A double blind parallel group placebo controlled comparison of sedative and amnesic effects of etifoxine and lorazepam in healthy subjects

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ABSTRACT

This paper describes the psychomotor and amnesic effects of single oral doses of etifoxine (50 and 100 mg) and lorazepam (2 mg) in healthy subjects.

Forty-eight healthy subjects were included in this randomized double blind, placebo controlled parallel group study. The effects of drugs were assessed by using a battery of subjective and objective tests that explored mood and vigilance (Visual Analog Scale), attention (Barrage test), psychomotor performance (Choice Reaction Time) and memory (digit span, immediate and delayed free recall of a word list).

Whereas vigilance, psychomotor performance and free recall were significantly impaired by lorazepam, neither dosage of etifoxine (50 and 100 mg) produced such effects.

These results suggest that 50 and 100 mg single dose of etifoxine do not induce amnesia and sedation as compared to lorazepam.

INTRODUCTION

Benzodiazepines are widely used in the treatment of insomnia, anxiety and epileptic disorders as well as for the induction and maintenance of anesthesia [1,2].

A common side-effect of this therapeutic class of drugs is dose-related anterograde amnesia (forgetfulness for events that occur following drug intake), which persists for several hours and which has since been observed following oral administration [3,4]. The intensity of this amnesic effect depends on the nature of the benzodiazepine; generally, benzodiazepines with short elimination half-life and rapid onset of action, such as lorazepam, induce the greatest amnesic effects. Finally, there are other significant adverse effects, such as sedation and impairment of psychomotor performance, associated with the use of these compounds [5].

Etifoxine is a nonbenzodiazepine drug registered in France for psychosomatic manifestations of anxiety [6]. It is hypothesized to act through GABA-benzodiazepine-macromolecular complex [7,8], acting as a partial agonist. A recent double-blind multicenter controlled study have confirmed the interest of using etifoxine in the treatment of adjustment disorder with anxiety [9].

Herein, we studied the psychomotor and amnesic effects of a single oral dose of etifoxine 50 and 100 mg and a 2-mg single oral dose of lorazepam in healthy subjects. We chose lorazepam for this study because its central nervous system effects are widely documented and because it is a widely used anxiolytic. A battery of tasks including subjective and objective evaluation of vigilance and mood, attention, psychomotor and memory performance was performed before and at several times after drug administration.

MATERIALS AND METHODS

Subjects

Forty-eight subjects (24 women, 24 men) aged from 18 to 35 years (mean = 24.9 ± 3.5 years of age) participated in the study. Subjects' body weight was within predefined limits for height: their weight did not exceed 10% of the ideal weight as defined by the tables of the Metropolitan Life Insurance company (mean weight: 65.7 ± 9.9 kg; mean height: 172.3 ± 8.7 cm). All subjects smoked less than 10 cigarettes per day and were able to abstain from smoking on treatment days.

All were in good physical health and underwent a complete medical assessment including a medical history questionnaire, a physical examination, a laboratory profile (haematologic and biochemical analyses, breath alcohol quantification) and an electrocardiogram.

Urinary tests were performed so as to eliminate individuals under psychoactive drugs (barbiturate, benzodiazepines, cannabinoid, cocain, opioids). The women's urine was also checked for hormonal levels so as to eliminate pregnant subjects from the study.

On the basis of psychiatric interview and Hamilton Anxiety Scale Rating score [10], all subjects were judged as not anxious (mean = 1.4 ± 1.1). Excluded from the study were subjects with a history of alcoholism or drug abuse. None of the subjects had used benzodiazepines or other psychotropic drugs within the last four weeks and none were currently taking any prescription drug other than oral contraceptives. All subjects were right-handed and had normal or corrected-to-normal visual acuity.

Approval was obtained from the local Ethics Committee (CCPPRB Marseille). Each subject was registered on the French National File and gave his informed written consent before entering the study.

