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# Reversal of the Central Effects of Midazolam by Intravenous Flumazenil After General Anesthesia and Use of a Long-Acting Opioid in Hospitalized Patients: Report of a Multicenter Double-Blind Clinical Study

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

## ABSTRACT

A double-blind clinical trial was conducted to evaluate the efficacy and safety of flumazenil, a benzodiazepine antagonist, in 146 hospitalized patients, who had had general anesthesia induced by midazolam and a long-acting opioid. Ninety-eight patients received flumazenil and 48 received placebo. Administered postoperatively at a mean intravenous dose of 0.84 mg (range: 0.2 mg to 1 mg), flumazenil reversed benzodiazepine-induced sedation to a greater extent than did placebo. At 5 minutes posttreatment, 61 (76%) of 80 flumazenil-treated patients and 7 (18%) of 40 placebo-treated patients had attained a score of 4 or 5 on the Observer's Assessment of Alertness/Sedation Scale, indicating that they were drowsy or fully awake and alert. This level of arousal was maintained for the full 180-minute posttreatment assessment period in 79% of flumazenil-treated patients. Between-group differences in mean change from baseline in level of alertness were statistically significant ($P<0.01$) until 60 minutes posttreatment, when the spontaneous recovery of placebo-treated patients resulted in declining intergroup differences. The global efficacy rating (based on the physician's general impression of the effectiveness of the reversal of sedation 5 minutes after test drug administration) was good or excellent in 64 (80%) of the 80 flumazenil-treated patients and 5 (13%) of the 40 placebo-treated patients evaluated. Flumazenil, compared with placebo, was not associated with an increased frequency of operative-site pain, and no serious adverse effects of this benzodiazepine antagonist were re-

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0149-2918/92/$3.50

ported. The most frequent adverse experiences in both treatment groups were nausea, shivering, and operative-site pain. Vomiting, dizziness, and injection-site reactions were also reported in ≥5% of patients treated with flumazenil.

## INTRODUCTION

Benzodiazepines, administered intravenously (IV) as part of a balanced general anesthesia regimen, are frequently used to achieve sedation, hypnosis, muscle relaxation, and amnesia during operative procedures.[1] Because of the complex relationship of many factors, one often cannot predict the magnitude and duration of effect of the benzodiazepine.[2] Therefore, anesthesiologists sometimes choose less than optimal sedation at the end of a procedure to minimize the persistence of sedation in the postoperative period.

Flumazenil, an imidazobenzodiazepine, competitively blocks the central effects of benzodiazepines at the receptor sites.[3–5] In controlled clinical trials,[6–11] postoperative reversal of sedation and psychomotor impairment was obtained within 5 minutes in approximately 83% of patients administered flumazenil in IV doses up to 1 mg, compared with approximately 25% of patients administered placebo. Significant intertreatment group differences usually were sustained through 60 minutes after administration.

This report presents the results of a multicenter double-blind study conducted in six US hospitals. The purpose of this study was to assess the effectiveness and safety of flumazenil IV titrated in 0.2-mg increments to a maximum dose of 1 mg for the reversal of sedation and other residual central depressant effects of midazolam given in conjunction with a long-acting opioid in hospitalized patients undergoing a variety of procedures.

## PATIENTS AND METHODS

### *Patients*

The local institutional review board of each of the six hospitals had previously approved the protocol. Each patient gave written informed consent before entry into the study.

Inpatients who met the American Society of Anesthesiologists (ASA) Physical Status Classification 1, 2, or 3 and who were to undergo procedures requiring general anesthesia with midazolam and a long-acting opioid (morphine or meperidine) were eligible for participation in the study. Patients were excluded if they were scheduled to have major operative procedures that might present complex problems (eg, thoracic, vascular, abdominal, or neurosurgery), which could have precluded adherence to the protocols or confounded the assessments. Also excluded were patients who had clinically significant coronary artery disease, increased intracranial pressure, a history of abuse of benzodiazepines or other drugs of abuse, or pregnancy except when the procedure included termination.

Patients were randomly assigned to postoperative treatment with flumazenil or placebo in a ratio of 2 flumazenil to 1 placebo. This unbalanced design was chosen to obtain a larger number of patients exposed to flumazenil.

