Effect of Intravenous Flumazenil on Reversal of the Central Effects of Midazolam Used with Short-Acting Opioids for General Anesthesia in Hospitalized Patients: Report of a Multicenter, Double-Blind Clinical Study

*The Flumazenil in General Anesthesia in Hospitalized Patients Study Group I**

ABSTRACT

Midazolam, a short-acting benzodiazepine central nervous system (CNS) depressant widely used for the induction and maintenance of general anesthesia, is often supplemented with short-acting opioids for general anesthesia. Administered postoperatively, flumazenil, a specific benzodiazepine antagonist, reverses the CNS sedative effects of midazolam. In a double-blind clinical trial in hospitalized patients, flumazenil, administered postoperatively at an average intravenous dose of 0.89 mg (range: 0.4 mg to 1 mg), was more effective than placebo in reversing sedation and other residual effects of benzodiazepines in patients recovering from general anesthesia induced by midazolam (mean dose 29 mg) in conjunction with fentanyl (mean dose 0.4 mg) or sufentanil (mean dose 0.056 mg). Five minutes posttreatment, 87 (83%) of 124 flumazenil-treated patients and 6 (10%) of 60 placebo-treated patients had attained the criterion response for reversal of sedation. Of these patients, 60% in the flumazenil group, compared with 100% in the placebo group, retained their degree of alertness throughout the 3-hour observation period. Between-group differences were significant until 60 minutes posttreatment, when the effect of the benzodiazepines had spontaneously waned in the placebo group. The Physician's Global Efficacy Rating, providing an overall measure of efficacy 5 minutes after test drug administration, was good or excellent for 86% of the flumazenil-treated patients, as compared with 7% of the placebo-treated patients evaluated. Measurements of psychomotor function and memory also showed significant between-group differences. Flu-

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INTRODUCTION

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INTRODUCTION

Flumazenil, a specific benzodiazepine antagonist, blocks the central effects of benzodiazepines by competitive interaction at the receptor site.[1-3] Results of controlled clinical trials[4-9] have demonstrated that flumazenil, at mean doses ranging from 0.4 mg to 1 mg, is effective in antagonizing the residual sedative effects of midazolam in the majority of patients within 5 minutes after intravenous (IV) administration. Differences in response to tests for sedation were statistically significant between flumazenil-treated and placebo-treated groups of patients, and the significant difference usually persisted for at least 60 minutes after administration. Other studies[10-13] have shown that flumazenil is safe and well-tolerated.

This multicenter, double-blind, placebo-controlled study was designed to assess the efficacy and safety of IV flumazenil used for the reversal of the sedative effects of midazolam administered in conjunction with a short-acting opioid. The subjects were hospitalized patients undergoing a variety of procedures that required general anesthesia.

PATIENTS AND METHODS

Patients

Six surgical centers that could contribute a variety of operative procedures were selected for the study. The local institutional review board of each of the centers approved the protocol. Informed consent was obtained from each patient before entry into the study.

Hospitalized patients scheduled to undergo surgical procedures that required general anesthesia and who met the American Society of Anesthesiologists (ASA) Physical Status Classification 1, 2, or 3 were eligible for participation in the study. Excluded were patients scheduled for major operative procedures (eg, thoracic, vascular, abdominal, or neurosurgery) that might have compromised the efficacy and safety assessments. Also excluded were patients with clinically significant coronary artery disease, increased intracranial pressure, or a history of alcohol or drug dependence, including benzodiazepines, and pregnant patients except those whose pregnancy was to be terminated during the procedure.

Twice as many patients were randomly assigned to receive flumazenil postoperatively as were assigned to receive placebo.

Methods

All patients received midazolam and a short-acting opioid (fentanyl or sufentanil) to induce and maintain general anesthesia. The investigators were requested to rely more on the use of midazolam, nitrous oxide, and the volatile anesthetics than on the use of opioids during the operative procedure to minimize potential residual sedative effects that would not be antagonized with flumazenil.

The test drugs were supplied by Hoffmann-La Roche Inc., Nutley, NJ. Each 10-ml ampule contained 0.1 mg/ml

of flumazenil in aqueous solution or 10 ml of placebo. Test drug administration was titrated in 2-ml increments at 1-minute intervals until either the patient reached the desired level of responsiveness (slightly drowsy or fully alert) or a maximum of 10 ml (equivalent to 1 mg flumazenil) had been administered.

Efficacy Assessments

The primary efficacy variable for the evaluation of sedation was the Observer's Assessment of Alertness/Sedation (OAA/S),[14] specifically developed for the flumazenil program to aid in the evaluation of a patient's alertness. Secondary measurements of efficacy included the Finger-to-Nose Test[15] (measuring psychomotor function), the Picture Recall Test[16] (measuring memory), and the Physician's Global Efficacy Rating[17] (used as an overall measurement of efficacy).