Drugs

Lorazepam, orally administered, is rapidly and readily absorbed, reaching, within 2 h, maximum blood levels proportional to the dose. These concentrations decline thereafter, with a biological half-life of about 12 h [11]. The psychomotor and amnesic effects of lorazepam (2 mg) is well documented in several studies [12,13]. This explains the choice of this compound, used in this study as a positive control.

Etifoxine is completely absorbed after oral administration with blood concentrations peaking to 2.5 h postdose and half-life of about 6 h. An active metabolite (the desethyl-etifoxine) appeared quickly with a maximum concentration of 4 h (Dossier AMM etifoxine, Laboratoire Biocodex, Compiègne, France). The recommended daily dose of etifoxine ranged from 150 to 200 mg (in 3 or 4 capsules of 50 mg by day) [6]. The dosages using in this study (50 mg and 100 mg of etifoxine) correspond also to the unit dose.

Experimental design

A randomized parallel group, placebo-controlled study was used to compare the two treatments (lorazepam, etifoxine). Subjects were randomly assigned to one of the four treatment groups (12 subjects per group) as follows:
1 one group received a single dose of etifoxine (50 mg);
2 one group received a single dose of etifoxine (100 mg);
3 one group received a single dose of lorazepam (2 mg); and
4 one group received a placebo.

Subjects were administered either drug (lorazepam or etifoxine) or placebo treatment orally, using identical capsules administered between 8:30 and 9:30 am.

No concomitant treatment was allowed during the study. Alcohol, tobacco, tea, coffee or other substances containing caffeine were prohibited on testing day.

Assessment criteria

A battery of tests was performed in order to explore vigilance and mood, psychomotor and amnesic performance of the healthy subjects before and after treatment administration.

Visual analog rating scales
Ten cm horizontal line visual analog scales were used to assess subjects' subjective state [14]. Six of these scales assessed complementary aspects of sedation (drowsy, woozy, clumsy, fine, energetic, tired) and five assessed different aspects of mood (anxious, happy, relaxed, sad, depressed).

Barrage test
This test involved the visual attention and is similar to the Toulouse–Pieron Test [15,16]. Three target symbols were presented on the top of the screen. Under these symbols, two lines containing 10 symbols appeared.

Subjects' task was to move across each line, using a joystick, and to match all symbols in the line corresponded to the target symbols. Each line was replaced after the subject had gone through it, for a short period (5 min). The number of correct responses, omissions and false alarms were recorded.

Choice reaction time (CRT)
The subjects' task, described in detail elsewhere [17,18] consisted of a choice reaction time procedure in which the subjects were to perform a button press with their index fingers according to the location of a visually presented response signal (LED). Stimuli were of either weak or strong intensity.

Each trial began with the onset of an auditory warning and the LED display.

There were two mapping conditions: subjects were to press the button ipsilateral to the imperative stimulus in the incompatible condition and the button controlateral to the imperative stimuli in the incompatible one. As soon as a bulb lit up, the subject had to press one of two buttons to turn it off. For each condition (compatible or incompatible), response time (in ms) was automatically recorded for each stimulus intensity. For each test, 64 attempts were recorded.

Immediate and delayed free recall of pictures
Subjects were given 20 drawings, each depicting an object. They were given 10 seconds to look at each sheet and to name the object. Immediately thereafter, they were allotted five minutes to recall the maximum of drawings (immediate free recall) [18]. The score represented the number of pictures recalled. The same exercise was repeated 50 min after acquisition (delayed free recall).

Digit span
In a first task, the subject had to repeat in the same order each sequence of number after hearing them. If the subject responded correctly to the first series of three digits, the series was increased by one up to a maximum of 6 digits, dependent upon correct response. After incorrectly responding to two trials of the same span length the procedure was ended. In a second task, the subject had to recall progressively longer series (two to a maximum of six) of digits in the reverse order from that learned by the investigator [15,16]. The score represented the number of correct responses for each task.

