Differential effects of acute diazepam on emotional and neutral memory tasks in acutely hospitalized depressed patients

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Abstract: With the hypothesis that depression affects memory through a mechanism other than that of the benzodiazepines, the present study evaluated the acute effect of diazepam 10 mg upon explicit memory in patients with major depression. A double-blind, placebo (starch 50 mg) controlled experiment was carried out with 19 patients randomly divided into diazepam (n = 10) and placebo (n = 9) groups. They were evaluated by the Mini-Mental State Examination, and tests were conducted for immediate and delayed (short-term) memory with emotionally toned stimuli (negative, positive, neutral), recognition, and semantic memory in visual or auditory modality. The Visual Analog Mood scale (VAMS) was applied to measure anxiety and mood changes after the administration of drugs (30 minutes and 6 hours). Higher scores in the positively toned list among patients who received diazepam were observed, at the 30-minute compared with the 6-hour evaluation. The recall index of positive words in the diazepam group was positive and significantly different from the index of the placebo group. No anterograde amnesia following diazepam was observed. The neural model of a dysfunction of limbic prefrontal cortical structures that impairs the modulation of the amygdala in major depression may explain the present results. Consequently, the action of diazepam on the amygdala, which has been proposed to be the basis of its anxiolytic action, might be altered, modifying the modulation of memory in our patients.

Keywords: major depression, diazepam, emotional memory tasks, amygdala

Introduction

There is extensive evidence that benzodiazepines, the most widely prescribed psychotropic drug class (Greenblatt et al 1983), induce anterograde amnesia in both humans and animals (Lister 1985; Thiebot 1985). The findings of several experiments suggest that the anxiolytic properties of benzodiazepines involve effects mediated by the amygdala. Intra-amygdala injections of benzodiazepines produce anxiolytic effects comparable to those induced by systemic injections (Nagy et al 1979; Scheel-Krüger and Petersen 1982; Shibata et al 1982; Niehoff and Kuhar 1983; Petersen et al 1985). Furthermore, intra-amygdala injections of the benzodiazepine antagonist flumazenil attenuate the anxiolytic effects of systemically administered benzodiazepines (Hodges et al 1987). Recent findings by Izquierdo and colleagues (1990) suggest that benzodiazepine impairment of memory involves GABAergic type A receptors in the amygdala. Post-training intra-amygdala injection of flumazenil causes memory facilitation comparable to that found with systemic injections, and systemic injection of flumazenil before training attenuates the amnestic effects of post-training intra-amygdala injection of muscimol.

Studies examining the memory-modulating effects of drug treatments have provided evidence that memory can be modulated by systemic as well as intra-

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amygdala GABAergic compounds. When administered shortly after training, GABAergic agonists (eg, muscimol and baclofen) impair memory retention, while GABAergic antagonists (eg, picrotoxin and bicuculline) enhance retention (Breen and McGaugh 1961; Brioni and McGaugh 1988; Brioni et al 1989; Castellano et al 1989; Ammassari-Teule et al 1991). On the other hand, there is extensive evidence indicating a key role for GABA neurotransmission in the modulation of fearful/defensive behaviors. It has been found that systemic or intra-amygdala injections of GABA agonists reduce and GABA antagonists enhance experimental fear and anxiety (Graeff 1990). Furthermore, lesions of the amygdala attenuate the antianxiety as well as the memory-modulating effects of GABAergic drugs (Shibata et al 1989; Ammassari-Teule et al 1991). A recent study with magnetic resonance spectroscopy revealed low GABA levels in the occipital cortex of depressed patients, but in vivo GABA(A)-receptor binding activity with benzodiazepine radioligand was not altered. Cortical benzodiazepine binding to GABA(A) receptors has been measured with ^{123}I-labeled flumazenil and single photon emission computed tomography in unmedicated patients with major depression and healthy volunteers (Kugaya et al 2003).

Depression is currently seen as a chronic medical disorder that produces as much functional limitation and morbidity as chronic diseases such as hypertension and diabetes (Angst 1999). One of the most frequent and neuropsychologically well investigated symptoms in depression is reduced memory capacity (Burt et al 1995; Ilsley et al 1995). The condition is thought to result from dysfunctions in monoaminergic systems affecting norepinephrine, serotonin, and dopamine at several effector sites. Disturbances of the limbic–hypothalamic–pituitary–adrenal axis and the serotonin system were found, and changes in adrenoceptors associated with the pituitary–adrenal axis function strongly implicate a disorder in central noradrenergic transmission (Leonard 2000). The effect of corticotropin-releasing factor in modulating the activity of noradrenergic neurons in the locus ceruleus may provide a link between environmental trigger factors and central noradrenergic dysfunction (Leonard 2000).