Pretreatment assessments of sedation (OAA/S) and psychomotor performance (Finger-to-Nose Test) were conducted prestudy (before the operative procedure) and at baseline (following the procedure and immediately preceding test-drug administration). Baseline assessments were not started until the concentrations of volatile anesthetics had decreased to <0.1% at 1 atmosphere ambient pressure and there was no excessive residual effects of muscle relaxants. Posttreatment assessments of sedation and psychomotor performance, using the aforementioned tests, were made 5, 15, 30, 60, 120, and 180 minutes after the administration of flumazenil or placebo. The Picture Recall Test for picture cards shown at prestudy, baseline, and 5, 15, 30, and 60 minutes posttreatment was performed at the 180-minute assessment. The Physician's Global Efficacy Rating was made at the 5-minute evaluation.

The OAA/S Scale used to assess the depth of sedation is composed of four categories: responsiveness (with possible scores of 1 to 5), clarity of speech (with possible scores of 2 to 5), aspects of facial expression, and eyes (each with possible scores of 3 to 5). The OAA/S composite score, with a range of 1 to 5, corresponded to the lowest score recorded for each individual in any category during that evaluation period. A score of 1 indicated that the patient was in a deep sleep, and a score of 5 designated a patient who was fully awake and alert. In addition to providing an instrument for the assessment of response, the OAA/S Scale was used during titration of the test drug to determine whether the patient had reached the criterion level of alertness (score of 4 or 5), at which time drug administration was discontinued.

The primary measurement used to determine the clinical efficacy of flumazenil was the change in OAA/S score from baseline (immediately preceding test drug administration) to the 5-minute posttreatment assessment. This variable was considered the most relevant objective indicator of the success of benzodiazepine antagonism. Any subsequent decline in the OAA/S after a 5-minute response was considered resedation.

The Finger-to-Nose Test was used to measure psychomotor function at each assessment by means of a 4-point scale (4 = normal, 3 = mild impairment, 2 = moderate impairment, 1 = severe impairment, and 0 = patient too sedated to perform the test). The percentage of patients with a criterion level of psychomotor recovery (score of 3 or 4) at the 5-minute

assessment was considered ment of efficacy.

The Picture Recall Test, the 180-minute assessment patient to recall pictures t shown in random sequen times before and after test tration. A different picture object (eg, tree, book) was dom sequence at each ass prestudy through 60 min ment. At 180 minutes, th asked to recall, in any orde that had been displayed.

The Physician's Global ing provided an overall r ficacy of the test drug 5 administration. A 4-point cellent, 3 = good, 2 = n 1 = insufficient) was used investigator's general clini

Safety Evaluations

Adverse experiences were recorded throughout assessment period. For e perience, the investigator sessment of the severity (r or severe) and the relatio drug (unrelated or remot probably related).

Vital signs were charte ment. These included s stolic blood pressure, respiration rate.

Data Analysis Method

Patients who had pre violations that would in cacy ratings (such as rec opioids during the post

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The Picture Recall Test, performed at the 180-minute assessment, required the patient to recall pictures that had been shown in random sequence at various times before and after test drug administration. A different picture of a familiar object (eg, tree, book) was shown in random sequence at each assessment from prestudy through 60 minutes posttreatment. At 180 minutes, the patient was asked to recall, in any order, the pictures that had been displayed.

The Physician's Global Efficacy Rating provided an overall measure of efficacy of the test drug 5 minutes after administration. A 4-point scale (4 = excellent, 3 = good, 2 = moderate, and 1 = insufficient) was used, based on the investigator's general clinical impression.

Safety Evaluations

Adverse experiences of all patients were recorded throughout the 180-minute assessment period. For each adverse experience, the investigator recorded an assessment of the severity (mild, moderate, or severe) and the relationship to the test drug (unrelated or remotely, possibly, or probably related).

Vital signs were charted at each assessment. These included systolic and diastolic blood pressure, heart rate, and respiration rate.

Data Analysis Methods

Patients who had predefined protocol violations that would invalidate the efficacy ratings (such as receiving additional opioids during the postoperative period) were removed from the efficacy analyses from the time of the violation. No patient who received the test drug and had at least one posttreatment evaluation was excluded from the analysis of safety.

Four types of analyses were performed, depending on the nature of the variable. For most efficacy and safety variables, the change from prestudy or baseline scores to values at postadministration assessment periods were calculated. Changes from baseline reflected the extent of reversal produced by test drug administration and were analyzed by means of an analysis of variance (ANOVA) to compare differences between treatment groups. The ANOVA tested the null hypotheses that (1) the mean changes from baseline in the OAA/S and (2) the mean scores of the Physician's Global Efficacy Rating were equal in the two treatment groups. The Mantel-Haenszel Test[18] or the two-sided Fisher's Exact Test was used for analysis of the percentage of patients in each treatment group who accurately performed the Picture Recall Test.

Data presented without statistical analysis include (1) the percentage of patients who had complete, partial, or no reversal of sedation (OAA/S) at the 5-minute assessment, (2) the percentage of patients who had a complete response on the Finger-to-Nose Test at the 5-minute assessment, and (3) the percentage of patients who became resedated.

