Reversal of the Central Effects of Midazolam by Intravenous Flumazenil After General Anesthesia in Outpatients Premedicated with an Opioid and a Muscle Relaxant: Report of a Multicenter Double-Blind Clinical Study

*The Flumazenil in General Anesthesia in Outpatients Study Group II**

ABSTRACT

Flumazenil was studied in a double-blind multicenter trial to confirm its efficacy and safety in antagonizing the central effects of benzodiazepines after general anesthesia (midazolam, short-acting narcotic, nitrous oxide) with muscle relaxants and selected potent volatile anesthetics as needed. One hundred seventy-two outpatients were randomly assigned to receive either flumazenil or placebo titrated to the point of reversal of sedation or a maximum dose of 1 mg of flumazenil or 10 ml of placebo. The test drug was given intravenously (0.2 mg flumazenil or 2 ml placebo) at 1-minute intervals. Tests of alertness, psychomotor function, and memory were conducted prestudy and at baseline before the administration of flumazenil and at 5-, 15-, 30-, 60-, 120-, and 180-minute intervals after administration. The changes from prestudy or baseline scores were analyzed to compare differences between treatment groups.

Seventy-five percent of the 105 flumazenil-treated patients and 14% of the 55 placebo-treated patients who met the qualifications for efficacy evaluations obtained a criterion level of response as measured by the Observer's Assessment of Alertness/Sedation Scale. Most (76%) patients who were alert at 5 minutes maintained their level of wakefulness throughout the 180-minute observation period.

All 172 patients were included in evaluations of safety. Fifty percent of 113 flumazenil-treated patients and 31% of 59 placebo-treated patients reported one or more adverse experiences. The most

*Verna L. Baughman, M.D., Michael Reese Hospital and Medical Center, Chicago IL; Doris A. Chernik, Ph.D., Hoffmann-La Roche Inc., Nutley NJ; Arnold B. Davidson, Ph.D., Hoffmann-La Roche Inc., Nutley NJ; Surinder Kallar, M.D., Medical College of Virginia, Richmond VA; T. Keller Matthews, M.D., Scott and White Hospital, Temple TX; Robert Phelps, M.D., Ph.D., University of Colorado Health Sciences Center, Denver CO; Beverly K. Philip, M.D., Brigham & Women's Hospital, Boston MA; Judith L. Siegel, Ph.D., Hoffmann-La Roche Inc., Nutley NJ; Craig Weinstein, M.D., Robert Wood Johnson University Hospital, New Brunswick NJ.

0149-2918/92/$3.50

frequently reported were iting, and dizziness. C effects in the flumazenil the placebo group were vere; the remainder were ate. None were consid potentially serious.

Postoperative adminis mazenil (mean dose, 0. provided a prompt, contr the sedative and psycho midazolam in most patie

INTRODUCTION

Benzodiazepines, becaus cific pharmacologic effe facilitate induction and general anesthesia. How gery is completed, pro awakening of the patient particularly in outpatient be achieved with a new diazepine antagonist.

Flumazenil, an imi pine, antagonizes the cen tem effects of benzodiaz petitive interaction at the receptor site.[2-5] Its selecti utilized after general ane intravenous dose of ≤1 promptly antagonize the of benzodiazepines.[6-11] reversal lasts about an h

The aim of this double controlled, single-dose, was to demonstrate th safety of intravenous trated, 0.2-mg to 1-mg onizing the central effect especially sedation, afte and maintenance of ge

m
nesthesia
d and a
Double-Blind

*s Study Group II**

ebo. The test drug was
ly (0.2 mg flumazenil
at 1-minute intervals.
psychomotor function,
e conducted prestudy
fore the administration
l at 5-, 15-, 30-, 60-,
nute intervals after ad-
changes from prestudy
were analyzed to com-
tween treatment groups.
percent of the 105
l patients and 14% of
eated patients who met
s for efficacy evalua-
criterion level of re-
ired by the Observer's
lertness/Sedation Scale.
nts who were alert at 5
ed their level of wake-
it the 180-minute obser-

nts were included in
ety. Fifty percent of 113
d patients and 31% of
d patients reported one
experiences. The most

0149-2918/92/$3.50

frequently reported were nausea, vomiting, and dizziness. Only 6 adverse effects in the flumazenil group and 1 in the placebo group were considered severe; the remainder were mild or moderate. None were considered serious or potentially serious.

Postoperative administration of flumazenil (mean dose, 0.85 mg) safely provided a prompt, controlled reversal of the sedative and psychomotor effects of midazolam in most patients.

INTRODUCTION

Benzodiazepines, because of their specific pharmacologic effects,[1] are used to facilitate induction and maintenance of general anesthesia. However, when surgery is completed, prompt, controlled awakening of the patient may be desired, particularly in outpatients. This can now be achieved with a new specific benzodiazepine antagonist.

Flumazenil, an imidazobenzodiazepine, antagonizes the central nervous system effects of benzodiazepines by competitive interaction at the benzodiazepine receptor site.[2–5] Its selective action can be utilized after general anesthesia, with an intravenous dose of $\leq$1 mg in adults, to promptly antagonize the sedative effects of benzodiazepines.[6–11] The duration of reversal lasts about an hour.

The aim of this double-blind, placebo-controlled, single-dose, six-center study was to demonstrate the efficacy and safety of intravenous flumazenil (titrated, 0.2-mg to 1-mg dose) in antagonizing the central effects of midazolam, especially sedation, after the induction and maintenance of general anesthesia in a regimen that also included a short-acting opioid (fentanyl or sufentanil), nitrous oxide, muscle relaxants (nondepolarizing drugs and succinylcholine), and selected potent volatile anesthetics as needed.

