1183

The Interactions of Midazolam and Flumazenil on Human Memory and Cognition

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Background: Previous research has been unable to show unequivocally whether flumazenil can reverse completely, partially, or not at all the memory effects of benzodiazepines. The effects of midazolam on implicit memory are also unknown. The behavioral effects of flumazenil by itself, and the acute reversal of benzodiazepine effects, are also controversial. The current study was designed to investigate these questions.

Methods: Using a prospective randomized, double-blind crossover study design, memory was assessed using both direct (free recall and recognition) and indirect (word completion) measures. Other cognitive effects were assessed using the digit symbol substitution task. Sedation and other mood effects were assessed using subjective rating scales. Seventy-two healthy subjects were assigned to three equal groups according to the dose of midazolam received (0, 0.05, and 0.1 mg/kg). Each subject received varying doses of flumazenil (0, 1, and 3 mg) in three sessions, at least 1 week apart. After baseline administration of the tasks, midazolam was administered. The assessments were repeated 20 min later, followed by administration of flumazenil. The assessments were repeated 5 and 30 min after administration of flumazenil. After a 2-h recovery period, delayed memory tests were given.

Results: Both doses of midazolam decreased all scores in the memory and digit symbol substitution tests and mood ratings. Flumazenil reversed both the sedative and the memory effects of the benzodiazepine. The reversal was as complete with the 1-mg dose of flumazenil as with the 3-mg dose. Flumazenil by itself, and the acute reversal of midazolam effects, caused no significant behavioral reactions.

Conclusions: Midazolam impairs explicit and implicit memory. Flumazenil reverses both the sedative and memory effects of the drug. Flumazenil, in the doses used, has no intrinsic actions. (Key words: Anesthetics, hypnotics: midazolam. Antagonists, benzodiazepines: flumazenil. Memory, amnesia: explicit; implicit.)

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MIDAZOLAM, a widely used benzodiazepine, is reputed to produce a striking degree of amnesia compared with other benzodiazepines.[1-2] One aspect of the amnesic effects of the drug that needs to be elucidated is its effects on implicit or unconscious memory. Flumazenil, a specific antagonist of the pharmacologic effects of benzodiazepines, acts by competitive inhibition of binding of these drugs to the central GABA-benzodiazepine receptor complex.[3] Flumazenil alone may have some intrinsic actions,[4-9] but other researchers could not confirm these actions.[10-12] The drug effectively reverses the sedative-hypnotic and psychomotor effects of benzodiazepines, but there is limited and contradictory information regarding the efficacy of reversal of amnesia.[13] The contradictory results are caused by variability in the doses of benzodiazepines and flumazenil used, flaws in the memory tasks, absence of a control group for the benzodiazepine, and absence of pretreatment assessments.

It is important to determine the efficacy of flumazenil in reversing memory impairment produced by benzodiazepines, for the following reasons. First, learning and memory are crucial mental functions. Patients and health professionals should know whether or not information presented after the administration of the antagonist can be retained and recalled. This may be particularly important for ambulatory patients who are discharged from the hospital on the same day of surgery or diagnostic procedures. Second, the issue may also be of medicolegal concern, such as the validity of signing a consent form after treatment with benzodiazepine and flumazenil. Apart from the memory effects, the reversal of benzodiazepine effects has, occasionally, been reported to produce untoward effects.[14,15] However, other studies failed to confirm this.[16,17] Recurrent sedation has also been reported after treatment with flumazenil, because of its relatively short half life.[17]

The current study was designed to assess the memory, cognitive, and mood effects of midazolam, flumazenil, and their combination in healthy young volunteers.

Memory was assessed using both direct (free recall and recognition) and indirect (word completion) measures. Other cognitive effects were assessed using the digit symbol substitution task (DSST), which evaluates changes in attention, focus and visual perception, search and scanning ability, and visuomotor coordination. Sedation and other mood effects were assessed using subjective rating scales.

Materials and Methods

Subjects

There were 72 subjects, 36 men and 36 women. They were paid, healthy volunteers between 18 and 40 yr of age. Subjects were recruited by newspaper advertisements and provided a medical history and information about drug use during a preliminary screening visit. Individuals were excluded if they were taking any medications that could influence the effects of midazolam or flumazenil, if they had used three or more illicit drugs, or if they were heavy users of alcohol or marijuana.