### *Methods*

All patients received midazolam and morphine or meperidine as part of the

g-acting opioid in hos-
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## D METHODS

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received midazolam and
neperidine as part of the

general anesthesia regimen. The test drugs were supplied by Hoffmann-La Roche Inc., Nutley, NJ. Each 10-ml ampule contained either flumazenil (0.1 mg/ml aqueous solution) or placebo. The titration method of administering 0.2 mg flumazenil (or an equivalent volume of 2 ml placebo) at 1-minute intervals allowed the physician to control the level of arousal (slightly drowsy or fully alert) with doses to a maximum of 1 mg flumazenil or 10 ml placebo.

### *Efficacy Assessments*

Efficacy was assessed by means of the Observer's Assessment of Alertness/Sedation (OAA/S), the Finger-to-Nose Test, the Picture Recall Test, and the Physician's Global Efficacy Rating. The OAA/S was the primary efficacy variable.

Pretreatment assessments of sedation and psychomotor impairment were made prestudy (before the operative procedure) and at baseline (after the procedure and immediately before test-drug administration). Baseline assessments were not started until the concentrations of volatile anesthetics had fallen below 0.1% at 1 atmosphere ambient pressure and there were no excessive residual effects of muscle relaxants. Posttreatment assessments of sedation (OAA/S) and psychomotor performance (Finger-to-Nose Test) were made at 5, 15, 30, 60, 120, and 180 minutes after the administration of flumazenil or placebo. The Picture Recall Test for picture cards shown prestudy, baseline, and at 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[12] was used at each assessment to estimate the depth of sedation. Each of four assessment categories—responsiveness, clarity of speech, aspects of facial expression, and eyes—was rated on a 5-point scale. The lowest score in any category was the value recorded for that evaluation. An OAA/S score of 1 designated a patient who was deeply asleep, and a score of 5 indicated one who was fully awake and alert. The OAA/S Scale was used during titration of the test drug to indicate when the patient reached the criterion level of alertness (OAA/S score of 4 = drowsy or 5 = alert), as determined by the physician. Prior to the initiation of the study, all principal investigators had convened to standardize their interpretations of the scores.

The OAA/S score at the 5-minute posttreatment assessment was chosen as the principal measure of the clinical effectiveness of flumazenil, because prompt reversal of sedation was considered the most significant clinical factor of benzodiazepine antagonism in the postoperative period.

Psychomotor function was evaluated at each assessment by means of the Finger-to-Nose Test,[13] a 5-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 complete reversal of impairment (score of 3 or 4) at the 5-minute assessment was considered in the assessment of efficacy.

Benzodiazepine-induced amnesia was determined at the 180-minute assessment by means of the Picture Recall Test,[14] which tested the patient's ability to recall previously shown pictures of familiar objects (eg, tree, book). A different picture

was shown at each assessment from pre-study through 60 minutes posttreatment. At 180 minutes, patients were asked to recall, in any order, the series of pictures that had been displayed.

The Physician's Global Efficacy Rating[15] provided an overall measure of efficacy. In this assessment, the investigator judged the initial effectiveness of antagonizing the residual effects of midazolam 5 minutes after the start of test drug administration. A 4-point scale reflected the investigator's general clinical impression of benzodiazepine reversal (4 = excellent, 3 = good, 2 = moderate, and 1 = insufficient).

*Measurements of Safety*

All patients were observed throughout the 180-minute assessment period for the occurrence of adverse experiences. The severity of each adverse experience was judged by the investigator as mild, moderate, or severe, and the attribution to the test drug as unrelated, remotely related, possibly related, or probably related. Vital signs, including heart rate, arterial blood pressure, and respiration rate, were measured at each assessment.

### *Data Analysis Methods*

Patients were excluded from the study if their baseline OAA/S score was >3. Data from patients who had predefined protocol violations that would invalidate the efficacy ratings (such as receiving additional opioids during the postoperative recovery period) were removed from further efficacy analyses as of the time of the violation.

The changes from baseline scores or the actual categorical data were analyzed, as appropriate, using an analysis of variance (ANOVA) to compare differences between and within treatment groups. The ANOVA was used to test the null hypotheses that (1) the mean changes from baseline in the OAA/S were equal in the two treatment groups, and (2) the mean scores of the Physician's Global Efficacy Rating were equal in the two groups. The Mantel-Haenszel Test[16] 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.

Although not analyzed statistically, data are also presented for the percentage of patients who had complete, partial, or no reversal of sedation (OAA/S) at the 5-minute assessment and the percentage of patients who became resedated. Resedation was defined as a reduction in the OAA/S after a complete response. Partial resedation was a reduction in the OAA/S to a level of sedation that was still higher than the baseline level, compared with complete resedation, which was a reduction to or below the baseline level.