Resedation was defined as a reduction in the OAA/S score after a criterion response had been achieved. Partial resedation was defined as a reduction in OAA/S score to a level higher than the baseline level, compared with a reduction in OAA/S score to or below the baseline level (complete resedation).

RESULTS

A total of 184 patients were enrolled in this study. Of these, 124 were randomly assigned to the flumazenil group and 60 were assigned to the placebo group. The demographic and other characteristics of the patients in each treatment group were similar (Table I).

All patients were given either fentanyl or sufentanil in addition to midazolam for the induction and maintenance of general anesthesia. The mean doses of these drugs, which were adjusted according to each patient's need, are listed in Table II. The mean dose of midazolam (28.9 ± 12 mg) is somewhat higher than usual because of the request to rely more on the use of midazolam, nitrous oxide, and the volatile anesthetics, instead of narcotics, during the operative procedure.

Other perioperative medications were administered before or during the procedure but before the test drug. These included isoflurane and other inhalation agents, muscle relaxants and their antagonists, and other medications given for the treatment of adverse experiences resulting from the operative procedure or the medications given during the procedure. Each of these medications was administered to a similar percentage of

Table I. Patient characteristics.

	Flumazenil (n = 124)	Placebo (n = 60)
Sex (M/F)	56/68	28/32
Age (yr)		
Mean	40.7	41.0
Range	16–75	18–70
Weight (kg)		
Mean	71.3	70.2
Range	44–100	40–100
ASA class (n)		
1	68	24
2	53	33
3	3	3
Procedures (n/%)		
Gynecologic	44/36%	21/35%
Orthopedic	38/31%	23/38%
General surgery	29/23%	8/13%
Genitourinary	4/3%	3/5%
Miscellaneous*	9/7%	5/9%

*Includes plastic, neurologic, ear-nose-throat, ophthalmologic, and dental surgery.

Table II. Medications u

Midazolam
(% of patients)
Mean dose (mg)
Opioids
Fentanyl
(n/% of patients)
Mean dose (mg)
Sufentanil
(n/% of patients)
Mean dose (mg)

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Table II. Medications used to induce and maintain general anesthesia.

	Flumazenil (n = 124)	Placebo (n = 60)
Midazolam		
(% of patients)	100	100
Mean dose (mg)	28.9	26.3
Opioids		
Fentanyl		
(n/% of patients)	81/65%	38/63%
Mean dose (mg)	0.4	0.4
Sufentanil		
(n/% of patients)	43/35%	22/37%
Mean dose (mg)	0.056	0.067

Placebo (n = 60)
28/32
41.0
18–70
70.2
40–100
24
33
3
21/35%
23/38%
8/13%
3/5%
5/9%

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patients, at similar dosages, in each treatment group.

The test drug was injected intravenously to all sufficiently sedated patients (predefined as an OAA/S score ≤3) in 2-ml increments until the criterion level of sedation (OAA/S score ≥4) was attained or until a total of 10 ml of drug had been administered. All of the placebo-treated patients received the maximum dose of 10 ml, whereas 38% of flumazenil-treated patients attained a criterion response with 0.2 to 0.8 mg of flumazenil. The mean effective dose of flumazenil was 0.89 mg (8.9 ml), compared with 10 ml of placebo. The distribution of doses of flumazenil and placebo are presented in Table III.

Efficacy

Nineteen flumazenil-treated patients and one placebo-treated patient were eliminated from all efficacy analyses because of violations stipulated in the protocols. Additional patients had missing assessments or other protocol violations that invalidated their data from the analysis. These exclusions and missing data account for the variations in the total numbers of patients at each observation time.

Sedation (OAA/S Scale)

The mean level of alertness among flumazenil-treated patients increased to the OAA/S criterion score of 4 immediately after flumazenil administration, as shown by the mean 5-minute assessment score depicted in Figure 1. On the other hand, the mean OAA/S scores for the placebo group did not reach the criterion response level until 60 to 120 minutes after test drug administration. Both groups showed increasing alertness through the final 180-minute assessment period.

The mean change in OAA/S score from baseline to the 5-minute assessment, designated as the primary measure of efficacy for the reversal of benzodi-

Table III. Distribution of test drug doses.

	Flumazenil (n = 124)		Placebo (n = 60)	
Dose (ml)*	n	%	n	%
4	1	1	0	0
6	19	15	0	0
8	28	23	0	0
10	76	61	60	100
Mean (ml)	0.89		10	

*Flumazenil concentration = 0.1 mg/ml.

