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Time Course of Antagonism of Sedative and Amnesic Effects of Diazepam by Flumazenil

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Reversal of the sedative and amnesic effects of intravenous diazepam by the benzodiazepine antagonist flumazenil was investigated in 30 patients undergoing conscious sedation for dental surgery. Verbal memory tasks were administered and patients' subjective ratings of mood were obtained before and after diazepam and then periodically after intravenous administration of flumazenil or placebo under double-blind conditions. Immediate and delayed recall and recognition tests showed that diazepam impaired memory and that flumazenil partially reversed this impairment. The subjective ratings showed that diazepam produced physical and mental sedation and that flumazenil reversed this sedation. The reversal produced a return to presurgery scores for mental sedation but not for physical sedation or memory. For physical sedation, the difference between flumazenil and placebo was not demonstrable for more than 15 min after flumazenil administration; for mental sedation, it was demonstrable for as long as 60 min. The reversal by flumazenil of diazepam-induced memory impairment did not change significantly over time. (Key words: Amnesia. Anesthetics, hypnotics: diazepam. Antagonists, benzodiazepine: flumazenil.)

BENZODIAZEPINES HAVE profound and specific effects on memory. Most notably, the drugs greatly impair ability to learn new information, *i.e.*, they produce anterograde amnesia.[1] They also have anxiolytic, sedative, and hypnotic actions.[2] These properties have proved valuable for hypnosis the night before surgery, preanesthetic medication, induction of anesthesia, and supplementation of nitrous oxide-opioid or ketamine anesthesia. The duration of action of these drugs is, however, rather long, even after single moderately sized doses with individual benzodiazepines, which possess a rapid rate of distribution and/or short elimination half-life.[1,3] This is particularly disadvantageous for patients who are not hospitalized following surgery and diagnostic investigations. Due to variability in responses to benzodiazepines,[4] occasionally patients receive a relative overdose of these drugs. Even in hospitalized patients, excessive sedation and amnesia after surgery or diagnostic procedures are undesirable and interfere with the patients' cooperation with therapeutic regimens. A benzodiazepine antagonist would, therefore, be useful in many situations where drowsiness, sedation, and amnesia need to be antagonized.

Flumazenil, a benzodiazepine antagonist,[5] is currently undergoing clinical trials in this country. This report assesses the reversal of sedation and amnesia produced by intravenous diazepam (Valium) through the use of flumazenil in patients who underwent surgical removal of impacted third molars under local anesthesia.

Methods

PATIENTS

Thirty patients ASA physical status 1 referred to the Oral Surgery Clinic for removal of impacted third molars were studied. Exclusion criteria included: severe pulmonary insufficiency; clinically significant arrhythmias; increased intracranial pressure; seizure disorders; acute narrow angle glaucoma; allergies to benzodiazepines; consumption of benzodiazepines continuously within 2 weeks before the study; pregnancy or nursing; consumption of sedative medications; alcohol or drug dependency; and conditions that impaired the patients' cooperation, *e.g.*, inability to understand instructions for the tests or to use the dominant hand for writing. Patients were randomly allocated to two groups (table 1) with similar characteristics. The sizes of the two groups were unbalanced in order to gain more information about the experimental drug.

DRUG ADMINISTRATION

Conscious sedation was produced by the intravenous injection of diazepam 5 mg per ml, slowly administered until the patients' speech became thickened and slurred while maintaining responsiveness to verbal commands. Supplemental doses were administered later during surgery when indicated to maintain this level of sedation. Local anesthesia was produced by the injection of bupivacaine (Marcaine) 0.5% and lidocaine (Zylocaine) 2%. For testing the antagonist after surgery, ampules containing either flumazenil (0.1 mg per ml) or placebo solution (with the same solvents, *i.e.*, edetate disodium, acetic acid, and sodium chloride) were provided by Hoffmann-La-Roche Pharmaceutical Company. The ampules were labeled only with a code number. The double-blind code was broken only at the end of the study. The test medications were administered intravenously in 2-ml incre-