## RESULTS

Of the 146 patients enrolled in the study, 98 were randomly assigned to the flumazenil group and 48 were assigned to the placebo group. Both treatment groups had a predominance of women because of the high frequency of gynecological procedures represented (Table I).

The median dose of midazolam in both groups was approximately 22 mg. The mean dose was larger (approximately 26 mg in each group) because 10 flumazenil patients and 8 placebo patients received as much as 40 mg to 60





Table I. Patient charac

| |
|---|
| Sex (M/F) |
| Age (yr) |
| Mean |
| Range |
| Weight (kg) |
| Mean |
| Range |
| ASA class (no. and %) |
| 1 |
| 2 |
| 3 |
| Procedure category (no. a |
| Gynecologic |
| Orthopedic |
| General surgery |
| Genitourinary |
| Miscellaneous* |

*Plastic, neurological, and

mg of midazolam durin
procedures.

All patients receive
or meperidine in
midazolam to induce
eral anesthesia. The m
phine was 10 mg in the
(n = 76) and 10.6 mg
group (n = 77). The
meperidine was 39.3 n
nil group (n = 14) an
placebo group (n = 1C
tients, the opioid give
a premedicant (given
fore the procedure); m
phine were 6.5 mg

Table I. Patient characteristics.

| | Flumazenil (n = 98) | Placebo (n = 48) |
|---|---|---|
| Sex (M/F) | 35/63 | 15/33 |
| Age (yr) | | |
| Mean | 44.6 | 47.3 |
| Range | 19–77 | 26–75 |
| Weight (kg) | | |
| Mean | 72.3 | 76.9 |
| Range | 47–104 | 45–118 |
| ASA class (no. and %) | | |
| 1 | 39 (40%) | 13 (27%) |
| 2 | 54 (55%) | 33 (69%) |
| 3 | 5 (5%) | 2 (4%) |
| Procedure category (no. and %) | | |
| Gynecologic | 33 (34%) | 16 (33%) |
| Orthopedic | 33 (34%) | 15 (31%) |
| General surgery | 27 (28%) | 14 (29%) |
| Genitourinary | 3 (3%) | 2 (4%) |
| Miscellaneous* | 2 (2%) | 1 (2%) |

*Plastic, neurological, and vascular.

mg of midazolam during lengthy surgical procedures.

All patients received either morphine or meperidine in conjunction with midazolam to induce and maintain general anesthesia. The mean dose of morphine was 10 mg in the flumazenil group (n = 76) and 10.6 mg in the placebo group (n = 77). The mean dose of meperidine was 39.3 mg in the flumazenil group (n = 14) and 37 mg in the placebo group (n = 10). For some patients, the opioid given was recorded as a premedicant (given within an hour before the procedure); mean doses of morphine were 6.5 mg in the flumazenil group (n = 29) and 6.1 mg in the placebo group (n = 11), and those of meperidine were 53.6 mg in the flumazenil group (n = 22) and 54.2 mg in the placebo group (n = 12).

All patients also received nitrous oxide; 96% and 98% of patients in the flumazenil and placebo groups, respectively, received isoflurane as well. Muscle relaxants were administered to 93% and 90% of patients in the flumazenil and placebo groups, respectively, and muscle relaxant antagonists (eg, neostigmine or edrophonium) were administered to reverse their effects perioperatively, as needed. The percentages of patients re-

ceiving similar perioperative medications were comparable in both treatment groups.

The test drug was administered until the criterion level of alertness (OAA/S score of 4 or 5) was reached or until a total of 10 ml had been given. The mean effective dose of flumazenil was 0.84 mg, with 43% of the flumazenil patients attaining a criterion response after 0.2 to 0.8 mg of flumazenil. In contrast, all but two of the placebo-treated patients received the maximum dose of 10 ml (Table II).

## *Efficacy*

Eighteen flumazenil-treated patients and 8 placebo-treated patients were eliminated from all efficacy analyses because of protocol violations that could have compromised the evaluation of their data. 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 number of patients at each observation. The results of the evaluations of alertness, psychomotor performance, memory, and global efficacy in the remaining 80 flumazenil-treated and 40 placebo-treated patients are summarized in Tables III and IV and Figures 1 through 5.