We hypothesized that depression may affect the amygdala noradrenergic modulation of memory and, through the noradrenergic/GABAergic connection, may modify the anterograde amnestic effect of benzodiazepines. Furthermore, the action of benzodiazepines may block the negative tendency on emotional memory tasks described for depressed patients. The purpose of the present study was evaluation of the effect of diazepam on explicit memory (emotional and non-emotional tasks) in patients with major depression who were not previously receiving benzodiazepines.

Methods

A double-blind, placebo-controlled experiment with diazepam 10 mg (Novaquim-Sigma®) was carried out with DSM-IV Major Depression patients (by certificated psychiatrists) during the first 24 hours after admission in the psychiatric unit of a general university hospital. All patients who fulfilled inclusion criteria during a 12-month period entered the study. The inclusion criterion was a major depression episode (DSM-IV). Exclusion criteria were psychotic symptoms, other psychiatric comorbidity (eg, alcohol and drug abuse), long-term use of benzodiazepines (last 30 days), cognitive deficit, use of tricyclic antidepressants, and previous ECT. Cognitive status was checked with the Mini-Mental State Examination (Folstein et al 1975) with cut-offs 24 and 17 for education of >4 and ≤ 4 years, respectively (baseline Mini-Mental). During this period, 19 patients were included (15 women, age range 25–58 years). Drug groups did not differ in age, education, and sex distributions (Table 1).

All patients signed a written consent after the nature of procedures and objectives of the study were explained. The study was approved by the Research Ethics Committee.

Only patients who were not taking benzodiazepines were selected for the study (before and after hospitalization). Nontricyclic antidepressant drugs were not taken as a reason for exclusion. There were no group differences (diazepam versus placebo) in the dose or type of antidepressant being taken. Patients who presented severe insomnia received promethazine 25 mg, whereas anxiety was behaviorally handled.

All patients were given either placebo (50 mg of starch) or diazepam (10 mg) on the morning of the fourth day

Table 1 Demographic variables and baseline Mini-Mental (MM) of the studied groups; mean and standard deviation (range)

Variable	Diazepam	Placebo	p-value
Age (y)	37.3 ± 9.6 (25–48)	44.2 ± 8.82 (37–58)	0.796[a]
Education (y)	8.9 ± 3.6 (4–15)	5.9 ± 2.8 (2–8)	0.143[a]
Sex (M/F)	2/8	2/7	0.667[b]
MM baseline	27.11 ± 2.32 (23–30)	26.33 ± 2.74 (23–30)	0.589[a]

[a] Student's t-test.
[b] Chi-square (Fisher's test).

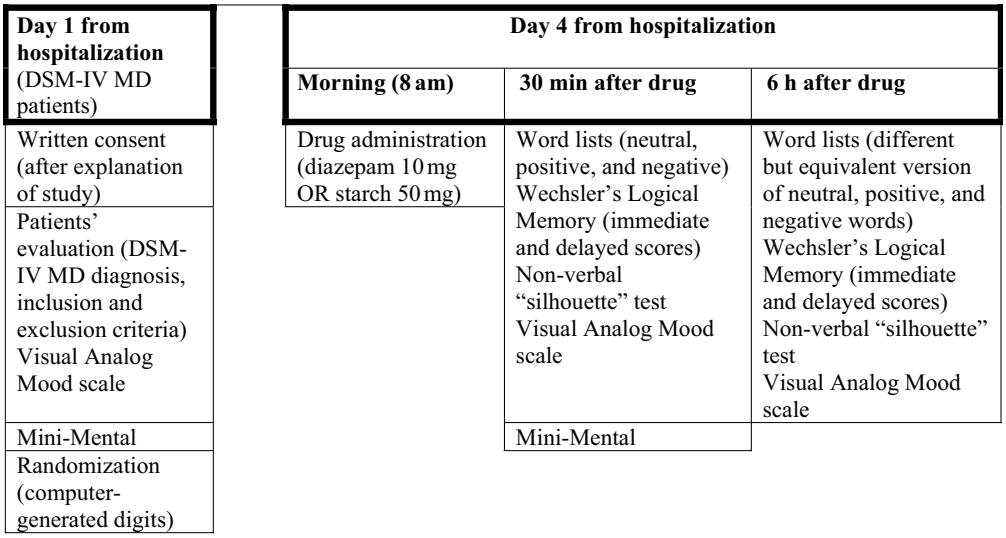

Figure 1 Study procedures and randomization. **Abbreviations:** MD, major depression.