Design and Drug Conditions

Each subject participated in three sessions and received the same dose of midazolam in each session. There were three groups, differing in the dose of midazolam (0, 0.05, and 0.1 mg/kg). Twenty-four subjects were randomly assigned to each group. Each subject received varying doses of flumazenil in his or her three sessions (0, 1, and 3 mg). The order of administration of these doses was counterbalanced within each group, using a Latin Square design. All active drugs and placebos were administered intravenously under double-blind conditions for subjects and research assistants. Randomization schedules and administration of drugs were performed by persons not involved with the conduct of the study.

Procedure

Subjects were tested at intervals of at least 1 week, usually in groups of three. They were instructed not to use caffeine for 4 h before each session, and not to use alcohol, marijuana, or other drugs for 24 h before. They were asked to sleep at least 8 h on the night before each session, and to skip the meal immediately before.

Subjects were tested while reclining on operating room transport carts. After baseline administration of word completion, free recall, picture memory, DSST,

and visual analog scales assessing moods and feelings, midazolam or placebo was administered. The assessments were repeated 20 min later, followed by administration of flumazenil or placebo. The assessments were repeated 5 and 30 min after administration of the second treatment. The assessments at each time took about 12 min. After a 2-h recovery period, delayed memory tests were given. These took about 15 min.

Tasks

Memory Tests. The memory tests consisted of presentation of a list of words, followed by word completion and free recall tests in the specified order. (This fixed order of tests reduced carryover effects more than would have counterbalancing of the tests.) Each of 12 lists consisted of 16 different words. The lists were balanced on word frequency and normative free recall.[18-20] None of the words on these lists had the same initial three letters. For each word on the lists, there were multiple words in the English language that began with the same three letters.

Tape recordings of the lists were presented at a rate of one word every 5 s. In each tape recording, two and four additional words were placed at the beginning and end of the list, respectively. Performance with these words, which were included to reduce primacy and recency effects on recall, were not scored. To encourage subjects to pay attention to the meaning of the words, they were given a test booklet and told to make a rating of how much they liked or disliked the thing denoted by each word on a 5-point scale (ranging from "dislike very much" to "like very much").

Immediately afterward, word completion was administered without explaining its relationship to the preceding list. The subject was given a page containing the first three letters (e.g., "hea") of the 16 words on the previously presented list (e.g., "health"), mixed randomly with 16 other three-letter word beginnings of distinct but comparable "distractor" words. Two variant recordings of each presentation list were used, so that the words serving as distractors and as words from the previously presented list were counterbalanced. For each three-letter word beginning, the subject was asked to write the first word that came to mind beginning with those letters. A maximum of 3.5 min for completion was allowed. Immediately afterward, subjects were asked to recall and write in their test booklet as many of the words as they could from the previous list. They were given 3 min for immediate recall.

GHONEIM *ET AL.*

statistical tests was $P < 0.05$ (adjusted for the numbers of comparisons done using Bonferroni t tests).

Results

Table 1 provides data concerning characteristics of subjects. The groups receiving different midazolam doses did not differ in any of these characteristics, except weight and height, $F(2, 69) = 3.8$ and 3.5, respectively, $P < 0.05$. Followup tests indicated that subjects receiving the high midazolam dose were slightly heavier than those receiving placebo midazolam, and slightly taller than those receiving the low midazolam dose.

The figures show the effects of midazolam and flumazenil for immediate word recall (fig. 1), immediate word completion (fig. 2), immediate picture recall (fig. 3), and mood averaged over all 16 rating scales (fig. 4). The data showed similar patterns for the delayed tests (word recall, word completion, picture recall, and picture recognition), DSST, and mood averaged over sets of four rating scales pertaining to mental sedation, physical sedation, and attitudes or other feelings. The rating scales pertaining to tranquilization were the only exception, and are discussed, along with other minor discrepancies, after describing the general patterns of the data.

General Patterns

ANOVAs. With three inconsequential exceptions, all effects in the ANOVAs (table 2) were significant for all memory tests (*e.g.*, figs. 1–3), DSST, overall mood averaged over all rating scales (fig. 4), and ratings of mental sedation and physical sedation. For attitudes or other feelings, the overall effect of time, and the midazolam × time and midazolam × flumazenil interactions, were significant (table 2), and the data appeared quite similar to that for the other dependent variables.