General procedure
Prior to the study, each subject came to the laboratory for a preliminary training session. This involved familiarization with, and practice on, all the tests to be employed in the study and enabled us to ensure that subjects were able to understand the tests. The day before the test, healthy subjects were admitted to the Center.

The time of assessments was chosen on basis of the pharmacokinetic parameters of the drugs.

The VAS and Barrage tests were performed before and 1, 2, 4 and 6 h after drug administration (TBase, T1 h, T2 h, T4 h and T6 h, respectively).

CRT and memory tests (digit span and immediate and delayed recall) were assessed before and 2 h after drug administration.

Eight hours following administration, subjects were taken home back with instructions not to drive a motor vehicle until the following morning.

Safety
Side-effects were monitored continuously throughout the study and were reported spontaneously by the subjects.

Statistical analysis
Sample size was calculated using a mean comparison method (alpha = 0.05; power = 0.80) based on a difference of 5% between choice reaction time mean under lorazepam and placebo.

The initial equivalence of four groups was determined by an analysis of variance (ANOVA) for both demographic characteristics and the variables measured on Tbase (VAS, CRT, Digit span, pictures tests, Barrage test).

The treatment effect was assessed:
1 using ANOVA (group effect) for variables CRT, digit span, immediate and delayed recall followed if necessary, by multiple comparison procedure (Scheffé test);
2 using repeated measures ANOVA for variables Barrage test and VAS (group and time effects, interaction time/group), followed if necessary by ANOVA at each time (group effect) and Scheffé test;

Statistical analysis was performed using the Statistical Analysis System (Version 6.04). The significant level was set at 5%.

RESULTS

At baseline, the four groups were found to be equivalent regarding demographic criteria as well as performance on CRT, all items of the VAS, Barrage test, digit span, pictures tests (*Table I*).

Tolerance
No serious side-effects occurred during the study. Seven subjects presented common and reversible adverse effects such as drowsiness, sweating and feeling of drunkenness.

Five adverse events (sweating, feeling of drunkenness and three cases of drowsiness) occurred after a single

Table I Demographic and baseline characteristics of the four groups.

	etifoxine 50 mg	etifoxine 100 mg	lorazepam 2 mg	placebo
Number	12	12	12	12
Age (years)	24.8 ± 3.3	24.5 ± 4.1	25.3 ± 3.8	24.9 ± 3.2
Height (cm)	174.8 ± 10.2	176.7 ± 7.5	167.3 ± 7.2	170.3 ± 7.4
Weight (kg)	68.5 ± 12.2	68.4 ± 8.8	62.4 ± 8.0	63.6 ± 9.8
CRT compatible (ms)				
Strong intensity	260.9 ± 24.3	264.2 ± 18.6	256.5 ± 24.7	257.8 ± 23.7
Weak intensity	278.3 ± 23.2	283.8 ± 19.3	279.3 ± 22.1	283.2 ± 27.8
RT incompatible (ms)				
Strong intensity	306.3 ± 26.2	311.6 ± 22.6	307.8 ± 29.5	313.3 ± 34.9
Weak intensity	324 ± 27.2	328.5 ± 27.8	331.4 ± 30.1	325.6 ± 33.3
Memory tests				
Immediate recall*	12.8 ± 2.2	14.0 ± 2.2	13.5 ± 1.2	13.1 ± 1.8
Delayed recall*	11.8 ± 2.2	12.1 ± 2.0	13.1 ± 1.9	11.9 ± 2.5
Digit span direct order**	8.3 ± 1.5	8.5 ± 2.0	8.4 ± 1.3	8.8 ± 1.4
Digit span reverse order**	7.7 ± 1.8	8.5 ± 1.7	8.9 ± 2.0	8.5 ± 2.0
Barrage test				
Number of correct responses	126.3 ± 26.9	122.5 ± 16.3	150.5 ± 53.9	140.6 ± 23.1
Number of errors	1.2 ± 2.6	0.6 ± 0.7	1.3 ± 1.7	1.0 ± 1.5
Number of omissions	9.2 ± 6.4	6.4 ± 5.9	6.7 ± 4.1	4.1 ± 3.8

