore puzzling. This study differs from all the others in two main respects: priming tasks were performed repeatedly by the same subjects, and the effect of the drug was assessed 2 h after drug administration of 1 h, at the peak concentration of diazepam. It could be argued that the repetition of priming tasks in the same subjects might induce performance changes between the first and the subsequent tasks, either by virtue of an interaction between successive tests (e.g. a proactive interference), or by virtue of a change in the nature of the task (e.g. a contamination of implicit task by explicit memory, changing the completion task, at least partially, into a cued-recall task). A proactive interference between priming tasks seems unlikely owing the fact that the 180 selected items were unique and that none of the word stems could be completed by the name of a picture. As discussed by Bowers and Schacter (1990), the risk of an explicit contamination is increased if subjects catch on to the nature of the test and are not prohibited from using explicit strategies; this risk seems particularly high in a picture-completion task, since the vast majority of subjects become aware, during the task, of the relationship between pictures shown at study and at test (Sellal et al. 1992). Therefore, to prevent contamination in this task, subjects participating in the study were informed that some fragmented pictures could be completed with pictures from the previously studied list, but were then instructed to indicate what they actually saw. In spite of this precaution, the possibility of an explicit contamination in priming tasks cannot be ruled out. This explicit contamination would lead to higher priming performance in the placebo group than in the active groups, since the former would have made use of explicit memory for boosting implicit performance, whereas this would not have been possible for the latter because explicit memory was impaired by the drugs. Such an interpretation is supported by recent findings showing that the age-related decline in implicit performance arises from the elderly's impairment of explicit memory (Russo and Parkin 1993). To circumvent this methodological limitation, which occurs because the priming tasks are not process-pure, the "process-dissociation procedure" developed by Jacoby (1991) could be helpful. Rather than identifying different memory processes with different tasks, this method separates the contributions of these memory processes within a single task. The "process-dissociation procedure" measures the respective contributions of unconscious and conscious controlled influences when they operate, firstly in opposition and secondly in conjunction, on word-stem completion performance (Jacoby et al. 1993). It also permits the assessment of the two forms of memory using the same cues; this methodological requirement has rarely been taken into account by pharmacological studies, which have usually used free-recall as an explicit measure. The other difference between this study and previous ones concerns the time elapsed between drug administration and the acquisition phase, which was longer in the present study. It is unlikely that the deleterious effect observed in the diazepam groups was provoked by nordiazepam, the active metabolite of diazepam, since its serum concentration is still low 2 h after the administration of diazepam (Guentert 1984). What is conceivable is that diazepam and lorazepam share a common deleterious effect on priming, but that its expression requires a sufficient amount of time to elapse after drug administration. In other words, if assessed too early, this effect could not be demonstrated. This could explain why Sellal et al. (1992), who assessed the influence of lorazepam and diazepam at their peak concentration, i.e. 2 h and 1 h, respectively, after their administration, observed apparent differential effects of the drugs, the former, but not the latter, impairing priming. Further studies are clearly required to test specifically the part played by time in the negative effect of benzodiazepines on priming. The confirmation that diazepam exerts a delayed effect on priming, compared to its effect on explicit memory, would provide a supplementary argument in favour of the hypothesis that two psychobiologically distinct memory systems underlie the two forms of memory.

Three final points relating to the determinants of the deleterious effect of lorazepam and of diazepam on priming ought to be discussed. The first concerns the link between this effect and sedation. It is acknowledged that sedation plays a role in the negative effect of benzodiazepines on explicit memory, even though it is not clear if the amnesia can be accounted for entirely by sedation (reviews in Lister 1985; Ghoneim and Mewaldt 1990; Curran 1991). In contrast, the role, if any, of sedation and of decreased arousal and attention seems far less critical in implicit tasks, as indicated by experimental and pharmacological manipulation of these variables (Graf et al. 1982; Danion et al. 1989; Kihlstrom et al. 1990). The absence in this study of a significant correlation between priming and sedation or between priming and sustained attention is consistent with this view. However, no firm conclusion can be drawn since the study was not specifically designed to evaluate the role of sedation. The second point concerns the possible link between the priming impairment induced by lorazepam and the deficit of the identification of fragmented pictures. The fact that diazepam-treated subjects exhibited a significant decrease in priming, in the absence of a clear impairment of the identification of fragmented pictures, suggests that the impairment of priming induced by benzodiazepines is not necessarily linked to a decreased ability to identify fragmented pictures. The last point concerns the psychobiological basis of priming. Recent evidence from positron emission tomography suggests that priming reflects a transient activation in the right posterior cortex, occurring during the acquisition of items, with the result that information processing is more effective when the items are presented for the second time (Squire et al. 1992). These data, in conjunction with the present study showing the deleterious effect of benzodiazepines on the acquisition of items, offer some support for the

suggestion by Brown et al. (1989) that benzodiazepines inhibit the activation of the memory system which underlies perceptual priming, possibly via GABAergic mechanisms.

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