Effects of Midazolam. Relative to baseline, almost all test scores and mood ratings, except tranquilization, declined at time 2 after administration of both low and high midazolam doses in all flumazenil conditions, *i.e.*,

Table 1. Characteristics of Subjects

	Midazolam Dose		
	High	Low	Placebo
Means ± SE (n = 24)			
Age (yr)	23.8 ± 0.8	24.7 ± 1.0	22.8 ± 0.7
Education (yr)	15.1 ± 0.3	15.5 ± 0.4	14.9 ± 0.3
Weight (kg)	75.6 ± 2.6*	68.7 ± 1.8	67.7 ± 2.2
Height (cm)	178.3 ± 1.7*	172.1 ± 1.7	173.3 ± 1.9
Drug use frequency			
Tobacco (daily)	2.0 ± 0.9	0.4 ± 0.3	0.5 ± 0.3
Alcohol (weekly)	5.5 ± 0.8	2.9 ± 0.6	5.3 ± 1.1
Marijuana (weekly)	0.04 ± 0.03	0.1 ± 0.05	0.05 ± 0.03
Psychedelics (lifetime)	0.3 ± 0.2	0.3 ± 0.2	1.0 ± 0.6
Frequency distributions (numbers of subjects)			
Sex			
Men	12	12	12
Women	12	12	12
Race			
White	24	24	23
Nonwhite	0	0	1
Employment status			
Full-time	6	8	3
Part-time	13	12	15
Unemployed	5	4	6
Student status			
Student	17	18	20
Non-student	7	6	4
Birth control pills (women using)	6	2	3

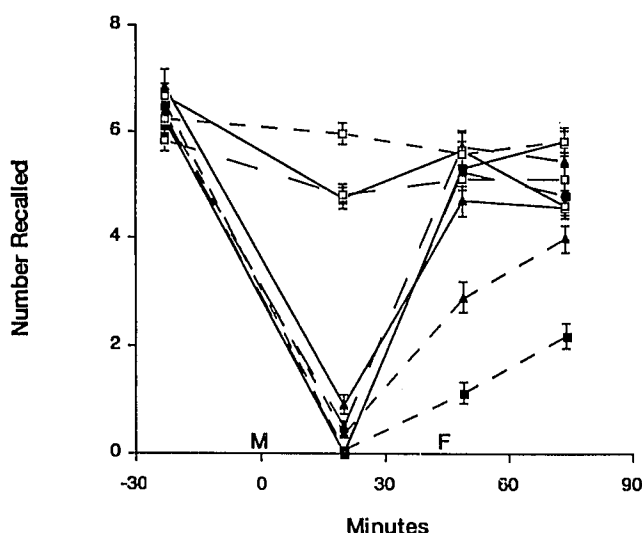* $P < 0.05$. Please see text for explanation.

Fig. 1. Effects of midazolam and flumazenil on immediate word recall. The maximum possible score was 16 words. "M" and "F" indicate the times at which administration of midazolam and flumazenil, respectively, were completed. The former event defines "time 0" on the x-axis. The bars indicate standard errors. The doses of midazolam are indicated as follows: —■— high dose, —▲— low dose, —□— placebo. The doses of flumazenil are indicated as follows: — high dose, — — low dose, - - - placebo.

sessions subsequently involving administration of low, high, or placebo flumazenil doses (figs. 1–4). Comparisons of performance at time 2 after administration of low and high midazolam doses *versus* placebo midazolam, done separately for each flumazenil condition, showed similar patterns.

Reversal of Midazolam's Effects by Flumazenil. In all assessments showing midazolam effects at time 2 (*i.e.*, all except tranquilization), reversal of these effects by flumazenil was almost always complete at time 3, and there was no reemergence of midazolam's effects at time 4 or (for mood ratings) time 5, as evidenced by nonsignificant differences from corresponding values for placebo midazolam at the same time (figs. 1–4).

Time Course of Midazolam's Effects. Sessions involving administration of placebo flumazenil provided information about the time course of midazolam's effects. For the high midazolam dose, scores or ratings remained below baseline levels at both times 3 and 4 in DSST, immediate (fig. 1) and delayed word recall, delayed picture recall and recognition, overall mood ratings (fig. 4), mental sedation, physical sedation, and attitudes or other feelings; and at time 3, but not 4, for immediate (fig. 2) and delayed word completion and

immediate picture recall (fig. 3). With the low midazolam dose, such effects occurred at both times 3 and 4 for immediate (fig. 1) and delayed word recall and delayed picture recall; and at time 3, but not 4, for delayed picture recognition, overall mood ratings (fig. 4), mental sedation, and physical sedation.