There were no significant differences between the four treatments with regard to baseline values on age, height, weight and performance tests before dosing.
*The score of the immediate and delayed recall ranged from 0 to max 20.
**The score of the digit span ranged from 0 to 12.
Data represent mean ± SD.

dose of lorazepam 2 mg. One subject under 100 mg etifoxine and one under placebo experienced drowsiness.

Psychomotor performance

At T2 h, mean choice reaction time differed significantly between the four groups as a function of both light intensity and compatibility condition (ANOVA: $P < 0.001$).

Subjects under lorazepam displayed significant longer mean CRTs on both measures than did subjects of the others groups (*Table II*).

Vigilance assessment

Barrage test

Repeated measures ANOVA performed on the Barrage test revealed a significant interaction group*time, respectively, for the number of correct responses ($P < 0.001$) and for the number of omissions ($P = 0.033$). On overall assessment, the number of errors differed significantly between the four groups.

At T1 h, there was a significant group effect for the number of correct responses and errors. However, multiple comparison of means (Scheffé test) did not

Table II Mean ± SD results of the Choice Reaction Time (CRT) two hours after administration of drugs (placebo, lorazepam, etifoxine 50 and 100 mg).

	etifoxine 50 mg	etifoxine 100 mg	lorazepam 2 mg	placebo	ANOVA (Scheffé test)
Number	12	12	12	12	
CRT compatible (ms)					
Strong intensity	261.1 ± 24.9	263.1 ± 18.8	333.8 ± 65.6	262.3 ± 31.1	$P < 0.001$
Weak intensity	280.9 ± 20.7	285.4 ± 16.0	348.9 ± 59.9	279.2 ± 30.8	$P < 0.001$
CRT incompatible (ms)					
Strong intensity	307.9 ± 41.3	308.7 ± 26.2	398 ± 75.7	298.8 ± 29.5	$P < 0.001$
Weak intensity	327.0 ± 38.5	327.3 ± 23.0	412.5 ± 76.3	315.3 ± 24.2	$P < 0.001$

Lorazepam significantly differed from others groups in both compatible and incompatible CRT. (Comparison are performed using ANOVA and Schéffe test.)

Table III Mean ± SD results of Barrage test performed 2 h after administration.

	etifoxine 50 mg	etifoxine 100 mg	lorazepam 2 mg	Placebo	ANOVA (Scheffe test)
Number	12	12	12	12	
Number of correct responses	148.8 ± 35.3	135.9 ± 31.8	108.7 ± 20.5	154.2 ± 25.6	$P = 0.002*$
Number of errors	0.8 ± 1.0	0.6 ± 0.9	2.9 ± 3.6	0.5 ± 0.5	$P = 0.013†$
Number of omissions	6.3 ± 3.1	8.3 ± 4.8	5.1 ± 6.0	3.9 ± 2.7	NS

Lorazepam impaired significantly performance on barrage test as compared to etifoxine 50 mg and *placebo. The number of errors was higher under lorazepam than †placebo.

display a significant difference between lorazepam, etifoxine and placebo.

At T2 h, the treatment effect was also significant on the number of correct responses ($P = 0.002$); subjects under lorazepam had a lower score than subjects under etifoxine 50 mg and subjects under placebo. Moreover, there was a significant treatment effect on number of error for all four drugs ($P = 0.013$). Only lorazepam showed a difference as compared to placebo, due to an increased number of errors (*Table III*). No difference was observed between groups on number of omissions.

At T4 h and T6 h, no significant differences of performance on Barrage test was observed between the four groups.