(Figure 1). The drugs were given orally in enteric capsules, and patients were assigned to the two groups by a double-blind design. The medications were specially processed for the experiment in the hospital pharmacy, where they were assembled in identical capsules. Only one member of the team carried out the randomization and kept the codes of identification of the medications. This person was unaware of patient results. Those who applied tests and gave medication to patients did not know which was being administered to each patient, and patients did not know which medication they were receiving.

Thirty minutes and 6 hours after drug or placebo administration, patients were exposed to an emotionally neutral word list, and to two closely matched and emotionally arousing lists – negative and positive (Ceitlin et al 1995). Also administered were the Logical Memory (subtest of the Wechsler Memory scale; a neutral short story) (Wechsler 1973) and the non-verbal "silhouette" test (black images of universally recognized buildings) (Rosat et al 1990). Two sets of equivalent tests (word lists, short story, and silhouettes) were used in the study. The order of presentation of sets was the same for the two groups. The Mini-Mental State Examination was also administered at the 30-minute evaluation. These tests for explicit memory were selected because they evaluate immediate and delayed (short-term) memory, recognition, and semantic memory in visual or auditory modality and were well studied in the population from which the sample was recruited.

The Brazilian Portuguese words were obtained in two studies (Ceitlin et al 1995) for the development of emotionally negative, positive, and neutral lists. The emotional content of the words, effect on other words in mixed lists, and effect of age, education, and symptoms of depression were evaluated before the final lists were achieved. The Portuguese idiom in Brazil still lacks population studies on quantitative linguistics (such as word frequency and age of acquisition). Therefore, the Ceitlin study covered most of these factors for generation of the present word lists.

The effect of the emotionally arousing word lists on a patient's subjective states (mood and anxiety) was evaluated by the Visual Analog Mood scale (VAMS) (Norris 1971), which consists of 16 analog items composed of two adjectives with opposite feelings, separated by a 10-cm line on which the subject has to mark the point which best describes his/her feelings at the time. These items were combined into four factors (anxiety: calm–excited, relaxed–tense, tranquil–troubled; physical sedation: quick-witted–mentally slow, proficient–incompetent, energetic–lethargic, clear-headed–muzzy, gregarious–withdrawn, well coordinated–clumsy, strong–feeble; mental sedation: alert–drowsy, attentive–dreamy; other feelings and attitudes: interested–bored, amicable–antagonistic, happy–sad, contented–discontented) according to a factorial analysis performed on a Brazilian sample (Zuardi et al 1993).

Statistical analysis

All procedures were executed by the Statistical Package for the Social Sciences (SPSS/PC Plus) and EPI-INFO 6.4. Parametric data were analyzed by Student's t-test for independent samples and by multivariate procedures of MANOVA. Categories were tested by analysis of association

(chi-square test with Yates correction or Fisher's exact test). Neuropsychological scores were submitted to a pegboard test (normal probability plot) before being analyzed by MANOVA (either between or within effects). The univariate analysis within the multivariate procedure was family-wise controlled for alpha values, and two-tailed significance values were chosen.

An index of variation (rate) for the word lists was calculated from the recalls at 30 minutes and 6 hours, based on the calculation for rate of forgetfulness (Isaac and Mayes 1999):

$$D = (xi - xii)/xi \quad (1)$$

where xi is the score of recall 30 minutes after drug intake and xii of recall at 6 hours.

This rate may enhance the effect of the intervention because both retrievals occurred after exposure to the list (auditory task); consequently, second recall was more likely to be higher owing to the learning effect. In the case of a positive index, first retrieval was higher than second, expressing a greater effect of the drug than of practice.

Results

Performance on word lists with positive emotional content showed a statistically significant score gradient from 30 minutes to 6 hours after drug administration only in the group of patients who received diazepam (Figure 2). Patients who received diazepam presented higher and more positive indexes for positive words, while negative and neutral words presented negative rates. Patients receiving placebo showed negative rates for the three classes of words. Although not statistically significant, the index negativity was lower for negative and higher for neutral words. We observed a very large standard deviation for recall of neutral words; however, individual scores of this word list were all negative within the diazepam group and both negative and positive within the placebo group. For positive words, the gradient showed the least variation among the diazepam group, significantly less than in placebo patients. These findings may suggest a facilitatory effect of diazepam (10 mg) on the recall of positive words (30 minutes after administration). At the 6-hour evaluation, performance on the positively loaded words decreased to a similar level to that of the placebo group.