The persistence of midazolam's effects was also examined by comparing performance of subjects receiving midazolam *versus* placebo midazolam. Most comparisons (77%) agreed in significance with those described in the preceding paragraph. Except for attitudes or other feelings, all discrepancies were in the direction of greater midazolam effects, *i.e.*, effects with the low dose or at time 4. The mood ratings at time 5 showed no persisting effects of midazolam (fig. 4).

Dose-Related Effects. Reversal of midazolam's effects was virtually as complete with the low flumazenil dose as the high dose.

The high midazolam dose produced greater impairments at time 2 than the low dose in DSST, immediate picture recall (fig. 3), and delayed picture recognition. These effects were significant in all flumazenil condi-
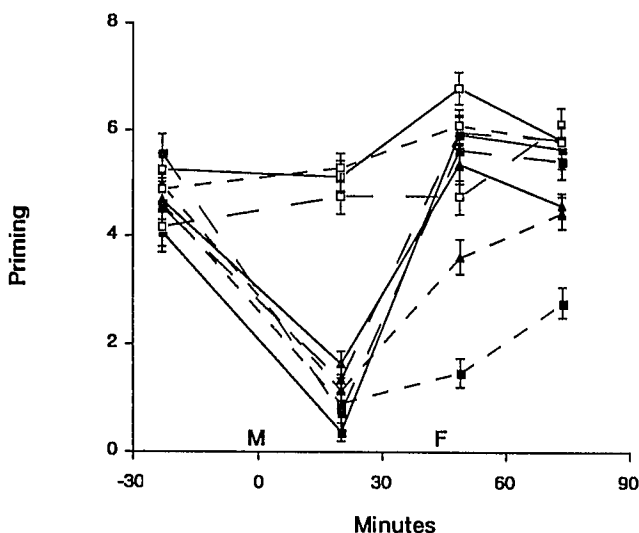
Fig. 2. Effects of midazolam and flumazenil on immediate word completion. The vertical axis represents the priming score, which is corrected for chance performance by subtracting the number of "distractor" words given on the test from the number of words on the previously presented list given on the test. The maximum possible score was 16 words. "M" and "F" indicate the times at which administration of midazolam and flumazenil, respectively, were completed. The former event defines "time 0" on the x-axis. The bars indicate standard errors. The doses of midazolam are indicated as follows: —■— high dose, —▲— low dose, —□— placebo. The doses of flumazenil are indicated as follows: — high dose, — — low dose, - - - placebo.
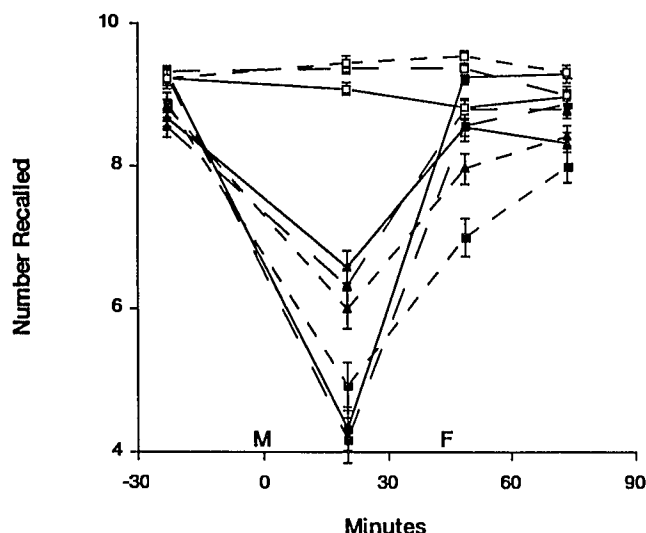
Fig. 3. Effects of midazolam and flumazenil on immediate picture recall. The maximum possible score was 10 pictures. "M" and "F" indicate the times at which administration of midazolam and flumazenil, respectively, were completed. The former event defines "time 0" on the x-axis. The bars indicate standard errors. The doses of midazolam are indicated as follows: —■— high dose, —▲— low dose, —□— placebo. The doses of flumazenil are indicated as follows: — high dose, — — low dose, - - - placebo.

tions except the effect on immediate picture recall in sessions subsequently involving administration of placebo flumazenil.