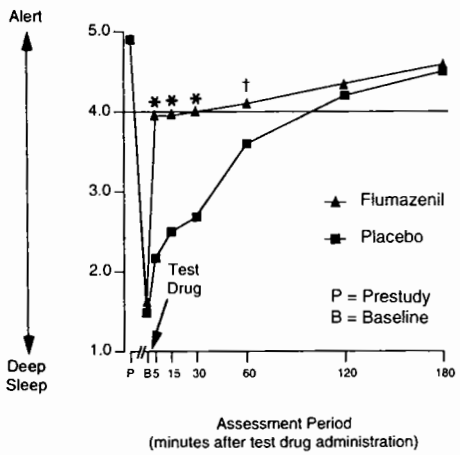

Figure 1. Mean scores on the Observer's Assessment of Alertness/Sedation Scale. *$P<0.01$, †$P<0.05$, between-treatment comparisons of change from baseline.

azepine-induced sedation by flumazenil, is shown in Table IV, which includes the statistically significant between-group differences in mean changes in OAA/S scores at all assessment periods. These data demonstrate that flumazenil was effective in reversing sedation from 5 minutes through 60 minutes. After that time, spontaneous recovery was apparent in the placebo-treated patients, and between-group differences were no longer significant.

Table IV. Posttreatment ch

Mean baseline
Change from baseline scores
posttreatment:
5 min
15 min
30 min
60 min
120 min
180 min

*The OAA/S is scored from 1 to
approximate mean score can be
†$P<0.01$; ‡$P<0.05$: Statistical
F-test).

Rate of Response. A lar
of flumazenil-treated pa
n = 87) attained the criterio
reversal of sedation (OAA
at the 5-minute assessm
placebo-treated patients (1
shown in Figure 2. Only
treated patient had no c
OAA/S score at the 5-n
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Resedation Rate. It was
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Table IV. Posttreatment changes from mean baseline OAA/S score.*

	Flumazenil	Placebo	Treatment Difference
Mean baseline	1.7	1.7	
Change from baseline scores posttreatment:			
5 min	+2.3	+0.54	1.7†
15 min	+2.3	+0.90	1.4†
30 min	+2.3	+1.2	1.2†
60 min	+2.4	+1.9	0.47‡
120 min	+2.6	+2.5	0.05
180 min	+2.8	+2.8	0.00

*The OAA/S is scored from 1 to 5, with 1 representing deep sleep and 5 representing full awakening. The approximate mean score can be determined by adding the mean change score to the baseline score.
†$P<0.01$; ‡$P<0.05$: Statistical significance of between-treatment comparison of mean changes (two-sided F-test).

Rate of Response. A larger percentage of flumazenil-treated patients (83%, n = 87) attained the criterion response for reversal of sedation (OAA/S score ≥4) at the 5-minute assessment than did placebo-treated patients (10%, n = 6), as shown in Figure 2. Only 1 flumazenil-treated patient had no change in the OAA/S score at the 5-minute assessment, compared with 34 (58%) placebo-treated patients. Analyses of demographic characteristics, including age, sex, and body mass, indicated no correlation between these characteristics and the response rate of patients.

Resedation Rate. It was expected that a percentage of patients alert at the 5-minute assessment might become resedated during the 180-minute study because flumazenil has a shorter elimination half-life than midazolam. Eighty-six of the 87 flumazenil-treated patients who were alert at 5 minutes could be evaluated at all of the subsequent posttreatment evaluations, and 52 (60%) of these patients had no decrease in the OAA/S score. Of the remaining patients in the flumazenil group, 31 (36%) had decreases in the OAA/S score that did not reach baseline levels, and 3 (3%) of the patients had decreases to the baseline score. In the placebo-treated group, all 6 patients who were alert at the 5-minute assessment maintained their OAA/S scores throughout the 180-minute observation period. Thus the effect of flumazenil was maintained in most patients despite the fact that two thirds of them had received potentially sedating medications (for treatment of operative-site pain or adverse experiences) after the 5-minute assessment.

Psychomotor Impairment (Finger-to-Nose Test)

Flumazenil-treated patients demonstrated better psychomotor function than

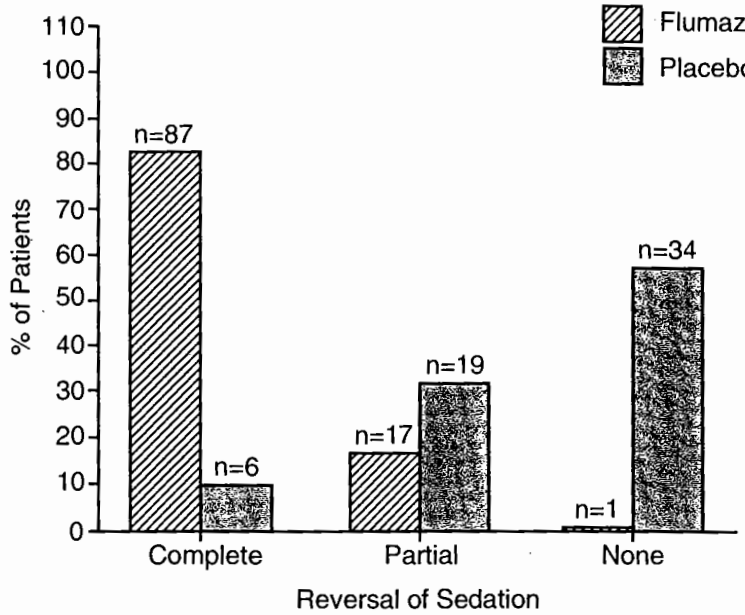

Figure 2. Responses on the Observer's Assessment of Alertness/Sedation at the 5-minute assessment.

