Dissociation between perceptual processing and priming in long-term lorazepam users

Anne Giersch and Pierre Vidailhet
INSERM U666, Department of Psychiatry, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

Abstract

Acute effects of lorazepam on visual information processing, perceptual priming and explicit memory are well established. However, visual processing and perceptual priming have rarely been explored in long-term lorazepam users. By exploring these functions it was possible to test the hypothesis that difficulty in processing visual information may lead to deficiencies in perceptual priming. Using a simple blind procedure, we tested explicit memory, perceptual priming and visual perception in 15 long-term lorazepam users and 15 control subjects individually matched according to sex, age and education level. Explicit memory, perceptual priming, and the identification of fragmented pictures were found to be preserved in long-term lorazepam users, contrary to what is usually observed after an acute drug intake. The processing of visual contour, on the other hand, was still significantly impaired. These results suggest that the effects observed on low-level visual perception are independent of the acute deleterious effects of lorazepam on perceptual priming. A comparison of perceptual priming in subjects with low- vs. high-level identification of new fragmented pictures further suggests that the ability to identify fragmented pictures has no influence on priming. Despite the fact that they were treated with relatively low doses and far from peak plasma concentration, it is noteworthy that in long-term users memory was preserved.

Received 9 August 2005; Reviewed 1 September 2005; Revised 18 October 2005; Accepted 19 October 2005; First published online 2 December 2005

Key words: Benzodiazepine, long-term effects, lorazepam, memory, visual perception.

Introduction

Lorazepam is a benzodiazepine widely prescribed for its anxiolytic and hypnotic properties. Here we study the consequences of chronic intake of lorazepam for memory and visual perception and ask whether its deleterious effect on visual perception has an impact on a subject's ability to identify and memorize fragmented pictures.

Acute administration of benzodiazepines has very strong amnestic effects (Brown et al., 1982; Buffet-Jerrott and Stewart, 2002; Curran, 1991; Danion et al., 1992). The memory consequences of long-term use are more controversial. Some studies have shown the persistence of memory impairments, sometimes with partial tolerance (Angus and Romney, 1984; Birzele, 1992; Curran et al., 1994; Ghoneim & Mewaldt, 1990; Gorenstein et al., 1995; Hanlon et al., 1998; Pomara et al., 1989; Tata et al., 1994), while others have found no memory impairment (Lucki et al., 1986; McAndrews et al., 2003; Paterniti et al., 2002; Vignola et al., 2000). Studies have also differed widely in their design, with some exploring the effects of benzodiazepines administered to healthy volunteers with a double-blind controlled design over a period of 1–6 wk. The controlled vs. placebo design is a way of avoiding many methodological caveats, but it is impossible to draw any firm conclusions about longer intake effects. Even if it is recommended that the drugs should not be prescribed for longer than a few months, many patients take benzodiazepines for much longer periods. For obvious ethical reasons, the only way to address the question of such a long-term intake is to study cognitive functions in chronic users of these drugs. Among the many methodological caveats inherent in such studies, the effects of different benzodiazepines are usually confounded. In the case of lorazepam, which has been shown to differ qualitatively from other benzodiazepines in terms of its acute effects on cognition, this is problematic (Giersch and Herzog, 2004; Legrand et al., 1995; Vidailhet et al., 1994). Like all benzodiazepines, lorazepam administered in acute dosage impairs explicit memory,
as explored in classic recall and recognition tasks where subjects are explicitly instructed to recollect past information voluntarily and consciously (Brown et al., 1982, 1989; Danion et al., 1992). Unlike other benzodiazepines such as diazepam or oxazepam, however, a single dose of lorazepam has also repeatedly been shown to impair perceptual priming, a form of implicit memory (Brown et al., 1989; Curran et al., 1992; Knopman, 1991; Legrand et al., 1995; Martin et al., 2002; Pompeia et al., 2003; Sellal et al., 1992; Vidalilhet et al., 1994, 1999). Perceptual priming is explored in tasks such as word-stem or picture completion, where prior presentation of a stimulus facilitates its subsequent identification (Tulving and Schacter, 1990). To the best of our knowledge, only one study has looked specifically at the long-term effects of lorazepam on explicit memory and perceptual priming (Curran, 1992), and its results showed that chronic intake of lorazepam impaired word-stem completion when testing time coincided with the theoretical peak plasma concentration. The originality of the present study is that it focuses on the everyday memory effects of lorazepam in long-term users, i.e. not necessarily at times of peak plasma concentration. This is relevant, because lorazepam is usually prescribed as a sleeping pill, particularly in elderly subjects.