### *Sedation (OAA/S Scale)*

The actual mean OAA/S scores after administration of flumazenil or placebo are depicted in Figure 1. The mean level of alertness of the flumazenil-treated patients increased from a baseline OAA/S score of 1.7 to a score of 3.9 (minimum criterion score = 4) by the 5-minute assessment, whereas the placebo-treated patients did not reach this level until 60 to 120 minutes after test drug administration. Both groups showed increasing alertness through the remainder of the 180-minute study period.

The primary criterion of the efficacy of flumazenil in antagonizing the sedative effects of midazolam was the difference in magnitude of mean change in OAA/S scores from baseline, compared

Table II. Distribution of test drug doses.

| | Flumazenil (n = 98) | | Placebo (n = 48) | |
|---|---|---|---|---|
| Dose (ml) | n | % | n | % |
| 2 | 1 | 1 | 0 | 0 |
| 4 | 9 | 9 | 1 | 2 |
| 6 | 14 | 14 | 0 | 0 |
| 8 | 18 | 18 | 1 | 2 |
| 10 | 56 | 57 | 46 | 96 |
| Mean | 0.84 mg (8.4 ml) | | 9.8 ml | |

*Flumazenil concentration, 0.1 mg/ml.





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analysis show these
ferences were statis
($P<0.01$) from the 5-

Table III. Posttreatme

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

*The OAA/S is scored fro
†$P<0.01$: Statistical signifi

Figure 1. Mean score
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| Placebo (n=48) |
|---|
| % |
| 0 |
| 2 |
| 0 |
| 2 |
| 96 |
| 9.8 ml |

with placebo. The results of the efficacy analysis show these between-group differences were statistically significant ($P<0.01$) from the 5-minute through the 60-minute assessments (Table III). During this interval, the flumazenil-treated patients had larger increases from baseline OAA/S scores, indicating greater

Table III. Posttreatment changes from mean baseline OAA/S score.*

| | Flumazenil (n=80) | Placebo (n=40) | Treatment Difference |
|---|---|---|---|
| Mean baseline | 1.7 | 1.5 | |
| Change from baseline scores posttreatment: | | | |
| 5 min | +2.2 | +0.6 | 1.6† |
| 15 min | +2.5 | +1.1 | 1.4† |
| 30 min | +2.7 | +1.6 | 1.1† |
| 60 min | +3.0 | +2.1 | 0.9† |
| 120 min | +3.0 | +2.7 | 0.29 |
| 180 min | +3.1 | +3.1 | 0.04 |

*The OAA/S is scored from 1 to 5, with 1 representing deep sleep and 5 representing full awakening.
†$P<0.01$: Statistical significance of between-treatment comparison of mean changes (two-sided F-test).

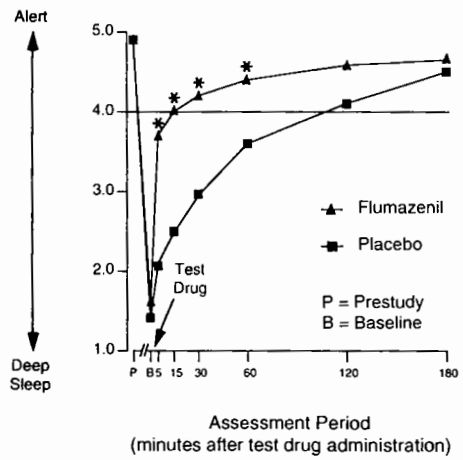


Figure 1. Mean scores on the Observer's Assessment of Alertness/Sedation Scale. *$P<0.01$, between-treatment comparisons of changes from baseline.