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TABLE 1. Patient Characteristics and Medications Administered

	Diazepam + Flumazenil	Diazepam + Placebo
Number	19	11
Age (years)	24 ± 1*	23 ± 1
Sex (F/M)	10/9	5/6
Weight (kg)	70 ± 3	69 ± 4
Diazepam induction dose (mg)	19 ± 1	20 ± 2
Total diazepam dose (mg)	34 ± 2	39 ± 2
Time between diazepam induction dose and baseline assessment (min)	55 ± 7	59 ± 4
Test drug solution administered (ml)	7.1 ± 0.5 (.71 mg ± 0.05)	9.3 ± 0.4

* Mean ± SE.

ments each minute up to a maximum dose of 10 ml or until the patient was assessed to have no signs of sedation (as measured by responsiveness to calling the patients name, character of speech, facial expression, and the appearance of the eyes, *e.g.*, ptosis, glazed).

ASSESSMENTS

Memory was assessed by a Verbal Memory Test.[1] Patients heard a different list of 16 nouns at each testing period. The words were presented by a cassette recorder at the rate of one word every 2 s. To ensure comparability across repeated tests, the lists have been equated on factors such as image-evoking ability of the words, their degree of meaningfulness, and their frequency of usage. The words were selected from the Paivio *et al.*[6] norms to have ratings of imagery and concreteness greater than 4.7, ratings of meaningfulness greater than 5.67, and, according to the Thorndike and Lorge[7] norms, frequencies greater than 40 per million. Immediately after the last item in each list was presented, patients were given 2 min to recall and write in any order as many of the words as they could remember.

To test for delayed free recall,[1] at 185 min following treatment with flumazenil or placebo, patients were given 5 min to write in any order as many of the words as they could remember from each of the five lists that they heard before. Delayed recognition was tested by giving patients five pages containing 80 pairs of words. One word of each pair had been presented before, while the other was a distractor. Their position on the right or left side of the page was balanced. The same criteria for choosing the presented words was used for the distractors. Patients were asked to mark the word in each pair that they heard before and to guess if they were not sure.

TABLE 2. Study Schedule

Time (Minutes)	Event
−90	Consent form, history and physical exam, and prestudy assessments.
−45	Administration of diazepam, local analgesia, and performance of surgery.
0	Baseline assessment followed by treatment with test drug.
5	Subjective ratings evaluation.
15	Same as 5-min session.
30	Presentation and immediate free recall of word list, and subjective ratings.
60	Same as 30-min session.
120	Same as 30-min session.
180	Delayed free recall and recognition of all word lists, and subjective ratings.

SUBJECTIVE RATINGS

Patients' ratings of their moods and feelings were measured on 16 scales by drawing a perpendicular line across a horizontal unmarked 100 mm line connecting two adjectives representing the extremes of the condition to be rated, *e.g.*, strong–weak. The position of the perpendicular line was measured in millimeters and used as the score. The 16 adjective pairs, which were derived with modifications from Norris,[8] fell into each of four categories of feelings: mental sedation, *e.g.*, alert–drowsy; physical sedation, *e.g.*, strong–weak; tranquilization, *e.g.*, tense–relaxed; and attitudes or other feelings, *e.g.*, happy–sad, interested–bored.

PROCEDURE

Patients reported to the clinic about 45 min before their scheduled surgery. The research was explained to them and their written consents were obtained as approved by the University Committee on Human Research. Patients were studied one at a time. After obtaining their history and physical examination, prestudy assessments were recorded. Patients were then taken to the operating room, intravenous diazepam was administered, nerve block was done, and the surgery was started. Following the operation, patients were taken to a recovery room located in a quiet area of the building that was designated for use only by patients in this study. The doors of the room were closed to attenuate external sounds and patients were assessed and supervised by the research nurse until discharge. Assessments were done on arrival at the recovery room as a baseline. Then flumazenil or placebo was administered, followed by tests at frequent intervals (table 2).