A second and related aim of our study was to find out whether such memory effects were associated with visual perception impairments, insofar as previous studies have examined whether the effects of lorazepam on perceptual priming could be linked to its effects on visual perception (Beckers et al., 2001; Vidalilhet et al., 1994; Wagemans et al., 1998). This question arose originally because lorazepam in acute dosage impairs not only perceptual priming, but also the identification of fragmented pictures that have not been primed (Figure 1). In other words, lorazepam-treated subjects need more contour information than placebo-treated subjects before they can name fragmented pictures accurately (Legrand et al., 1995; Sellal et al., 1992; Vidalilhet et al., 1994).

The observation that lorazepam impairs the identification of fragmented pictures (Vidalilhet et al., 1994; Wagemans et al., 1998) led to a series of experiments which showed that acute doses of lorazepam affect the processing of visual contour (Beckers et al., 2001; Giersch et al., 1997; Giersch, 1999, 2001; Giersch and Lorenceau, 1999). Lorazepam facilitates the detection of discontinuities located between collinear (on the same line) as opposed to parallel elements (Figure 2; Beckers et al., 2001; Elliott et al., 2000; Giersch, 1999, 2001). Edges, gaps and discontinuities in lines play a major role in the processing of the object form, by indicating its boundaries and enabling it to be separated from other objects and from the background (Nakayama et al., 1989; Shimojo et al., 1989). These segmentation signals are reinforced by lines produced perpendicular to line terminations (Figure 2).† They

† These are sometimes visible, like in the Ehrenstein illusion (Figure 2, Gove et al., 1995; Lesher and Mingolla, 1993; von der Heydt and Peterhans, 1989; Westheimer and Li, 1996). In our stimuli, perpendicular lines are not consciously perceived, but are nevertheless produced (Giersch, 2001; Giersch and Fahle, 2002; Giersch and Caparas, 2005; Gursey et al., 1999; von der Heydt and Peterhans, 1989).
have opposite effects depending on whether line segments are collinear or parallel. When they are collinear, lines perpendicular to the line terminations help to detect the gap. When the gap to be detected is between parallel elements, however, the two line terminations forming the gap produce a perpendicular line that is in exactly the same place as the gap and closes the stimulus (Figure 2b). We have suggested that the processing of line terminations is modulated in healthy volunteers (Giersch and Caparos, 2005; Giersch and Fahle, 2002), and that lorazepam affects this modulation (review in Giersch, 2001; Lorenceau et al., 2005), which explains why lorazepam-treated subjects separate elements even when they are collinear, at least when contour processing is modulated. Several studies have suggested that the effects of lorazepam on the processing of line terminations thus impairs the binding of the local elements composing the object (Giersch et al., 1997; Giersch and Lorenceau, 1999; Lorenceau et al., 2005). Since this implies difficulty recovering the global form of the objects, it provides justification for the hypothesis according to which the effect of lorazepam on discontinuity detection may impact on the identification of fragmented pictures. The task involving contour processing does not require picture identification and has previously been shown to be sensitive to the effects of an acute dose of lorazepam.

Method

Subjects

Patients and controls were recruited through medical practitioners and local advertisements. Patients and controls were individually and a priori matched on sex (11 women and 4 men in lorazepam users vs. 10 women and 5 men in the control group), age [54.7 (S.D. = 10.5) yr in the control group (range 30–67 yr) vs. 56.3 (S.D. = 12.6) yr in the lorazepam group (range 30–69 yr), with the same number of subjects of each decade in the two groups] and level of education [11.1 (S.D. = 2.5) yr in the control group vs. 10.9 (S.D. = 3.8) yr in the lorazepam group]. The subjects had no history of alcoholism, or drug abuse. In each group, three subjects smoked <10 cigarettes/d, and one smoked 20 cigarettes/d. The two groups did not differ on their alcohol consumption [0.7 glass of wine per day (S.D. = 0.2) in the control group vs. 0.5 (S.D. = 0.7) in the lorazepam group, F < 1]. Apart from high blood pressure and osteoarthritis, subjects had no medical disease. The absence of present or past psychiatric condition was checked through an interview with a senior psychiatrist from the research team. One subject with a history of psychiatric disturbances was discarded from the study. Controls were not chronic users of benzodiazepines and had not taken any medication acting on the central nervous system for at least 30 d. Chronic lorazepam users had been taking the drug for a duration of 2 months to 33 yr [mean 13.3 (S.D. = 11.1) yr]. Only the three youngest subjects had taken the drug for <2 years, whereas nine subjects had taken the drug for at least 10 yr. The majority of the subjects (n = 11) took the drug only at night, as a sleeping pill, and the posology was >1 mg in seven subjects ranging from 0.5 to 5 mg/d [mean 1.8 mg/d (S.D. = 1.7)]. Five subjects had started the medication after a traumatic event (the severe disease or death of a relative). One subject had a somatoform disorder, and three a generalized anxiety disorder. Two had started lorazepam after the break-up of a romantic relationship. Four subjects showed a mild anxiety level associated with high blood pressure or invalidating hip arthritis.