The scores of the VAMS were not different within each group ($p > 0.05$) or between groups ($p > 0.05$). Therefore, the significant rate of recall for positively loaded words among diazepam patients could not be explained by lower levels of anxiety or other symptoms. Patients, either

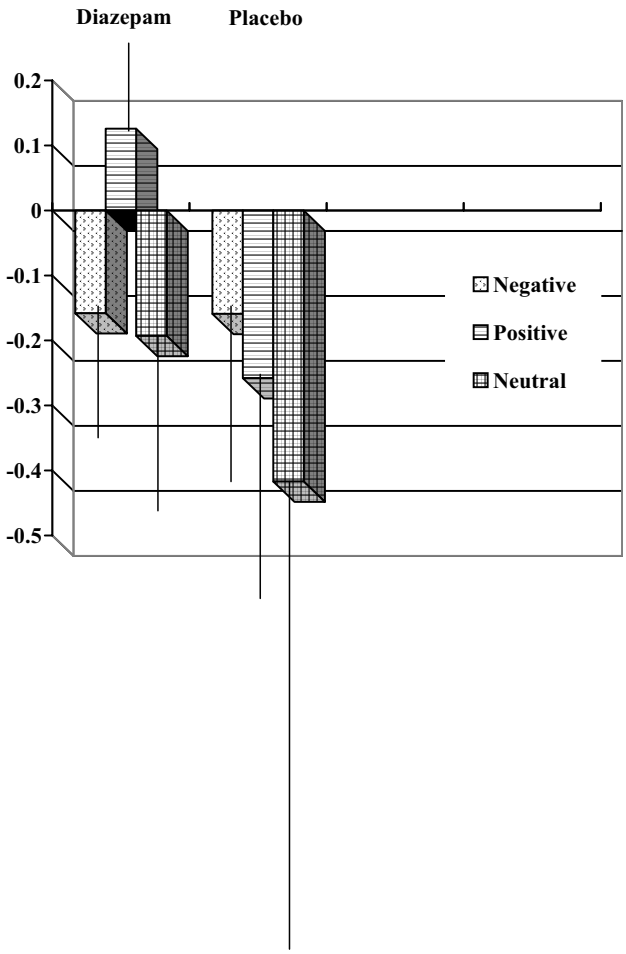

Figure 2 Mean and standard deviation of rate of recall of the word lists emotionally toned (positive, negative, neutral) of patients on diazepam and on placebo.

diazepam or placebo, showed similar levels of symptoms at the two time-points.

No parallel improvement on other immediate recall was seen at 30 minutes relative to 6 hours after dosing (diazepam group). The score of the immediate recall of the short history at 30 minutes was lower than at 6 hours ($p = 0.035$) (Table 2). There was no difference between the immediate and delayed retrievals of this test at 30 minutes after medication ($p = 0.361$). However, at the 6-hour evaluation, immediate recall was higher than delayed ($p = 0.028$).

For the positive word list, the score during the effect of diazepam was higher than 6 hours later ($p = 0.043$). The neutral and the negative lists did not show similar effects ($p = 0.260$ and $p = 0.093$, respectively).

The visual recognition task (silhouette test) showed higher performance at 6 hours than at 30 minutes for the immediate ($p = 0.018$) and delayed ($p = 0.028$) retrievals (Table 2). The effect of practice was probably responsible

Table 2 Mean and standard deviation (range) of scores of tests without emotional content and with immediate (I) and delayed (D) recalls

	Diazepam			Placebo		
Test	**30 min**	**6 h**	**p-value[a]**	**30 min**	**6 h**	**p-value[a]**
Short story I	6.77 ± 1.64 (4–10)	8.57 ± 2.00 (5–10)[b]	0.035	6.66 ± 0.86 (6–8)	8.00 ± 1.120 (7–10)	0.012
Short story D	6.56 ± 1.59 (4–10)	7.44 ± 1.81 (5–10)[b]	0.052	6.78 ± 1.20 (5–8)	8.11 ± 1.05 (7–10)	0.036
Visual recognition I	4.22 ± 1.30 (3–6)	5.89 ± 1.53 (4–8)	0.018	3.89 ± 1.76 (1–6)	5.33 ± 1.58 (3–7)	0.030
Visual recognition D	5.22 ± 1.20 (4–7)	6.57 ± 2.06 (4–10)	0.028	4.44 ± 1.33 (3–7)	5.22 ± 0.97 (3–6)	0.183

[a] Within-group comparison.
[b] $p = 0.028$ (immediate > delayed recall – short story at 6 hours).

for this difference. However, no significant difference was observed for the comparison of the immediate and delayed recalls 30 minutes and 6 hours after drug intake ($p = 0.139$ and $p = 0.234$, respectively).