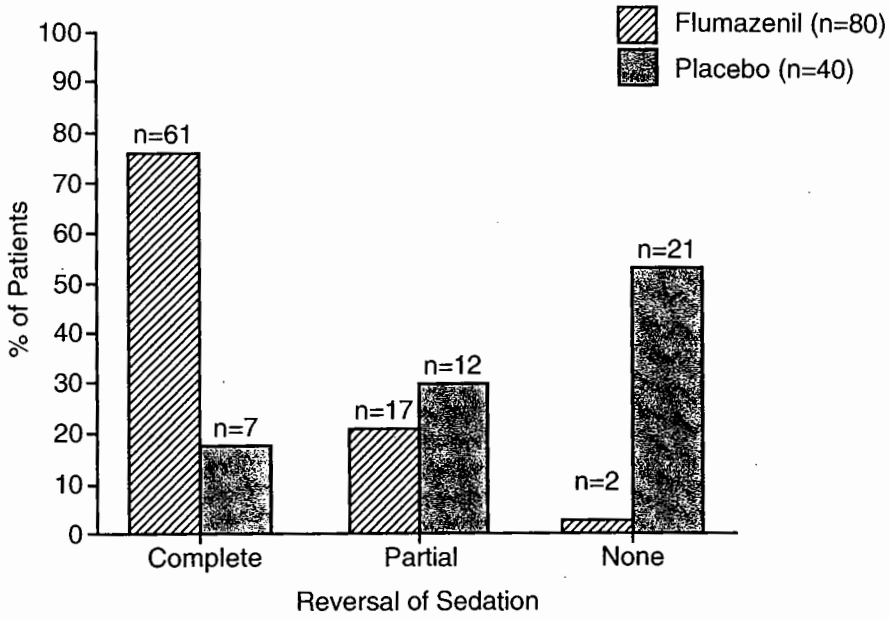


Figure 2. Responses on the Observer's Assessment of Alertness/Sedation at the 5-minute assessment.

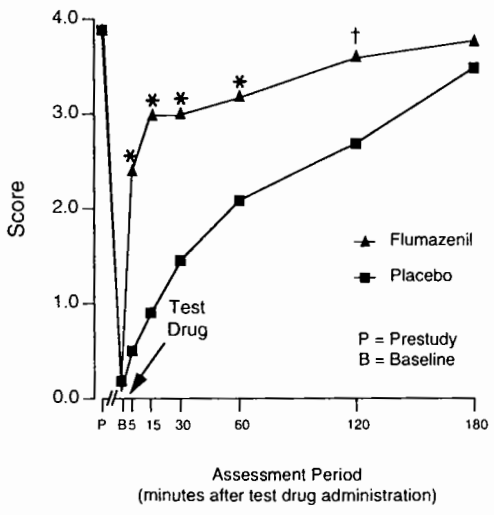


Figure 3. Mean scores on the Finger-to-Nose Test. (4 = normal; 3 = mildly abnormal; 2 = moderately abnormal; 1 = severely abnormal; 0 = patient could not be aroused). *$P<0.01$, †$P<0.05$, between-treatment comparisons of changes from baseline.





Figure 4. Percent of
*$P<0.05$, †

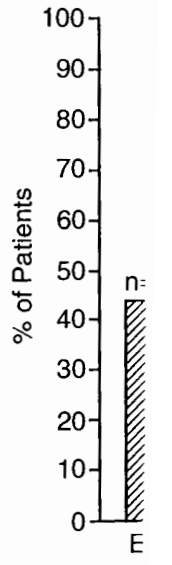


Figure 5. Investigato

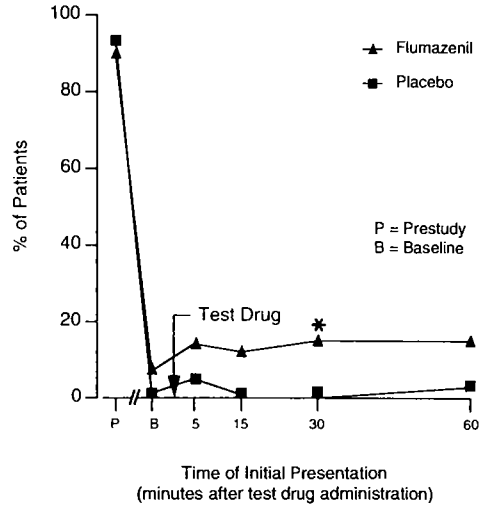


Figure 4. Percent of patients who were able to recall previously shown pictures. *$P<0.05$, between treatment groups.