In order to preserve a simple blind procedure, participants were first seen by a senior psychiatrist, who completed the Hamilton scale for anxiety. All other tests were performed by the subjects under the supervision of a neuropsychologist who was blind to the subject’s medication condition.

All participants gave written informed consent and were paid for their participation. The protocol was approved by the Faculty Ethics Committee. The study was carried out in accordance with the Declaration of Helsinki.

Memory investigations

Global memory competence was assessed using the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987).

Perceptual priming was assessed using a picture-completion task, with two paired sets of 15 pictures of common objects each (Snodgrass and Corwin, 1988). Each picture was progressively fragmented in order to obtain eight levels of fragmentation. Level 1 corresponded to the most fragmented picture and level 8 to the complete picture (Figure 1, Snodgrass et al., 1987). The pictures were displayed on a computer screen. During the study phase, subjects were shown...
19 complete pictures, one at a time, for 10 s each. The 19 pictures included 15 target pictures of a set, and two buffer pictures at the beginning and at the end of the list in order to control for recency and primacy effects. Subjects had to name each picture aloud and to remember it. In the test phase, 30 pictures were displayed, including 15 studied pictures or ‘old’ pictures, randomly mixed with 15 non-studied pictures or ‘new’ pictures of the paired set. Pictures were displayed 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 displayed in the same way, and so on until the picture was identified. The perceptual identification threshold (IT) was the level of fragmentation at which the picture was identified. Relative priming was taken as the primary measure of priming performance (Legrand et al., 1995; Sellal et al., 1992; Vidailhet et al., 1994), in order to take into account baseline group differences in the identification of fragmented pictures. It was calculated by subtracting the mean IT for old pictures from that for new pictures, and by dividing this score by the mean IT for new pictures. Priming corresponds to the fact that ‘old’ pictures are identified at a lower level of fragmentation than ‘new’ pictures. The two sets of pictures were used the same number of times as ‘old’ and as ‘new’ in each group.

Explicit memory was assessed using a free-recall task, which immediately followed the priming task. Subjects were asked to write down, in 3 min, as many names of pictures as they could remember from the study list. The number of pictures correctly recalled indexed explicit memory performance.

Discontinuity detection

The stimuli were presented in grey on a black computer screen background (screen resolution 640 × 480 pixels). Stimuli were composed of horizontal line segments (width 1 pixel, i.e. 2.4′ of arc). ‘Collinear’ stimuli (Figure 2) were composed of two collinear line segments: a 7 pixel-long line segment (16.8′ of arc) and a 21 pixel-long line-segment (50.4′ of arc), separated by a gap of 7 pixels (16.8′ of arc). The gap was located either on the right or the left side. ‘Parallel’ stimuli were composed of two 12 pixel-long parallel line segments (28.8′ of arc) separated by a gap of 7 pixels (16.8′ of arc). A vertical line linked the ends of the two line segments on one side, leaving a gap at the other end (Figure 3). The stimuli were arranged so that the gaps on one side were all at the same location on the screen, whatever the type of stimuli.