In sessions involving administration of placebo flumazenil, which permitted analyses of dose-related effects of midazolam in later assessments, such effects occurred at time 3 in immediate (fig. 1) and delayed word recall, immediate word completion (fig. 2), and delayed picture recall and recognition; and at time 4 in immediate word recall (fig. 1) and delayed picture recall.

Independent Effects of Flumazenil. In sessions involving administration of placebo midazolam, which permitted analyses of effects of flumazenil that were independent of midazolam, such effects were negligible.

Correlations of Immediate Word Recall and Word Completion. To determine if tests of implicit and explicit memory were independent, and whether their relationship changed with repeated testing, correlations of immediate word recall and word completion (figs. 1 and 2) were computed separately for each of the 12 tests administered to subjects who received placebo midazolam. These correlations averaged 0.36,

0.32, and 0.26 during the first, second, and third sessions, respectively. Only 33% of these correlations were significant.

Exceptions to General Patterns

Tranquilization. The data for tranquilization differed from that for the other dependent variables. Only the midazolam × time interaction was significant in the ANOVA (table 2). Followup Bonferroni t tests showed no effects of midazolam or changes from baseline levels in subsequent assessments.

Reversal of Midazolam's Effects by Flumazenil. At time 3 after administration of the low flumazenil dose, high or low midazolam doses were associated with poorer DSST performance than placebo midazolam. Some test scores or mood ratings remained below baseline levels after administration of active doses of midazolam and flumazenil. None of these findings provided convincing evidence of incomplete reversal of midazolam's effects by flumazenil, because incomplete reversal was never simultaneously indicated by both comparisons with placebo midazolam and baseline levels.
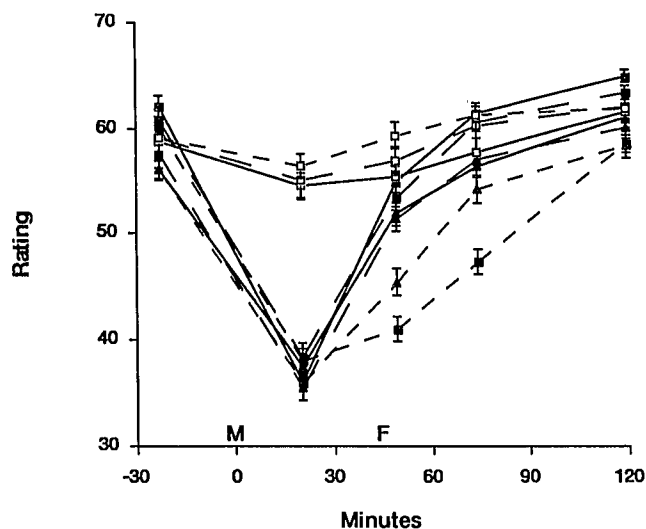
Fig. 4. Effects of midazolam and flumazenil on mood ratings averaged over all 16 rating scales. The range of possible values on each scale was 0 to 100. A decreasing score is associated with increasing effects of midazolam. "M" and "F" indicate the times at which administration of midazolam and flumazenil, respectively, were completed. The former event defines "time 0" on the x-axis. The bars indicate standard errors. The doses of midazolam are indicated as follows: —■— high dose, —▲— low dose, —□— placebo. The doses of flumazenil are indicated as follows: — high dose, — — low dose, - - - placebo.