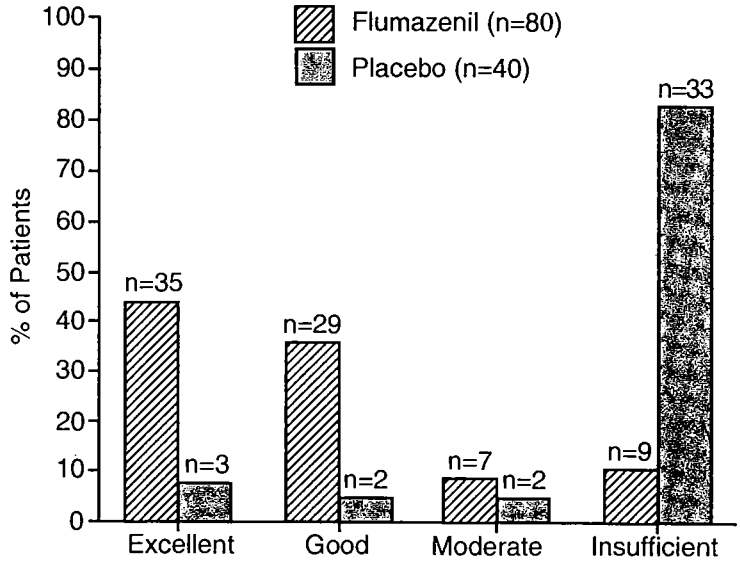


Figure 5. Investigator's global assessment ratings.

alertness, than did the placebo-treated patients. As the effects of midazolam waned spontaneously, the between-group differences were not significant after 60 minutes.

*Response Rate.* Sixty-one (76%) flumazenil-treated patients, versus 7 (18%) placebo-treated patients achieved the criterion for reversal of sedation (OAA/S score ≥4) at the 5-minute assessment (Figure 2). Only 2 (3%) flumazenil-treated patients had no change in the OAA/S score at the 5-minute assessment, compared with 21 (53%) of placebo-treated patients.

*Resedation Rate.* Of the 61 flumazenil-treated patients who were alert at 5 minutes, 48 (79%) remained so throughout the 180-minute observation, despite the fact that 26 of these 48 patients had received potentially sedating medications, such as opioids, for treatment of operative-site pain or adverse experiences. Twelve (20%) of the flumazenil patients became partially resedated, with OAA/S scores not decreasing to the baseline level. In almost all cases this decline in alertness involved a change from an OAA/S score of 4 or 5 to a score of 3. Such changes were not considered clinically significant because the patients maintained sufficient responsiveness throughout the assessment period. The remaining patient (who had received morphine and droperidol after flumazenil was administered) became resedated below the baseline level at the 120-minute assessment. This patient's OAA/S score increased from 3 at baseline to 4 at 5 minutes, reverted to the baseline level at 15 minutes and decreased to 2 at 120 minutes. The score increased again to 4 at 120 minutes and remained at this level at 180 minutes.

*Psychomotor Impairment (Finger-to-Nose Test)*

The mean scores of the Finger-to-Nose Test[13] were higher among flumazenil patients than those of placebo-treated patients at all posttreatment assessments, indicating that flumazenil promptly reversed the psychomotor impairment induced by midazolam (Figure 3). Although both groups of patients were severely impaired (mean scores <1.0) at baseline, patients given flumazenil improved to a level of mildly abnormal function (mean score of 3) within 15 minutes after administration. This level of performance was not attained by placebo-treated patients until the 180-minute assessment.

The differences between treatment groups in the magnitude of mean change from baseline score were statistically significant at the $P<0.01$ level from the 5-minute through the 60-minute assessment, and at the $P<0.05$ level at the 120-minute assessment (Table IV). At the 180-minute assessment, the placebo-treated patients had recovered sufficiently that between-group differences were no longer significant.

*Amnesia (Picture Recall Test)*

The percentage of flumazenil patients who were able to correctly recall at 180 minutes the pictures shown them at earlier assessment periods[14] was higher than that of placebo-treated patients for each posttreatment assessment (Figure 4). However, recovery of memory was low in both groups throughout the period of study, with ranges of 11% to 16% among flumazenil patients and 0% to 6.3% among placebo patients. Between-group





Table IV. Posttreatment

| | |
|---|---|
| Mean baseline | |
| Change from baseline scor posttreatment: | |
| 5 min | |
| 15 min | |
| 30 min | |
| 60 min | |
| 120 min | |
| 180 min | |

*The Finger-to-Nose Test is representing normal performa †$P<0.01$; ‡$P<0.05$: Statistic F-test).

differences were statist ($P<0.05$) only for rec: shown at the 30-minute

*Overall Efficacy (Investigator's Global I*

Flumazenil surpasse investigators' ratings[15] tiveness at 5 minutes (n = 64) of the flumaze pared with 13% (n = 5) tients, received global r or 4 (excellent). The b ference in mean scores vs placebo, 1.3) was st cant ($P<0.01$).