A first stimulus was presented in the centre of the screen. The subjects were instructed to decide whether a gap was present on the right or on the left side. They pressed a right or left response key according to the side of the gap. The stimulus stayed on the screen until the subjects gave their response, and then disappeared (the screen went black), followed by a second stimulus after a delay of 100 ms. Subjects were instructed to decide again on which side the gap was located, and the stimulus disappeared after they gave their response. After a delay of 100 ms during which a mask was displayed, and an additional delay of 1000 ms during which the screen remained black, the sequence started again. The gaps of the first and second stimulus in each sequence were either composed of collinear or parallel elements. All possible configurations were randomly and equally represented: the side of the gap in the first and in the second stimulus, the position of the horizontal collinear elements, and the nature of the first and second stimulus (composed of collinear or parallel elements). Errors were signalled by a 300-ms sound, initiated after the execution of the response. There were 24 trials per condition, yielding a total of 192 trials. Measures were conducted with a monocular presentation, to avoid any contamination of the results by a lorazepam effect on oculomotor balance (Speeg-Schatz et al., 2001).

For the sake of simplicity, we focus here on the conditions allowing a modulation of contour processing to be observed, i.e. when the two consecutive stimuli change in form (Giersch and Fahle, 2002; Giersch and Caparos, 2005). These are the conditions in which a deleterious effect of an acute dose of lorazepam has been observed (Giersch, 2001). We compare the response times (RTs) for detecting a gap...
between collinear elements and the RTs for detecting a gap between parallel elements, when these stimuli have been preceded by a gap on the same side, between parallel or collinear elements respectively (more details on the methods can be found in Giersch, 2001).

Sedation

Pupillography

Pupillography allowed an objective measure of sedation. The diameter of the pupil is measured by means of infrared video pupillography during 11 min with a sampling frequency of 25 Hz. Afterwards, a Pupillary Unrest Index (PUI) is calculated, which corresponds to the pupil’s tendency to oscillate. Variations in the pupil diameter are taken into consideration only when below 1.56 Hz (for more details, see Lüdtke et al., 1998; Schaeffel et al., 1993).

Analogue self-rating of sedation (EVA)

A set of visual scales is used to assess the participants’ subjective state of sedation. Each scale consists of a 100-mm ungraduated horizontal line, anchored by contrasting states of mind. Subjects are asked to regard each line as a continuum and to rate their feelings by placing a vertical mark across each line. The scales are scored by measuring the length (in mm) from the positive end of each line to the subject’s mark. Nine of these scales assess complementary aspects of sedation (Bond and Lader, 1974). The mean score of these nine scales is calculated for each individual and is taken as a subjective indication of sedation.

Anxiety

Anxiety was evaluated by means of the Hamilton scale for anxiety (Hamilton, 1959), which has been translated and validated in French (Pichot et al., 1981).

Results

Memory assessed by the WMS-R

Neither the global score nor any subscore of the WMS-R differed between the control and the lorazepam group (F’s < 1) (Table 1).

Perceptual priming and free recall (Table 1)

Levels of identification for both new and old pictures were similar in the control group and in the lorazepam group (5.5 for new pictures and 4.6 for old pictures in both groups, F < 1).

Relative priming did not differ between groups either (0.17 in both groups, F < 1). This task may have been contaminated by explicit memory. In this case, subjects may have identified the fragmented pictures at a lower level of fragmentation when explicitly recalling them. This hypothesis is contradicted by the fact that results were identical when relative priming was calculated on the images that were not cited during free recall.

Recall performance was also similar in both groups (9.1 in the control group, vs. 8.8 in the lorazepam group, F < 1), and data did not correlate with the sedation level, the dosage or duration of treatment, or the anxiety level.

Table 1. Mean values of memory, measures of sedation and anxiety in the 15 controls and 15 long-term lorazepam users, with standard errors

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 15)</th>
<th>Lorazepam group (n = 15)</th>
<th>Group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wechsler Memory Scale – Revised</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal memory</td>
<td>93.4 ± 3.8</td>
<td>95.5 ± 3.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Visual memory</td>
<td>97.7 ± 3.5</td>
<td>100.7 ± 3.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>General memory</td>
<td>94 ± 3.5</td>
<td>96.7 ± 3.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Concentration–Attention</td>
<td>96.2 ± 4.4</td>
<td>95.8 ± 4.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Level of identification of new pictures</td>
<td>5.5 ± 0.1</td>
<td>5.5 ± 0.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Level of identification of old pictures</td>
<td>4.6 ± 0.15</td>
<td>4.6 ± 0.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Relative priming</td>
<td>0.17 ± 0.03</td>
<td>0.17 ± 0.02</td>
<td>n.s.</td>
</tr>
<tr>
<td>Free recall</td>
<td>9.1 ± 0.7</td>
<td>8.8 ± 0.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>PUI (objective measure of sedation)</td>
<td>5.5 ± 0.5</td>
<td>5.1 ± 0.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>EVA (subjective measure of sedation – max. 100)</td>
<td>22.3 ± 3.9</td>
<td>32.8 ± 3.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total score of anxiety (Hamilton scale – max. 56)</td>
<td>3.1 ± 0.7</td>
<td>12 ± 2.1</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