did placebo-treated patients from the 5-minute assessment through the 120-minute assessment (Figure 3). Between-group differences in the magnitude of mean change from baseline score were statistically significant ($P<0.05$) from the 5-minute assessment through the 60-minute assessment (Table V), by which time placebo-treated patients demonstrated spontaneous recovery. Both treatment groups had a normal level of performance (score = 4) at the prestudy assessment and demonstrated severe impairment (score ≤1) at the baseline assessment. At the 5-minute assessment, 64 (64%) of flumazenil-treated patients performed the Finger-to-Nose Test at or near a normal level (score of 3 or 4), whereas only 4 (7%) of placebo-treated patients had attained this level of response. The placebo group did not attain normal function until at least 120 minutes posttreatment.

Amnesia (Picture Recall Test)

At the 180-minute assessment, a higher percentage of flumazenil-treated patients than placebo-treated patients correctly recalled the pictures shown to them at each earlier assessment period (Figure 4). Between-treatment comparisons of these percentages were statistically significant at the $P<0.01$ level at the 5-, 15-, and 30-minute assessments and at the $P<0.05$ level at the 60-minute assessment. However, reversal of midazolam-induced amnesia was incomplete in both treatment groups, with fewer than 35% of flumazenil-treated patients and fewer than 15% of placebo-treated patients re-

Figure 3. Mean scores
2 = moderate
aroused). *
baseline.

Table V. Posttreatment

Mean baseline	
Change from baseline sc	
posttreatment:	
5 min	
15 min	
30 min	
60 min	
120 min	
180 min	

*The Finger-to-Nose Test
representing normal perfo
†$P<0.01$: Statistical signi

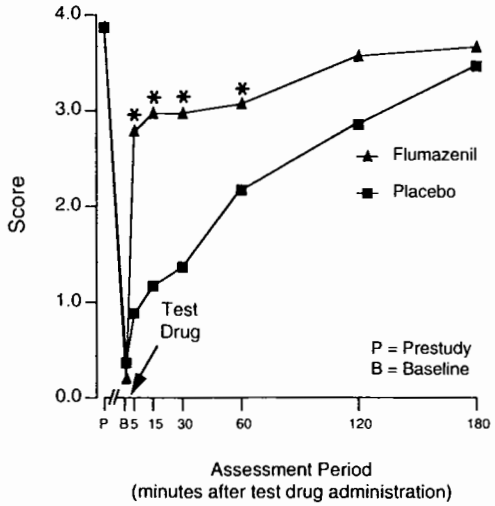

Figure 3. Mean scores on the Finger-to-Nose Test (4 = normal; 3 = mildly abnormal; 2 = moderately abnormal; 1 = severely abnormal; 0 = patient could not be aroused). *$P<0.01$, between-treatment comparisons of changes from baseline.

Table V. Posttreatment changes from mean baseline Finger-to-Nose Test score.*

	Flumazenil (n = 105)	Placebo (n = 55)	Treatment Difference
Mean baseline	0.5	0.5	
Change from baseline scores posttreatment:			
5 min	+2.3	+0.7	1.6†
15 min	+2.7	+1.1	1.5†
30 min	+2.7	+1.5	1.2†
60 min	+2.8	+2.2	0.7†
120 min	+2.9	+2.8	0.2
180 min	+3.3	+3.2	0.05

*The Finger-to-Nose Test is scored from 1 to 4, with 1 representing severe psychomotor impairment and 4 representing normal performance (0 = too sedated to perform test).
†$P<0.01$: Statistical significance of between-treatment comparison of mean changes (two-sided F-test).

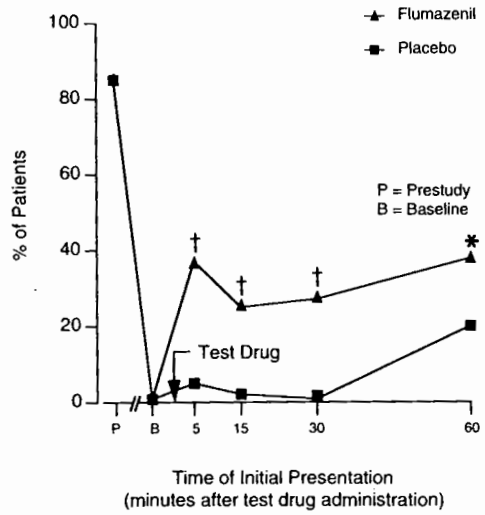

Figure 4. Percent of patients who were able to recall previously shown pictures. *$P<0.05$, †$P<0.01$, between treatment groups.

calling the pictures shown them at any previous assessment period.