## *Safety*

All 146 patients w evaluations of safety. N serious adverse expe ported. Flumazenil w

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

| | Flumazenil (n = 79) | Placebo (n = 40) | Treatment Difference |
|---|---|---|---|
| Mean baseline | 0.3 | 1.1 | |
| Change from baseline scores posttreatment: | | | |
| 5 min | +2.1 | +0.5 | 1.6† |
| 15 min | +2.5 | +0.9 | 1.7† |
| 30 min | +2.7 | +1.4 | 1.3† |
| 60 min | +3.0 | +2.0 | 0.9† |
| 120 min | +3.3 | +2.6 | 0.7‡ |
| 180 min | +3.5 | +3.2 | 0.4 |

*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).
†$P<0.01$; ‡$P<0.05$: Statistical significance of between-treatment comparison of mean changes (two-sided F-test).

differences were statistically significant ($P<0.05$) only for recall of the picture shown at the 30-minute assessment.

*Overall Efficacy (Investigator's Global Rating)*

Flumazenil surpassed placebo in the investigators' ratings[15] of overall effectiveness at 5 minutes. Eighty percent (n = 64) of the flumazenil patients, compared with 13% (n = 5) of the placebo patients, received global ratings of 3 (good) or 4 (excellent). The between-group difference in mean scores (flumazenil, 3.1 vs placebo, 1.3) was statistically significant ($P<0.01$).

## Safety

All 146 patients were included in evaluations of safety. No deaths or other serious adverse experiences were reported. Flumazenil was generally well tolerated, although treatment-related (probably, possibly, or remotely) adverse experiences were more frequent in the flumazenil group (39%, n = 38) than in the placebo group (21%, n = 10). The most frequently reported treatment-related adverse experiences were nausea, shivering, and operative-site pain (Table V).

Most of the adverse experiences were mild or moderate in severity. Four patients given flumazenil each had a different severe adverse experience (shivering, operative-site pain, nervousness, or airway obstruction); no severe adverse experiences were reported in the placebo group. Seventy-three (75%) patients in the flumazenil group and 30 (63%) patients in the placebo group were treated for adverse experiences (related or unrelated to the study medications).

Operative-site pain (whether treatment-related or not) was reported in 67% of patients in either group, although it

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

| Adverse Experience | No. and % of Patients | |
|---|---|---|
| | Flumazenil (n=98) | Placebo (n=48) |
| Nausea | 13 (13%) | 4 (8%) |
| Shivering | 11 (11%) | 4 (8%) |
| Operative-site pain | 9 (9%) | 5 (10%) |
| Vomiting | 6 (6%) | 1 (2%) |
| Dizziness | 5 (5%) | 1 (2%) |
| Injection-site reaction | 5 (5%) | 0 (0%) |
| Dry mouth | 2 (2%) | 0 (0%) |
| Anxiety | 2 (2%) | 0 (0%) |
| Total patients with adverse experiences | 38 (39%) | 10 (21%) |

was experienced earlier in the flumazenil group (mean, 37 min) than in the placebo group (mean, 95 min). The earlier onset of operative-site pain probably was due to the fact that flumazenil-treated patients were awake sooner. Treatment for operative-site pain was administered to 62% of flumazenil patients and 60% of placebo patients.

No serious vital sign measurements (arterial blood pressure, pulse, and respiration rate) were observed in either treatment group, and there were no clinically meaningful differences between the two groups.

## DISCUSSION

Both physostigmine[17-19] and aminophylline[20-23] have been used to terminate the residual effects of benzodiazepines postoperatively. These drugs, which act through indirect mechanisms,[24] have not been widely accepted for benzodiazepine reversal because of their slow onset of action, their lack of consistent efficacy, and their frequent side effects.[17-27] Because flumazenil is a specific benzodiazepine antagonist, it offers anesthesiologists the unique opportunity for greater flexibility in the use of benzodiazepines and optimal control of their patients' level of sedation.

A study[5] in animals showed that IV administration of isotope-labeled flumazenil provides measurable levels of radioactivity in the brain 1 minute after administration, with maximum levels measured 6 to 10 minutes after administration. The prompt onset of benzodiazepine antagonism attained with flumazenil is related to the rapidity with which flumazenil is taken up by the brain and to the high affinity with which it binds to central benzodiazepine receptors. The effects of flumazenil in laboratory animals have been shown to be dose depen-





dent and related to the
zodiazepine agonist or
receptor occupancy req
the agonist effect.[28]

The characteristics of
rolled in this study were
reported by Forrest et al
spective study of mo
healthy surgical patient
gone general anesthes
affiliated hospitals. Th
was conducted in six
widespread centers and
the use of flumazenil in
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procedures to establish
zodiazepine antagonism
clinical circumstances.