STATISTICAL ANALYSES

The comparability of the flumazenil and placebo groups before administration of the test drug was checked

by one-way analyses of variance (ANOVAs) on age, weight, diazepam induction dose, total diazepam dose, and the time elapsing between the diazepam induction dose and the baseline assessment. The comparability of the groups' sex distribution was checked by a chi-square test.

To document diazepam-induced impairment and to confirm that it did not differ between the flumazenil and placebo groups before administration of the test drug, performances in the prestudy and baseline assessments were compared with two-way Test Drug × Time ANOVAs. To analyze the effectiveness of the reversal produced by flumazenil, two-way Test Drug × Time ANOVAs were done comparing scores at each assessment time following administration of the test drug, after expressing these scores as improvements (change scores) relative to baseline performance. The ANOVAs for verbal recall also included an additional factor, immediate *versus* delayed recall. In these analyses, the F for drug (flumazenil *vs.* placebo) tested whether the reversal was significant averaged over all post-flumazenil assessment times, and the F for the drug × time interaction tested whether the reversal varied significantly at these different times. Significant interactions were followed up by Bonferroni t tests for each assessment time. In addition, Bonferroni t tests were done to compare performance following flumazenil administration with prestudy performance. A significance level of $P < .05$ was used for all statistical tests.

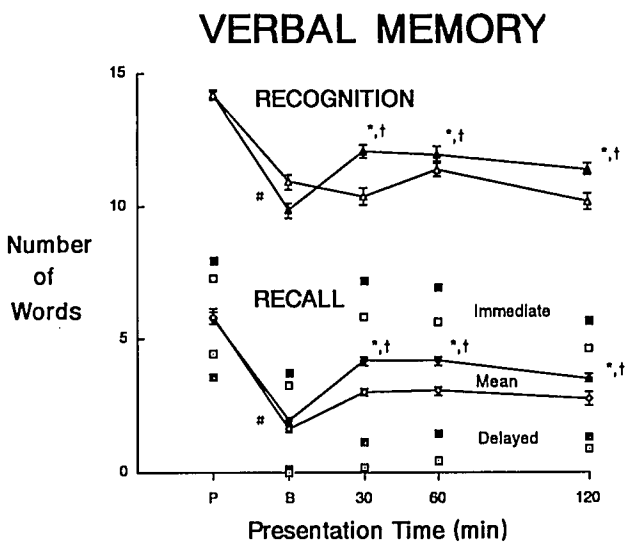

FIG. 1. Effects of diazepam and flumazenil on verbal memory, assessed by immediate and delayed recall and recognition of different 16 word lists. "P" is the time of prestudy testing. "B" is the time of baseline testing before treatment with flumazenil or placebo. The bars indicate standard errors. The plot symbols are as follows: ▲ flumazenil, △ placebo for mean recognition; ♦ flumazenil, ◇ placebo for mean recall (average of immediate and delayed); ■ flumazenil, □ placebo for immediate recall; ◘ flumazenil, ⊡ placebo for delayed recall. Significant ($P < .05$) effects are indicated as follows: # = impairment by diazepam, shown by ANOVA drug effect (see text); * = reversal of diazepam-induced impairment by flumazenil relative to placebo averaged over all post-B assessments, shown by ANOVA drug effect (see text); † = for post-flumazenil assessments, residual difference from P.

Results

Equivalence of Groups

The flumazenil and placebo groups did not differ significantly for age, sex, weight, diazepam induction dose, total diazepam dose, or the time elapsing between the diazepam induction dose and the baseline assessment (table 1). A smaller volume of flumazenil than placebo was administered to patients, as expected considering the double-blind administration procedure used, $P < .05$.

Memory and Mood Assessments

Figure 1 shows the means for verbal memory. Figure 2 shows the mean subjective ratings collapsed over all 16 scales, and table 3 provides the means for the four categories of feelings, *i.e.*, physical sedation, mental sedation, tranquilization, and attitudes or other feelings.