Visual analog scale (VAS)
A repeated measures ANOVA performed on VAS showed a significant group*time interaction for the following items: tired ($P = 0.003$), drowsy ($P < 0.001$), woozy ($P = 0.002$), clumsy ($P = 0.004$), energetic ($P = 0.001$) (*Figure 1*).

At T1 h, a significant difference was found between four groups on the items drowsy ($P = 0.046$), woozy ($P = 0.034$), clumsy ($P = 0.046$) and energetic ($P = 0.044$). Multiple comparisons of means (Scheffé test) did not display significant differences between lorazepam, etifoxine and placebo except for the item energetic: subjects under lorazepam felt significantly more energetic than subjects under 100 mg etifoxine.

At T2 h, ANOVA conducted on visual analog scales values revealed that differences were significant on the item tired ($P = 0.002$), drowsy ($P < 0.001$), woozy ($P < 0.001$) and clumsy ($P < 0.001$). Subjects under lorazepam felt more tired and more woozy than both subjects under etifoxine 50 mg and the placebo group. Moreover, they felt more drowsy and more clumsy in comparison to both etifoxine (50 and 100 mg) and placebo.

At T4 h, ANOVA showed a significant group-effect for the following items: drowsy ($P = 0.008$), woozy ($P < 0.001$),

clumsy ($P = 0.003$) and energetic ($P = 0.004$). Subjects under lorazepam felt more drowsy than subjects under 50 mg etifoxine; they were more clumsy and less energetic than both subjects under 50 mg etifoxine and subjects under placebo. They were also more woozy than subjects under etifoxine (50 and 100 mg) and placebo.

At T6 h, among the values tested, only item 'drowsy' exhibited a significant effect between groups, when submitted to analysis of variance ($P = 0.025$). However multiple comparisons of means (Scheffé test) did not display significant differences between lorazepam, etifoxine and placebo.

Memory tests
Treatment effect was highly significant ($P < 0.001$). Subjects under lorazepam 2 mg had a significantly lower score on immediate and delayed recall than did subjects of the other three groups (*Figure 2*). No significant treatment effect was found at T2 h on either direct digit span or reverse digit span.

DISCUSSION

In line with previous studies [5,19–22], the pattern of results obtained herein shows that significant sedation, psychomotor impairment and anterograde memory deficits occur following a single 2 mg oral dose of lorazepam in healthy subjects.

The subjectively perceived sedative effects and the time course of self-rated sedation scores by subjects under lorazepam were comparable to those reported by several authors [20–24], except for item energetic (subjects under lorazepam felt more energetic than subjects under 100 mg etifoxine, only at 1 h postdose). One explanation might be the paradoxical 'psychostimulant' effect reported by Bourin et al. [25] after low doses of lorazepam in healthy subjects.