In this study, postop
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1 mg promptly antago
and psychomotor effec
Spontaneous recovery
group was significantly
first 60 minutes posttr
minutes after admini
flumazenil-treated pa
plete or partial reversa
only two patients fai
improvement.

It was expected t
flumazenil-treated pa
completely alert at 5 r
sequently become res
flumazenil's shorter el
($t_{1/2}$=0.8 to 1.2 hr)[30]
that of midazolam (
hr).[31] However, 79%
who obtained a criteri
with flumazenil mair
throughout the entire
vation. By that time,
tion had diminished
onstrated in the place

ents in either treatment

| ents | Placebo (n = 48) |
|---|---|
| | 4 (8%) |
| | 4 (8%) |
| | 5 (10%) |
| | 1 (2%) |
| | 1 (2%) |
| | 0 (0%) |
| | 0 (0%) |
| | 0 (0%) |
| | 10 (21%) |

ted for benzodiazepine f their slow onset of ac- consistent efficacy, and le effects.[17-27] Because pecific benzodiazepine rs anesthesiologists the y for greater flexibility zodiazepines and opti- heir patients' level of

imals showed that IV f isotope-labeled flu- measurable levels of ie brain 1 minute after with maximum levels minutes after adminis- pt onset of benzodiaze- ittained with flumazenil apidity with which flu- up by the brain and to with which it binds to zepine receptors. The enil in laboratory ani- hown to be dose depen-

dent and related to the dose of the benzodiazepine agonist or to the degree of receptor occupancy required to produce the agonist effect.[28]

The characteristics of the patients enrolled in this study were similar to those reported by Forrest et al[29] in a recent prospective study of more than 17,000 healthy surgical patients who had undergone general anesthesia at university-affiliated hospitals. The present study was conducted in six geographically widespread centers and provided data on the use of flumazenil in a variety of inpatients and a wide assortment of operative procedures to establish the utility of benzodiazepine antagonism in a diversity of clinical circumstances.

In this study, postoperative IV administration of flumazenil in titrated doses to 1 mg promptly antagonized the sedative and psychomotor effects of midazolam. Spontaneous recovery in the placebo group was significantly slower during the first 60 minutes posttreatment. Within 5 minutes after administration, 97% of flumazenil-treated patients had complete or partial reversal of sedation, with only two patients failing to show any improvement.

It was expected that some of the flumazenil-treated patients who were completely alert at 5 minutes might subsequently become resedated because of flumazenil's shorter elimination half-life ($t_{1/2} = 0.8$ to 1.2 hr)[30] in comparison to that of midazolam ($t_{1/2} = 1.2$ to 12.3 hr).[31] However, 79% of the 48 patients who obtained a criterion level of reversal with flumazenil maintained that effect throughout the entire 180-minute observation. By that time, the residual sedation had diminished greatly, as demonstrated in the placebo group.

Flumazenil was most effective in antagonizing the sedative effects of midazolam, as opposed to the psychomotor and amnestic effects of the benzodiazepine. The residual effects of the opioids may have contributed to the sustained psychomotor impairment and amnesia despite the benzodiazepine-antagonizing effects of flumazenil. Data from earlier reports[3-5] suggest that doses of flumazenil larger than 1 mg may be required for complete recovery of psychomotor function and memory. It should be noted, however, that the titration endpoint in the present study was reversal of sedation, not reversal of psychomotor impairment or amnesia.

Nevertheless, clinicians should be aware that even lightly sedated patients may not remember verbal instructions given during the postoperative period and should provide such information in writing or entrust it to a responsible family member. Furthermore, it should be emphasized that the use of flumazenil does not eliminate the need for careful monitoring of patients during the postoperative recovery period.

## CONCLUSION

Flumazenil, a specific benzodiazepine antagonist, facilitates prompt, controlled reversal of the sedative effects of midazolam in the postoperative recovery period, even when patients have been given long-acting opioids in addition to midazolam. The ability to antagonize the effects of benzodiazepines offers physicians greater flexibility and control in the use of these agents for their patients who require general anesthesia and sedation.

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31. Package Insert, VERSED® Injection (Midazolam), Hoffmann-La Roche Inc., Nutley, NJ; Date Code 0988.