Overall Efficacy
(Physician's Global Efficacy Rating)

At the 5-minute assessment, 86% (n = 89) of flumazenil-treated patients, compared with 7% (n = 4) of placebo patients, received ratings of good (3) or excellent (4) in the investigator's global assessment of the effectiveness of reversal of sedation (Figure 5). A between-treatment comparison of the mean group scores (flumazenil = 3.4 ± 0.08; placebo = 1.3 ± 0.10) was significant at the $P<0.01$ level.

Safety

All 184 patients were included in evaluations of safety and tolerability. No deaths or other serious adverse experiences were reported during the course of the study.

Forty-four (36%) patients receiving flumazenil reported 63 treatment-related adverse experiences, and 18 (30%) patients receiving placebo reported 21 treatment-related adverse experiences. The most frequently reported adverse experiences were nausea and vomiting (Table VI). Adverse experiences were judged to be severe in 5 flumazenil-treated patients and 1 placebo-treated patient. The remainder were mild or moderate.

The frequency of operative-site pain was not substantially greater in the flumazenil group (77%) than in the placebo group (65%), although such pain was reported earlier in the flumazenil group. This earlier reporting may have been due to the earlier awakening of the flumazenil patients.

There were no serious posttreatment vital sign measurements in patients from

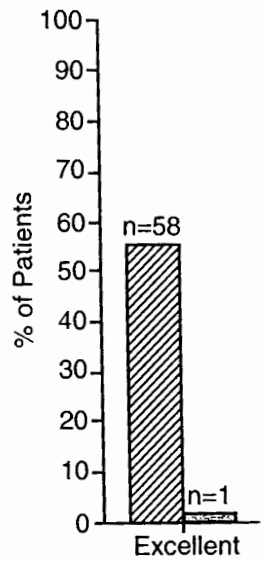

Figure 5. Physician's Gl

Table VI. Treatment-rela group.

Adverse Experience
Nausea
Vomiting
Operative-site pain
Abnormal vision
Hypotension
Shivering

either treatment group; any clinically meaning vital sign measurement groups.

DISCUSSION

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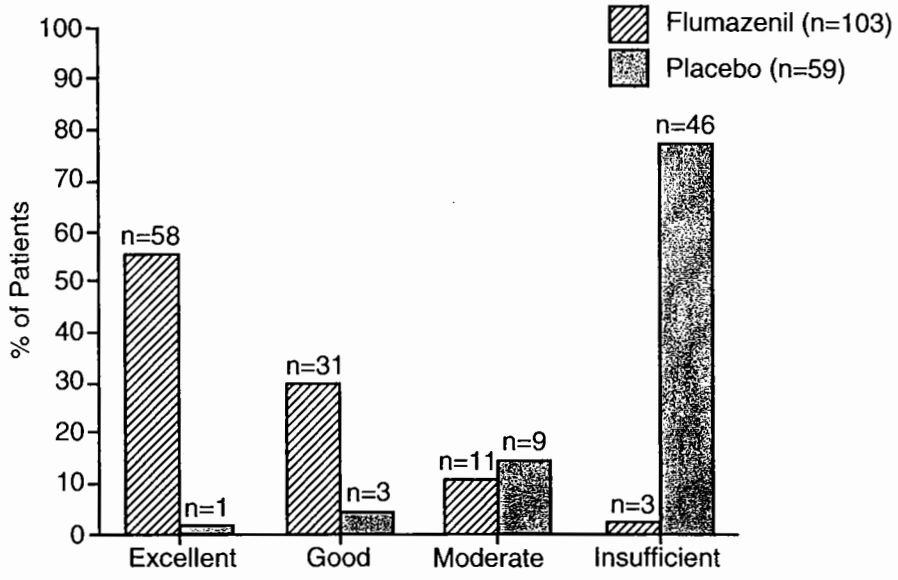

Figure 5. Physician's Global Efficacy Rating.

Table VI. Treatment-related adverse experiences reported by patients in either treatment group.

Adverse Experience	Number (%) of Patients	
	Flumazenil (n = 124)	Placebo (n = 60)
Nausea	29 (23%)	10 (17%)
Vomiting	12 (10%)	2 (3%)
Operative-site pain	6 (5%)	2 (3%)
Abnormal vision	4 (3%)	1 (2%)
Hypotension	3 (2%)	0 (0%)
Shivering	3 (2%)	1 (2%)

either treatment group; neither were there any clinically meaningful differences in vital sign measurements between the two groups.