PUI, Pupillary Unrest Index; EVA, Analogue self-rating of sedation.
In the lorazepam group, there was an advantage of 30 ms $[F(1, 14) = 11.2, p < 0.005]$ for stimuli composed of collinear elements compared to stimuli composed of parallel elements, in the condition where the variations in RTs are supposed to be the consequence of a modulation of the processing of discontinuities in lines (when the two consecutive stimuli differed on their type, one composed with collinear elements and the other one with parallel elements, and included gaps on the same side). There was no significant effect in the same condition in the control group (3 ms, $F < 1$). This effect resulted in a significant interaction between the group (lorazepam vs. control) and the type of the second stimulus [composed of collinear vs. parallel elements; $F(1, 28) = 5, p < 0.05$] (Figure 4). There was no significant difference between the two groups in the other conditions, and no correlation with the sedation level, the dosage or duration of treatment, or the anxiety level.

Discontinuity localization

Identification of fragmented pictures and perceptual priming

In order to ensure that there was no impairment in the perceptual priming task in a particular subgroup of patients, we compared relative priming within both groups directly as a function of the level of identification of new pictures. In each group, we compared relative priming in the seven subjects identifying the new pictures at the highest level with the one in the eight remaining subjects. Of course, the level of identification of new pictures was higher in the former subgroup (6.1 in the lorazepam group and 5.9 in the control group) than in the latter [5 in the lorazepam group and 5.1 in the control group; $F(1, 26) = 49.3, p < 0.001$]. Despite this, relative priming was strictly identical in both subgroups ($0.17$ in both lorazepam subgroups and $0.17$ and $0.16$ in the two control subgroups for low and high identification level respectively, $F's < 1$).

Sedation

The mean PUI was similar in controls (5.1) and in patients treated with lorazepam (5.5, $F < 1$). Subjective measures of sedation were slightly but not significantly higher in patients taking lorazepam (mean 32.8) than in controls [mean 22.3; $F(1, 28) = 3.5, n.s.$].

Anxiety

Anxiety was rated as significantly higher in the lorazepam group (12 for a maximal score of 56) than in the control group [3.1; $F(1, 28) = 16.7, p < 0.001$]. Both the psychic and somatic scores were increased in the lorazepam group compared to the control group (7.6 per maximal score of 28 for the psychic score in the lorazepam group vs. 2.5 in the control group $[F(1, 28) = 16.7, p < 0.001]$, and 4.4 vs. 0.7 per maximal score of 28 for the somatic score $[F(1, 28) = 9.4, p < 0.005]$. 

Discussion

The most striking effect observed in the present study is the contrast between the persistence of the effect of lorazepam on contour processing and the absence of any effect on explicit memory, perceptual priming or the identification of fragmented pictures. This result suggests a dissociation between the two series of effects.

The alteration in visual perception observed in long-term lorazepam users produced no impairment of perceptual priming, indicating that responsibility...
for such impairment does not lie with the deleterious effects of lorazepam on contour processing. Even if a replication of the effect on contour processing in long-term users were to be necessary, we are confident of the results, insofar as they replicate those observed in subjects treated with a single dose of lorazepam in the same paradigm (Giersch, 2001), and, more generally, they replicate the advantage repeatedly found in subjects treated with a single dose of lorazepam when it is a case of detecting a gap between collinear, rather than parallel elements (Giersch et al., 1997; Giersch, 1999, 2001; Lorenceau et al., 2005). The results are also consistent with studies involving chronic users of benzodiazepines which suggest that their visual processing might still be impaired (Curran et al., 2003, Golombok et al., 1988, Gorenstein et al., 1995, Petursson et al., 1983).