Effects of Diazepam

The memory tests showed declines in performance following diazepam administration, $P < 0.05$. Diazepam affected overall subjective ratings and three of the four categories; following treatment, subjects felt physically and mentally sedated and experienced more negative attitudes, $P < 0.05$. Tranquilization was not affected by diazepam, presumably because the subjects were relatively tranquil at the outset and the intervening dental surgery was not conducive to further tranquilization.

In no case did the diazepam-induced changes in memory or subjective ratings differ significantly for the flumazenil and placebo groups before administration of the test drug. For example, diazepam produced a 53% decline in immediate recall for the flumazenil group compared with a 55% decline for the placebo group. Both the flumazenil and placebo showed a 43% decline in overall subjective ratings following diazepam administration.

Reversal of Diazepam's Effects by Flumazenil

Flumazenil reversed the memory impairment and sedation produced by diazepam. The time course of the reversal differed for memory impairment and sedation and was determined mainly by the time course of recovery from diazepam's effects in the placebo group.

The improvements following flumazenil relative to placebo, averaged over all assessment times, were significant for both the recall and recognition tests, $P < 0.05$

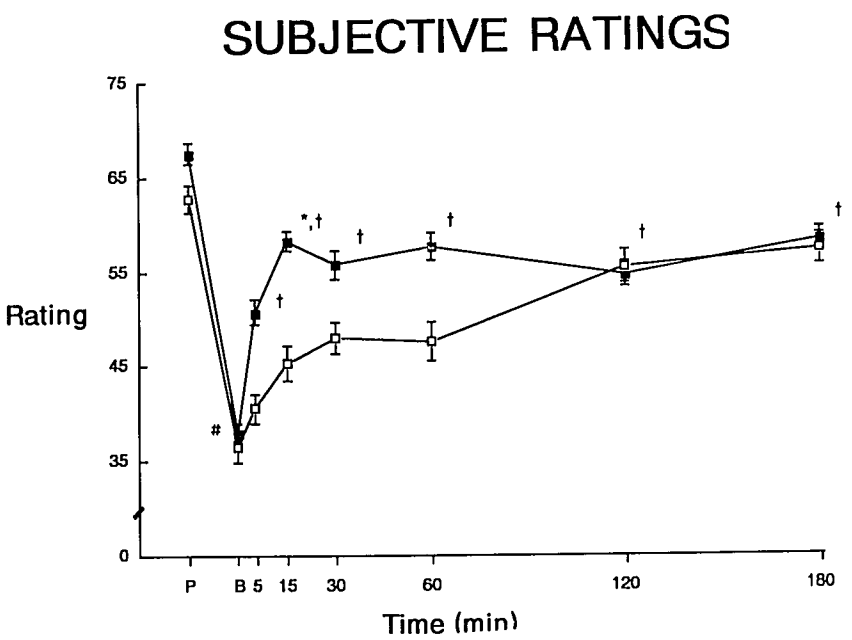

FIG. 2. Effects of diazepam and flumazenil on subjective ratings. The vertical axis represents the mean value of 16 scales. A decreasing score is associated with increasing diazepam effects. "P" is the time of prestudy testing. "B" is the time of baseline testing before treatment with flumazenil or placebo. The plot symbols are as follows: ■ flumazenil, □ placebo. The bars indicate standard errors. Significant ($P < .05$) effects are indicated as follows: # = impairment by diazepam, shown by ANOVA drug effect (see text); * = reversal of diazepam-induced impairment by flumazenil relative to placebo shown by follow-up analyses of the significant ANOVA drug × time interaction (see text); † = for post-flumazenil assessments, residual difference from P.

for drug effects. Immediate and delayed recall did not differ significantly in their sensitivity to the magnitude of the reversal, although delayed recall was much poorer overall than immediate recall and was especially low in the placebo group.