DISCUSSION

Benzodiazepines are commonly used for the induction and maintenance of general anesthesia. As central nervous system depressants, they induce sleep, relieve apprehension, and impair memory of perioperative events. However, they may have prolonged residual effects in the postoperative period. Although physostigmine[19,20] and aminophylline[21,22] have been used as nonspecific benzodiazepine antagonists, acceptance of these drugs

has been limited because their onset was slow, their effectiveness was inconsistent, and they frequently caused undesirable side effects.[23–25]

Flumazenil, the first specific benzodiazepine antagonist, has been used successfully to reverse benzodiazepine-induced sedation that persists postoperatively. It has the advantage of prompt onset of action, as demonstrated by the finding that the uptake of [^{11}C] flumazenil is highest in the cerebral cortex, reaching a maximum from 6 to 10 minutes after IV injection.[26,27]

Flumazenil binds competitively and with high affinity to central benzodiazepine receptors, and its antagonistic action is short-lasting ($t_{1/2}$, 2–3 hours) because of its fast hepatic elimination.[4] Furthermore, flumazenil has low toxicity, with a therapeutic index 10 times that of midazolam.[28] These characteristics of flumazenil offer anesthesiologists the opportunity to reverse residual benzodiazepine-induced sedation in the postoperative patient.

Short-acting opioids are often used as part of a balanced anesthesia regimen.[29] Therefore, it was important to evaluate the efficacy of flumazenil in antagonizing the sedative effects of benzodiazepines in the presence of such agents. Results of this study clearly indicate that the effects of flumazenil are not compromised by the addition of the opioids fentanyl or sufentanil.

Because flumazenil has a shorter elimination half-life ($t_{1/2}$, 0.8 to 1.2 hours)[30] than midazolam ($t_{1/2}$, 1.2 to 12.3 hours)[31] and its major metabolites are inactive,[32] it was considered that some patients would experience residual sedation consistent with the existing concentration of midazolam, until it was eliminated. Although 52 (60%) of the 86 patients who obtained a criterion level of sedation (OAA/S score ≥4) with flumazenil maintained that effect throughout the entire 180-minute observation, 31 (36%) experienced some residual sedation, with OAA/S scores remaining above baseline scores. Three (3%) patients experienced resedation, with scores returning to baseline levels. Apparently, these patients showed a loss of flumazenil effect at a time when residual sedation was still present.

Flumazenil performed better than placebo in reversing sedation, psychomotor impairment, and amnesia induced by midazolam. However, its most pronounced effect was in reversing sedation. Whereas 83% of flumazenil-treated patients demonstrated a complete reversal of sedation by reaching the criterion level of response (OAA/S score ≥4), only 64% were able to perform the Finger-to-Nose Test at or near the normal level, and fewer than 35% were able to recall pictures shown them at earlier assessment periods. Data from earlier reports[3,11] suggest that doses of flumazenil larger than 1 mg may be required for complete recovery of psychomotor function and memory.

CONCLUSION

Postoperative administration of flumazenil to hospitalized patients promptly reversed sedation and, to a lesser degree, psychomotor and memory impairment induced by midazolam used in conjunction with either fentanyl or sufentanil. By facilitating the reversal of these effects of benzodiazepines, flumazenil can promptly awaken patients from a general anesthetic regimen that includes midazolam and short-acting opioids.

REFERENCES

1. Dunton AW, Schwam al. US clinical pharm *Eur J Anaesthesiol* 198
2. Amrein R, Hetzel V Lorscheid TF. Clinical flumazenil. *Eur J An* 2:65–80.
3. Klotz U. Drug interact pharmacokinetics of fl *Anaesthesiol* 1988; 2:1(
4. Alon E, Baitella L, H blind study of the revers supplemented general Ro 15-1788. *Br J Anaes* 458.
5. Kaukinen S, Kataja J, tagonism of benzodiaze aesthesia with flumazen 1990; 37:40–45.
6. Klausen NO, Juhl O, S Flumazenil in total in thesia using midazola *Acta Anaesthesiol Scan* 412.
7. Raeder JC, Nilsen OG The use of flumazenil anaesthesia with mid patients. *Eur J Anaesth* 2:257–264.
8. Lebrault C, Gauneau P, al. Anexate™ (flumazer practice. *Eur J Anaesth* 2:271–273.
9. Ochs MW, Tucker M Anderson JA. The effe mazenil in reversing t amnesia produced by i azolam. *J Oral Maxill* 48:240–245.
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REFERENCES