Sedation can be ruled out as an explanation, given that sedation in the two groups was similar. Anxiety might play a role, since chronic lorazepam users were shown to have higher levels of anxiety than the controls. As far as we know, the processing of contour has not been explored in anxious people, but cannot explain the deleterious effects observed in healthy volunteers treated with a single dose. Moreover, lorazepam-treated subjects were only slightly more anxious than controls. In addition, the profile of patients with schizophrenia, whose symptoms include high levels of distress, is the exact opposite of that displayed by lorazepam-treated subjects (Giersch, in press).

At first sight, the fact that the identification of fragmented pictures was not significantly impaired even though the detection of discontinuities was still affected might seem surprising. However, a dissociation between the effects of lorazepam on the processing of discontinuities in lines and its effects on the identification of fragmented pictures has already been described in the literature (Beckers et al., 2001; Wagemans et al., 1998). Even if line termination processing is needed to identify fragmented pictures (Grossberg et al., 1997; Hummel and Biederman, 1992; von der Heydt and Peterhans, 1989), other mechanisms are also involved, including comparing the contour with the forms stored in memory. Such late, top-down effects are very effective in helping to identify incomplete forms (Peterson and Gibson, 1994; Peterson and Kim, 2001). Whereas such processes are impaired under the effect of a single dose of lorazepam (see Wagemans et al., 1998), their preservation in long-term users may explain why the lorazepam effect in the discontinuity task is not enough to induce a significant impairment in the identification of incomplete Snodgrass pictures. Investigations involving pictures, the physical properties of which are more controlled, might also reveal impairments that are not visible in the present experiment (Wagemans et al., 1998). It remains to be seen whether the effects on contour processing can explain the difficulties with visual search and discrimination observed in long-term benzodiazepine users, i.e. their difficulties with tasks where contour processing adaptations are more demanding than with the identification of objects (Curran et al., 2003; Golombok et al., 1988).

Together with their preserved perceptual priming, the absence found in long-term lorazepam users of any effect on the identification of fragmented pictures does not allow us to eliminate the hypothesis that these two effects are related, independently of any effect on contour processing (Legrand et al., 1995; Sellal et al., 1992; Vidailhet et al., 1994). Nevertheless, results were heterogeneous enough to allow for a comparison of perceptual priming in subjects showing a low vs. high level of identification of fragmented pictures. The results clearly showed that perceptual priming is stable whatever the level of identification of new pictures. This suggests that the two effects – on the identification of fragmented pictures and on perceptual priming – rely on separate mechanisms.

Another finding was that chronic lorazepam users showed no significant impairment of their free-recall performance with a list of pictures, nor of their performance in terms of any of the WMS subscores, or the picture completion task. The suggestion is, therefore, that explicit memory and perceptual priming were spared. Taken together with other results recently published (McAndrews et al., 2003; Paterniti et al., 2002; Vignola et al., 2000), our findings suggest chronic use of benzodiazepines is not associated with any substantial next-day explicit memory deficit, at least not in the case of low therapeutic doses. The performance in the same tests of subjects treated with a single dose of lorazepam has repeatedly been shown to be impaired, which suggests the tests are sufficiently sensitive. The impairment in terms of contour processing, and contrast sensitivity (Giersch et al., unpublished observations), also shows that it was possible to observe deficits in that particular group of patients. The main questions still pending are concerned with testing time and the dose of lorazepam administered. In our study, testing time was not controlled in relation to drug intake. Lucki et al. (1986) have shown that delayed free-recall of a list of words (explicit memory) was impaired in long-term benzodiazepine users when testing occurred shortly after
they had taken the medication, but not when the patient was assessed a few hours later (4–15 h). Similarly, Curran showed an impairment in word-stem completion tasks involving chronic lorazepam users with a similar dose. The main difference between Curran’s study (1992) and our own is that testing in the former occurred at the time of expected peak plasma concentration, whereas in our study testing time was not controlled in relation to drug intake. It is possible, therefore, that subjects who took part in our own study still display explicit and implicit memory impairment shortly after benzodiazepine intake, and, even if no significant correlation was found in our study between the dose of lorazepam and explicit or implicit memory performance, the possibility that higher doses of lorazepam are actually associated with persistent next-day explicit memory impairment cannot be ruled out. Despite these limitations, it is interesting to note that memory was spared in this particular group of patients.

**Acknowledgements**

This research was financed by the University Hospital of Strasbourg (PHRC) and by INSERM. We thank Catherine Kleitz, Jean-Charles Barthaud and Natacha Candelier for their invaluable help in testing patients.

**Statement of Interest**

None.

**References**