TABLE 3. Mean (SE) Scores for Categories of Subjective Ratings

Time (min)	Mental Sedation	Physical Sedation	Tranquilization	Other Attitudes/ Feelings
Flumazenil				
Prestudy	80 (4)	81 (3)	30 (4)	80 (3)
Baseline	30 (3)†	36 (4)†	28 (3)	59 (3)†
5	57 (5)*†	54 (4)*†	25 (3)	66 (4)†
15	70 (4)*	66 (4)*†	22 (3)	75 (4)
30	64 (5)	64 (5)†	21 (3)	74 (4)
60	66 (6)*	68 (5)	23 (3)	74 (4)
120	62 (5)†	65 (5)†	21 (3)	71 (4)
180	67 (5)	70 (4)	23 (5)	72 (5)
Placebo				
Prestudy	75 (4)	72 (5)	26 (5)	78 (4)
Baseline	33 (6)†	36 (5)†	21 (4)	57 (3)†
5	39 (5)†	37 (5)†	22 (5)	64 (5)†
15	48 (6)†	45 (6)†	21 (4)	67 (5)
30	52 (6)†	49 (5)†	22 (4)	69 (5)
60	48 (8)†	51 (7)†	23 (4)	68 (5)
120	65 (5)	63 (6)	25 (5)	69 (5)
180	69 (6)	66 (6)	23 (4)	70 (5)

All numbers are measurements in mm along a 100-mm line. Other Attitudes/Feelings consist of ratings for sad/happy, hostile/friendly, bored/interested, and withdrawn/outgoing, with lower numbers representing more negative affect. Lower numbers for the other categories represent deeper sedation or tranquilization.

* The increase from baseline ratings is significantly greater for flumazenil than for placebo, indicating reversal of diazepam's effects, $P < .05$.

† The decrease from prestudy ratings is significant, $P < 0.05$.

The drug × time interactions were not significant for recall or recognition, $P > .05$, indicating that the magnitude of the reversal produced by flumazenil did not change over time, *i.e.*, was comparable at 30, 60, and 120 min after flumazenil administration. For example, the immediate recall of the flumazenil group exceeded that of the placebo group at these times by 24%, 23%, and 24%, respectively. However, recall and recognition at each of these times remained below prestudy levels, $P < .05$.

The subjective ratings, in contrast to the memory tests, showed significant declines at later assessment times in the magnitude of the difference between flumazenil and placebo, *i.e.*, the drug × time interactions were significant over all 16 subjective rating scales and for the categories of physical sedation and mental sedation, $P < 0.05$. Because these interactions were significant, follow-up analyses were done. They indicated that both physical and mental sedation were reversed at 5 and 15 min following flumazenil administration (table 3); over all 16 rating scales, the reversal was significant only at 15 min. The physical sedation ratings of the flumazenil group differed from those of the placebo group by 46% and 47% at 5 and 15 min, respectively; the corresponding percentage for mental sedation was 46% at both 5 and 15 min. The difference between flumazenil and placebo in physical sedation was not demonstrable for more than 15 min after flumazenil administration due to recovery from diazepam's effects in the placebo group. Mental sedation, however, continued to show a difference between flumazenil and placebo as long as 60 min after flumazenil administration; the rating of the flumazenil group differed from that of the placebo group by 38% at this time. Moreover,

the ratings for mental sedation at 15 and 60 min increased sufficiently so that they did not differ significantly from prestudy ratings, whereas the flumazenil-induced reversal never produced a complete return to prestudy ratings for physical sedation or over all 16 scales, $P < 0.05$.

The 16 subjective rating scales were also examined individually. The two ratings most discrepant from the others were discontented–contented and troubled–peaceful. These were among the four scales contributing to the tranquilization category, which was not significantly affected by diazepam or flumazenil.