Concerning the digit span task, our results replicate those obtained by other experimenters showing a lack of effect of lorazepam [3,4,23,24,26].
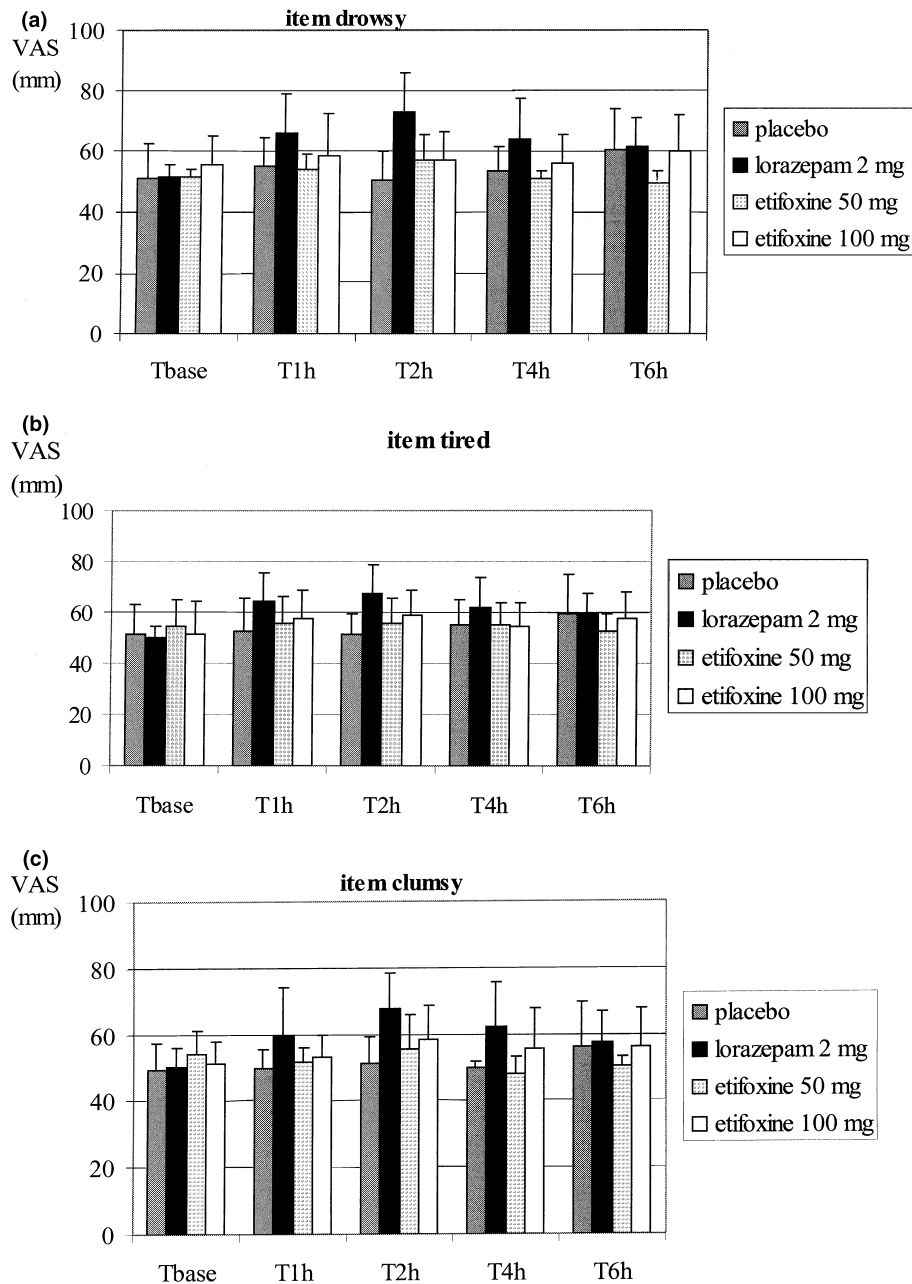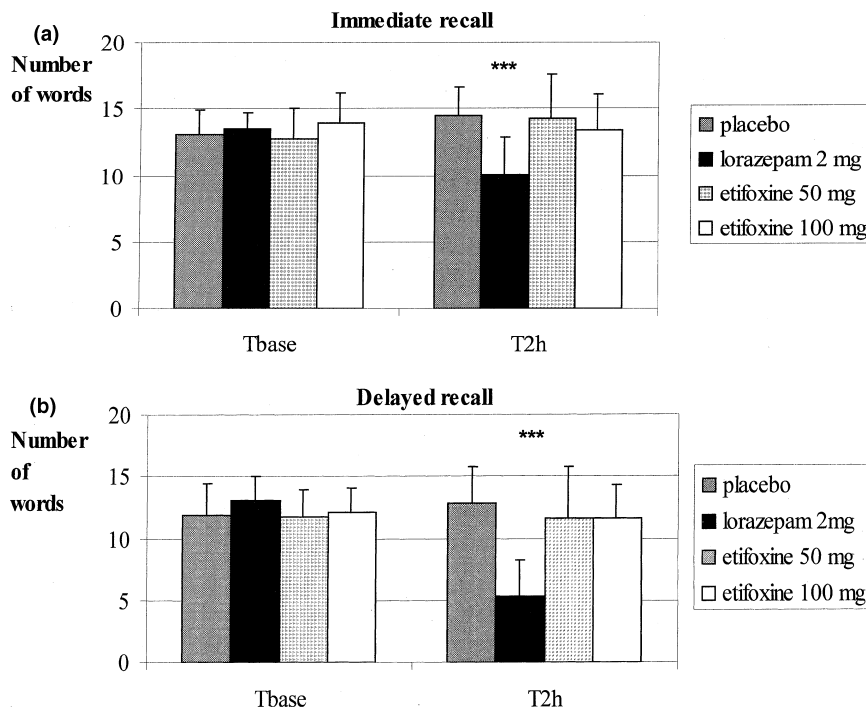
Figure 1 Effects of single oral doses of placebo, lorazepam (2 mg) and etifoxine (50 mg and 100 mg) on the Visual Analogue Scale (items (a) drowsy, (b) tired, (c) clumsy) assessed at baseline and 1, 2, 4 and 6 h postdose.