Table 2. F Tests of Effects in Analyses of Variance

	Midazolam	Flumazenil	Midazolam X Flumazenil	Time	Midazolam X Time	Flumazenil X Time	Midazolam X Flumazenil X Time
Word recall							
Immediate	12.7*	14.1*	13.4*	204.6*	33.6*	9.1*	4.3*
Delayed	1.0	7.1†	8.1*	91.1*	28.1*	9.6*	6.3*
Word completion							
Immediate	10.0*	6.3†	4.5†	45.3*	8.6*	3.7†	1.9‡
Delayed	5.0†	8.8*	4.9†	22.7*	4.0*	4.3*	0.7
Picture recall							
Immediate	17.9*	1.8	2.9‡	98.1*	34.6*	2.2‡	3.1*
Delayed	8.9*	6.0†	5.6*	135.1*	38.6*	13.4*	5.6*
Delayed picture recognition	59.2*	6.9†	3.5†	416.7*	125.5*	10.9*	7.2*
Digit–symbol substitution	12.1*	15.1*	4.3†	201.1*	52.2*	8.4*	4.5*
Mood ratings							
Mental sedation	6.4†	8.6*	6.8*	155.1*	19.7*	5.2*	4.5*
Physical sedation	4.8‡	5.4†	6.0*	128.8*	15.5*	3.6*	2.9*
Tranquilization	0.4	1.4	0.3	2.2	2.5‡	1.9	1.5
Attitudes or other feelings	1.1	3.0	2.5‡	45.6*	5.8*	0.9	1.5
Average overall ratings	5.1†	7.7*	6.7*	133.5*	16.4*	4.5*	3.8*

Values of the F statistics for tests of effects in the analyses of variance described in the text are indicated. For the mood ratings, degrees of freedom are 2 and 69 for midazolam, 2 and 138 for flumazenil, 4 and 138 for midazolam X flumazenil, 4 and 276 for time, 8 and 276 for midazolam X time, 8 and 552 for flumazenil X time, and 16 and 552 for midazolam X flumazenil X time; for all other assessments, degrees of freedom are 2 and 69 for midazolam, 2 and 138 for flumazenil, 4 and 138 for midazolam X flumazenil, 3 and 207 for time, 6 and 207 for midazolam X time, 6 and 414 for flumazenil X time, and 12 and 414 for midazolam X flumazenil X time.

* $P < 0.001$.

† $P < 0.01$.

‡ $P < 0.05$.

Other Exceptions. Results of seven other comparisons were discrepant from the general patterns described above, but none represented major, meaningful discrepancies, because they were isolated; highly restricted with respect to the dependent variable, type of comparison, midazolam dose, flumazenil dose, or time of assessment; and, in many cases, inconsistent with other aspects of the data. Considering the large number of analyses, some of these findings were probably type 1 or 2 errors.

Discussion

We used relatively large doses of midazolam to adequately investigate its effects on implicit memory. We have previously shown that 0.3 mg/kg diazepam spares this form of memory function.[24] (Midazolam may be three to four times as potent per milligram as diazepam.) We also wanted to explore the efficacy of flumazenil in reversing the effects of these doses, and the possible recurrence of midazolam's actions because of

the short duration of action of flumazenil. We also used relatively large doses of flumazenil to avoid the possibility that failure to reverse the amnesic effects of midazolam might be caused by treatment with inadequate doses of the antagonist. We also wanted to explore the possible intrinsic effects of the drug and effects of the reversal of agonists, both of which would be more apparent after larger doses.

Both low and high doses of midazolam produced substantial impairment of memory and DSST performance, as well as substantial sedation and other mood alterations. Midazolam's lack of effect on ratings of tranquilization is consistent with our findings over the years in studies with benzodiazepines,[25,26] and may be explained, in part, by our use of normal subjects with initially low anxiety levels.

In all assessments showing effects of midazolam, flumazenil reversed these effects at time 3, and no subsequent reemergence of these effects was observed. This reversal occurred equally for performance on the DSST and memory tests, and sedation and other subjective effects. Although scores or ratings after admin-

1190

GHONEIM *ET AL.*

istration of flumazenil remained below baseline for some dependent variables, they did not significantly differ from corresponding values in the group receiving placebo midazolam, so it would be difficult to maintain that these findings reflected incomplete reversal of midazolam's effects. Thus, reversal of midazolam's effects by flumazenil was, essentially, complete.

With a single, equivocal exception (delayed word recall, time 4, high midazolam dose), the 1-mg dose of flumazenil was uniformly as effective in reversing midazolam's effects as the 3-mg dose. The lower dose is consistent with current prescribing guidelines.‖ Future studies should investigate the efficacy of lower doses.

Based on the magnitudes of midazolam's effects, times 2, 3, and 4, respectively, can be considered the times of peak effects, and intermediate and late stages of recovery, respectively. The high dose of midazolam affected scores at time 2 more than the low dose for 3 of 13 dependent variables. In sessions involving administration of placebo flumazenil, which permitted analyses of dose-related effects of midazolam at later times, such effects occurred for five and two dependent variables at times 3 and 4, respectively. Thus, dose-related effects of midazolam were more apparent at an intermediate stage of recovery than at the time of peak effects or a late stage of recovery, *i.e.*, speed of recovery was most sensitive to differences in dose. However, floor effects in the verbal memory tests may have contributed to this pattern by making it difficult to distinguish the peak effects of the low and high doses of midazolam.