In the placebo group, the score of immediate recall of the short history at 6 hours after medication was higher than that at 30 minutes ($p = 0.012$), as was the delayed retrieval ($p = 0.036$). There was no significant difference between the immediate and delayed retrievals either 30 minutes or 6 hours after medication ($p = 0.753$ and $p = 0.655$, respectively). Immediate performance in the visual recognition task (silhouette test) after 6 hours was higher than at the 30-minute session ($p = 0.030$). The comparison of performances between immediate and delayed at 30 minutes and at 6 hours ($p = 0.484$ and $p = 0.675$, respectively) and between the delayed recognitions ($p = 0.183$) showed no statistical differences (Table 2).

Discussion

The enhancement of emotionally positive tasks in the diazepam group relative to the placebo group may suggest improvement of the retrieval of information by diazepam. Improvement of retrieval by benzodiazepines has been observed (Izquierdo and Chaves 1988; Chaves et al 1990), and it was hypothesized that the phenomenon would not be a true facilitation of retrieval processes, but the result of reduced interference from items presented after drug administration and thus a secondary consequence of drug-induced amnesia (retroactive interference) (Loftus and Palmer 1974; Chaves et al 1990). Because of the small sample size and the relatively large number of comparisons that were carried out, consideration of our results should take these limitations into account. For that reason, selection of the statistical techniques (analyses and alpha control) was especially careful. Therefore, further investigation with larger samples is mandatory. However, our results are provocative and raise an interesting hypothesis.

Comparisons between diazepam and placebo groups showed no difference on non-emotional memory tests. Patients did not present anterograde amnesia following administration of diazepam; however, this effect has been demonstrated in normal volunteers and animals (Sutton et al 1988; Zuardi et al 1993). Benzodiazepine effects are mediated through the GABA(A) complex by enhancing GABA-induced synaptic inhibition. As the GABAergic system in the amygdaloid complex is a site of action for the anxiolytic effects of benzodiazepines, it has been suggested that benzodiazepines may also influence memory through the amygdala. Lesions in the amygdaloid complex can block diazepam-induced retention deficits, and central and lateral, but not basolateral, amygdala nuclei lesions impaired retention (Tomaz et al 1993). The amygdala is a key structure in the brain's integration of emotional meaning with perception and experience and has been implicated in the pathophysiology of major depression (Drevets 1999; Bremner et al 2000). There is growing interest in understanding brain mechanisms of memory formation for emotionally arousing events, a development closely related to renewed interest in the concept of memory consolidation. There is little doubt that memory for emotionally arousing events is better than for neutral stimuli. This is clearly adaptive, because emotional stimuli, whether pleasant or aversive, are generally more important to species survival (Hamann et al 1999). Most current evidence indicates that the amygdala is not a site of storage of memory processes but plays a key role in modulation of emotional memory for both human (McGaugh et al 1996; Cahill and McGaugh 1998) and nonhuman subjects (Barros et al 1999; Bianchin et al 1999). Long-term, but not short-term, memory has been shown to be enhanced by emotional arousal (Quevedo et al 2003).

Depression may affect the amygdala noradrenergic modulation of memory and, through the noradrenergic/GABAergic connection, may modify the anterograde

amnestic effect of benzodiazepines. Functional neuroimaging studies of the anatomical correlates of familial major depressive disorder and bipolar disorder have identified abnormalities of resting blood flow and glucose metabolism in depression in the amygdala and the orbital and medial prefrontal cortical areas that are extensively connected with the amygdala (Drevets 1999). The amygdala metabolism in major depression and bipolar disorder is positively correlated with both depression severity and stressed plasma cortisol concentrations measured during scanning. Thus, a neural model of a dysfunction of limbic prefrontal cortical structures impairing modulation of the amygdala in major depression, leading to abnormal processing of emotional stimuli, may be considered. Consequently, the action of diazepam on the amygdala, which has been proposed to be the basis of its anxiolytic action, might be altered, modifying the modulation of memory in our patients.

Substantial evidence from animal and human subject studies converges on the view that memory for emotionally arousing events is modulated by an endogenous memory-modulating system consisting, at a minimum, of stress hormones and the amygdaloid complex. Within the normal range of emotions experienced, this system is viewed as an evolutionarily adaptive method of creating memory strength that is, in general, proportional to memory importance (Cahill 1997).

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