Verbal free recall, as assessed by word lists, was profoundly impaired and compatible with prior findings, such as those of Lister and File [27] and Curran et al. [19] which suggest that benzodiazepine selectively impairs the acquisition of new information. In the same way, we found similar trends concerning the

effects of lorazepam on psychomotor performance manifested as a lengthening of choice reaction time [12,22,23].

The results observed with lorazepam in this study showed a maximum effect at 2 h postdose for all tasks, which was consistent with previous findings [28,29] and

Figure 2 Effects of a single oral doses of placebo, lorazepam 2 mg and two dosages of etifoxine (50 mg and 100 mg) on memory tests (a) immediate and (b) delayed recall. Results are expressed as mean ± SD. Lorazepam significantly differed from placebo and etifoxine (***$P < 0.001$).

corresponds to the peak of plasma concentrations and pharmacodynamic effects of lorazepam [30].

In contrast, in the present study, etifoxine administered in a single oral dose did not significantly modify objective or subjective indices of psychomotor performance, vigilance and memory functions as compared to both placebo and lorazepam: no significant impairment of reaction time, on memory test and Barrage test performances was noted at different times. Moreover, the lack of impairment due to etifoxine was observed under both dosages (50 and 100 mg) and only one adverse event was reported under etifoxine 100 mg (drowsiness). Pharmacokinetic data for etifoxine reveal that it was rapidly absorbed, with peak plasma levels occurring approximately 2.5 h following administration, similar to that observed with lorazepam. Therefore, evaluations were performed at the peak concentration of both drugs. One hypothesis for this absence of effects might be due to the mechanism of action of etifoxine, i.e pharmacodynamic in nature. Indeed, a recent study investigating the effects of etifoxine has indicated that it facilitates GABAergic synaptic transmission in cultured hypothalamic neurones, and that it appeared to have a dual mode of action on these neurons: a direct positive allosteric modulation of GABA A receptors through a distinct site from that of benzodiazepine, and an indirect effect that might involve the stimulation of peripheral (mitochondrial)–type benzodiazepine receptors known to control neurosteroid synthesis [7].

CONCLUSIONS

In this clinical pharmacology study, the assessment of sedative effects and changes in vigilance, performances, attention and memory was performed with a battery of tests extensively used in psychopharmacology (VAS, CRT, digit span, Barrage test, free and delayed recall of a word list). We replicated sedative and amnesic effects of the benzodiazepine lorazepam. However, our study gave no evidence suggesting single oral doses of etifoxine (50 and 100 mg) has any deleterious effect on objective measurements of vigilance in comparison with lorazepam 2 mg, used as a positive control.

ACKNOWLEDGEMENTS

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