In addition to impairing recall of words, an indicator of explicit, conscious memory, midazolam reduced priming in word completion, an indicator of implicit or unconscious memory. We previously reported that priming in word completion resisted the memory-impairing effects of diazepam.[24] Three studies by Danion *et al.*[27-29] replicated our finding with diazepam. Weingartner *et al.*[30] also found that triazolam caused marked disruption of free recall and recognition of information presented after its administration in the absence of similar changes in ability to solve word completion problems. Previous studies with lorazepam, however, demonstrated that lorazepam impairs word completion performance, as well as free recall.[29,31,32] Curran and

‖ Physicians' Desk Reference, Medical Economics Data, Montvale, 1993, pp 1996–1999.

Birch[33] and Polster *et al.*[34] found that midazolam also impairs implicit memory in nonplacebo-controlled studies, which make interpretation of the results difficult. (Although Polster *et al.*[34] claim that impairment of savings in identification of pictures is smaller than the impairment of recognition, the analysis supporting this position is not convincing.)

Subjects in the current experiment received 12 immediate word recall and word completion tests, many more than in other studies that were cited. As a result of repeated recall instructions and testing, they may, conceivably, have inferred that they were "expected" to give the words that they had previously heard as responses on the word completion test, turning it into a cued recall test of explicit memory, rather than an assessment of implicit memory. This explanation implies that correlations between word recall and word completion would increase with repetition and be substantial. In fact, these correlations were very modest, and tended, if anything, to decrease in the course of the three sessions. These correlations indicate that word completion continued to function as an assessment of implicit memory throughout the experiment, and that the greater number of repetitions of the tests in the current study, relative to other studies, cannot explain the disparate results.

It is possible that, although different benzodiazepines exert similar effects on explicit memory, they differ in their effects on implicit memory. There is some evidence for distinct neural systems mediating implicit and explicit memory.[35] It is possible that different benzodiazepines may vary in their relative affinity for receptor sites in these distinct brain systems, *e.g.*, in the hippocampus and related structures *versus* posterior cortical structures. Whatever the explanation, one immediate practical result from our study is obvious. Implicit or unconscious memory is part of normal cognitive function, and reflects the activity of computations that are routinely performed during the course of perceiving, recognizing, and remembering in everyday life.[36] As such, a pharmacologic deficit that includes its impairment must be considered as a more severe and pervasive type of cognitive impairment than one in which implicit memory is preserved. Future studies should consider how dosages and concomitant sedative effects of drugs, experimental design, and type of tasks affect the results of implicit memory tests.

Administration of flumazenil alone and after midazolam produced no adverse behavioral effects that could be related to agonist-like or inverse agonist-like

Anesthesiology, V 79, No 6, Dec 1993

actions. Few, minor reactions were observed, e.g., some subjects complained of discomfort during the injection of flumazenil.

The fact that the amnesic effects of benzodiazepines can be reversed by the benzodiazepine antagonist, flumazenil, may indicate that the benzodiazepine receptor complex is involved in modulation of memory. In this study, we found that both the impairments in memory and the subjective measures of sedation were equally antagonized by flumazenil. However, the use of smaller doses (0.5 mg for antagonism of a mean 0.1 mg/kg midazolam dose),[33] or pretreatment with flumazenil before administration of the benzodiazepine,[37] result in dissociation between sedation and memory impairment, i.e., sedative effects of the benzodiazepine were alleviated without relief of a significant memory impairment. Thus, it appears that the amnesia produced by the benzodiazepines is a specific effect, and is not a by-product of sedation.

In summary, midazolam produced marked sedation and pervasive memory impairment. The latter included impairment of implicit memory, word and picture recall, and picture recognition. The dose-response effects of the drug were more apparent in rates of recovery than in magnitudes of peak effects. Flumazenil alone produced no significant behavioral effects, but produced complete reversal of the memory, cognitive, and sedative effects of midazolam. The 1-mg dose of flumazenil was as effective as the 3-mg dose for reversal.

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