Discussion

The types of memory impaired and spared by diazepam and the mechanisms of impairment have been extensively studied in young healthy volunteers.[9] Few studies have been carried out in patients receiving the drug for treatment of anxiety. It has been suggested by at least two studies[10,11] that subjects with high anxiety may not show amnesia when treated with a benzodiazepine, and may even show an improvement in their memory function. The present study, however, demonstrates that, in patients exposed to a stressful surgical procedure, diazepam impairs memory. Consistent with studies in normal volunteers,[1] diazepam produced an anterograde amnesia for episodic memory tasks; information presented before treatment was adequately recalled, while that presented afterwards was not. The impairment was evident for both recognition and recall tasks, despite the presence of cues in the former task that would prompt memory.[9] The nature, degree, and duration of amnesia are similar to those reported by our group in normal volunteers, using the same route of administration of the drug and similar methods of assessment. The study of normal volunteers also contained a placebo control group.[12]

Diazepam produced both physical and mental sedation. Their degree and duration were similar to those that have been found before in healthy volunteers. The absence of effects of the drug on the tranquilization scales was also similar, and may suggest that patients in the present study were not unduly concerned about the surgery. In a previous study with patients suffering from anxiety,[13] we found that diazepam, even in smaller doses, alleviated anxiety and changed their ratings on the scales.

Review of the literature available to use on the efficacy of flumazenil in reversing memory impairment produced by the benzodiazepines leads us to believe the following.

First, many studies[14–15] assessing the reversal in patients used methods that treat memory as an all-or-none phenomenon (which it is not) or as a unitary process (rather than multiple systems) and lack standardization, reproducibility, quantitation, and ease of statistical analysis. The temporal relationship between presentations of test material, treatments with benzodiazepines and the antagonist, and subsequent recall are also sometimes not adequately specified.[16–17] It, therefore, comes as no surprise that some studies did not show antagonism of the benzodiazepine-induced amnesia by flumazenil.[15,18]

Second, there are some methodologically sound studies assessing the antagonism of benzodiazepine-induced amnesia in healthy volunteers. However, some of their results need confirmation. For example, O'Boyle *et al.*[19] administered diazepam 20 mg concurrently with 200 mg of flumazenil orally, a method unlikely to be used clinically. Indeed, the time of administration of the antagonist in relation to the benzodiazepine is important. Administration of the antagonist before the benzodiazepine results in ineffective antagonism of the amnesia[20] § (alone or with other actions). Some of the tasks that have been used, *e.g.*, a triple associate task,[19] are not commonly used and may not permit easy generalization to more familiar learning situations. Also, some of the studies reported reversal of amnesia, but did not investigate the time course of the reversal.

Flumazenil reversed both the amnesia and sedation induced by diazepam. It produced a return to presurgery levels for mental sedation, but not for physical sedation and memory. However, the magnitude of reversal of diazepam's effects cannot be determined precisely in this study. Even a complete antagonism of the agonist's effects would not eliminate the possible deleterious effects on behavior produced by surgery and/or fatigue. The completeness of the reversal could be clarified by studying volunteers who did not undergo surgery and including a placebo control for diazepam treatment.

Neither the mood scales nor observation of the patients showed unpleasant moods after administration of the antagonist, in contrast to some reports[21] of a sensation of impending death, weeping, etc. Impairment of immediate and delayed free recall and recognition were antagonized. Concomitant physical and mental sedation were also ameliorated. These results are different from those of Hommer *et al.*,§ who suggested that flumazenil blocked the sedative but not the amnesic effects of diazepam. As noted before, their administration of the antagonist before diazepam, an order unlikely to be used frequently in clinical practice, may have contributed to separation of effects of the benzodiazepine. Nevertheless, the results of Hommer *et al.*§ are interesting from a theoretical viewpoint, because they demonstrate that benzodiazepine-induced amnesia is a specific effect on memory and is not dependent on

§ Hommer DW, Breier A, Paul SM, Davis M, Weingartner H: Ro15-1788, a specific benzodiazpine antagonist, blocks the sedative, anxiolytic and attentional, but not amnesic, effects of diazepam in humans. Abstracts of the 25th American College of Neuropsychopharmacology Annual Meeting in Washington, D. C., Page 204, 1985

the concomitant generalized sedation experienced by subjects. Our present finding of a difference between amnesia and sedation in the time course of flumazenil's effects also supports this proposition. Future studies should address the issue of whether the reversal of the benzodiazepine-induced amnesia and sedation can be increased and prolonged by changes in the dose, route, and/or method of administration of flumazenil.

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