1. Dunton AW, Schwam E, Pitman V, et al. US clinical pharmacology studies. *Eur J Anaesthesiol* 1988; 2:81–95.
2. Amrein R, Hetzel W, Hartman D, Lorscheid TF. Clinical pharmacology of flumazenil. *Eur J Anaesthesiol* 1988; 2:65–80.
3. Klotz U. Drug interactions and clinical pharmacokinetics of flumazenil. *Eur J Anaesthesiol* 1988; 2:103–108.
4. Alon E, Baitella L, Hossli G. Double-blind study of the reversal of midazolam-supplemented general anaesthesia with Ro 15-1788. *Br J Anaesth* 1987; 59:455–458.
5. Kaukinen S, Kataja J, Kaukinen L. Antagonism of benzodiazepine-fentanyl anaesthesia with flumazenil. *Can J Anaesth* 1990; 37:40–45.
6. Klausen NO, Juhl O, Sorensen J, et al. Flumazenil in total intravenous anaesthesia using midazolam and fentanyl. *Acta Anaesthesiol Scand* 1988; 32:409–412.
7. Raeder JC, Nilsen OG, Hole A, et al. The use of flumazenil after total i.v. anaesthesia with midazolam in outpatients. *Eur J Anaesthesiol* 1988; Suppl 2:257–264.
8. Lebrault C, Gauneau P, Guirimand F, et al. Anexate™ (flumazenil) in anaesthetic practice. *Eur J Anaesthesiol* 1988; Suppl 2:271–273.
9. Ochs MW, Tucker MR, Owsley TG, Anderson JA. The effectiveness of flumazenil in reversing the sedation and amnesia produced by intravenous midazolam. *J Oral Maxillofac Surg* 1990; 48:240–245.
10. Rosario MT, Costa NF. Combination of midazolam and flumazenil in upper gastrointestinal endoscopy, a double-blind randomized study. *Gastrointest Endosc* 1990; 36:30–33.
11. Weinbrum A, Geller E. The respiratory effects of reversing midazolam sedation with flumazenil in the presence or absence of narcotics. *Acta Anaesthesiol Scand* 1990; 34:65–69.
12. Jensen S, Knudsen L, Kirkegaard L, et al. Flumazenil used for antagonizing the central effects of midazolam and diazepam in outpatients. *Acta Anaesthesiol Scand* 1989; 33:26–28.
13. Radakovic D, Toia D, Bentzinger C. Double-blind, placebo-controlled study of the effects of Ro 15-1788 (flumazenil, Anexate™) on recovery of ventilatory function after total intravenous anaesthesia with midazolam-alfentanyl. *Eur J Anaesthesiol* 1988; Suppl 2:279–282.
14. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. *J Clin Psychopharmacol* 1990; 10:244–251.
15. DeJong RN, editor. *The neurological examination*, 4th edition. Philadelphia: Harper & Row, 1979:396–397.
16. Dundee JW, George KA. The amnesic action of diazepam, flunitrazepam, and lorazepam in man. *Acta Anaesthesiol Belg* 1976; 27:3–11.
17. Spilker B. *Guide to clinical studies and developing protocols*. New York: Raven Press, 1985:120–121.
18. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; 22:719–748.
19. Avant GR, Speeg KU, Freemon FR, et al. Physostigmine reversal of diazepam-

induced hypnosis. *Ann Intern Med* 1979; 91:53–55.

20. Garber JG, Ominsky AJ, Orkin FK, Quinn P. Physostigmine-atropine solution fails to reverse diazepam sedation. *Anesth Analg* 1980; 59:58–60.
21. Stirt JA. Aminophylline is a diazepam antagonist. *Anesth Analg* 1981; 60:767–768.
22. Hoegholm A, Steptoe P, Fogh B, et al. Benzodiazepine antagonism by aminophylline. *Acta Anaesthesiol Scand* 1989; 33:464–466.
23. Bidwai AV, Stanley TH, Rogers C, Riet EK. Reversal of diazepam-induced postanesthetic somnolence with physostigmine. *Anesthesiology* 1979; 51:256–259.
24. Spaulding BC, Choi SD, Gross JB, et al. The effect of physostigmine on diazepam-induced ventilatory depression: A double-blind study. *Anesthesiology* 1984; 61:551–554.
25. Gurel A, Elevli M, Hamulu A. Aminophylline reverses flunitrazepam sedation. *Anesth Analg* 1987; 66:333–336.
26. Pappata S, Samson Y, Chavoix C, et al. Regional specific binding of [^{11}C] Ro 15-1788 to central type benzodiazepine receptors in human brain: Quantitative evaluation by PET. *J Cereb Blood Flow Metab* 1988; 8:304–313.
27. Persson A, Pauli S, Swahn CG, et al. Cerebral uptake of ^{11}C-Ro 15-1788 and its acid metabolite ^{11}C-Ro 15-3890; PET study in healthy volunteers. *Hum Psychopharmacol* 1989; 4:215–220.
28. Amrein R, Hetzel W. Pharmacology of Dormicum® (midazolam) and Anexate® (flumazenil). *Acta Anaesthesiol Scand* 1990; 34(Suppl 92):6–15.
29. Bailey PL, Stanley TH. Narcotic intravenous anesthetics. In: Miller RD, ed. *Anesthesia*. 3rd edition. New York: Churchill Livingstone, 1990:281–366.
30. Package Insert, Mazicon® (Flumazenil), Hoffmann-La Roche Inc., Nutley, NJ; Date Code 1291.
31. Package Insert, VERSED® Injection, (Midazolam), Hoffmann-La Roche Inc., Nutley, NJ; Date Code 0988.
32. Hunkeler W. Preclinical research findings with flumazenil (Ro 15-1788, Anexate): Chemistry. *Eur J Anaesthesiol* 1988; Suppl 2:37–62.

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ABSTRACT

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