PATIENTS AND METHODS

Patients

Outpatients of the American Society of Anesthesiologists (ASA) Physical Status Classification Class 1, 2, or 3 needing general anesthesia could be included in the study if they met the entry requirements. Written informed consent was obtained from each participant. The institutional review board of each of the six centers had approved the protocol.

Patients with clinically significant coronary artery disease, increased intracranial pressure, known or suspected seizure disorder, or acute narrow-angle glaucoma were excluded. Also excluded were patients with a history of alcohol or drug dependence, or allergic or sensitivity reactions to study-required medications. Pregnant women were excluded, except those whose pregnancy was to be terminated in the procedure. Also excluded were patients scheduled for major neurosurgery or thoracic, abdominal, or vascular surgery. Patients with severe pulmonary insufficiency, clinically significant arrhythmia, or abnormalities on the electrocardiogram (ECG) could be included at the discretion of the investigator, as could patients with open-angle glaucoma who were receiving appropriate therapy.

Patients meeting all entry requirements were randomly assigned to receive either flumazenil or placebo in a ratio of 2 flumazenil patients to 1 placebo patient. This unbalanced design maximized the number of patients who would receive the active drug yet provided an adequate control group.

Methods

General anesthesia was induced with midazolam and fentanyl or sufentanil, and maintained with midazolam and nitrous oxide. Halothane or isoflurane was administered only as needed, and the use of muscle relaxants was optional.

The flumazenil and placebo for the study were provided by Hoffmann-La Roche Inc., Nutley, NJ. The drugs were given intravenously (0.2 mg flumazenil or 2 ml placebo) at 1-minute intervals. Doses of the study drugs were titrated to the endpoint of reversal of sedation or a maximum of 10 ml. The criterion of reversal of sedation was a score of 4 or 5 (equivalent to slightly drowsy or fully alert, respectively) on the Observer's Assessment of Alertness/Sedation Scale (OAA/S).[12]

Evaluations of sedation and psychomotor function were performed before the procedure and before administration of any medications (prestudy), at baseline (at end of procedure and before administration of test drugs), and at 5, 15, 30, 60, 120, and 180 minutes after test drug administration. Memory was evaluated at 180 minutes using a recall test of pictures shown at prestudy, baseline, and 5-, 15-, 30-, and 60-minute assessment periods. A global assessment of the effectiveness of the test drug was made by the physician at the 5-minute assessment.

Efficacy Measurements

Observer's Assessment of Alertness/Sedation

The OAA/S[12] was used to measure the patient's level of sedation at each assessment time. The patient's status was rated on a 5-point rating scale comprising 4 categories: responsiveness, speech, facial expression, and appearance of the eyes. A score of 1 represented deep sedation, while a score of 5 represented full alertness.

Finger-to-Nose Test

Psychomotor function was assessed with the Finger-to-Nose Test[13] using a 4-point scale with 4 = normal, 3 = mild impairment, 2 = moderate impairment, 1 = severe impairment. Patients too sedated to complete the task were given a score of 0.

Picture Recall Test

The Picture Recall Test[14] provided a measure of the reversal of midazolam-induced amnesia. Each patient was shown and asked to identify pictures of familiar items (eg, dollar bill, chair, bird) at prestudy, baseline, and 5-minute through 60-minute assessment periods. At the 180-minute assessment, the patient was asked to recall as many pictures as possible in any order.

Physician's Global Efficacy Rating

The Physician's Global Efficacy Rating[15] was completed at the 5-minute assessment. Reversal of sedation was rated

on a 4-point scale: 4
good, 2 = moderate, an

Safety Assessments

All patients were ob
experiences throughou
minute assessment per
verse experience, the
a judgment of severity
or severe) and relatic
drug (unrelated, remot
bly related, or probabl

Analysis of Data

All patients receivi
were included in th
safety. Patients who c
protocol-specified le
(OAA/S of ≤3) at th
ment were ineligible f
from eligible patients
had protocol violation
found the efficacy rati
potentially sedating r
the recovery portion c
excluded from furthe
time of the violation.

The change from ba
actual categorical data
appropriate, by means
ance to compare differ
within treatment gro
variance was used to te
eses that (1) the me
baseline in the OAA/S
Nose Test were equal
and the placebo treat
(2) the mean scores
Global Efficacy Rating
two treatment groups.
Test results were anal

on a 4-point scale: 4 = excellent, 3 = good, 2 = moderate, and 1 = insufficient.

Safety Assessments

All patients were observed for adverse experiences throughout the entire 180-minute assessment period. For each adverse experience, the investigator made a judgment of severity (mild, moderate, or severe) and relationship to the test drug (unrelated, remotely related, possibly related, or probably related).

Analysis of Data

All patients receiving the test drug were included in the evaluations of safety. Patients who did not satisfy the protocol-specified level of sedation (OAA/S of ≤ 3) at the baseline assessment were ineligible for the study. Data from eligible patients who subsequently had protocol violations that would confound the efficacy ratings (eg, receiving potentially sedating medication during the recovery portion of the study) were excluded from further analysis at the time of the violation.

The change from baseline scores or the actual categorical data were analyzed, as appropriate, by means of analysis of variance to compare differences between and within treatment groups. Analysis of variance was used to test the null hypotheses that (1) the mean changes from baseline in the OAA/S and the Finger-to-Nose Test were equal in the flumazenil and the placebo treatment groups, and (2) the mean scores of the Physician's Global Efficacy Rating were equal in the two treatment groups. The Picture Recall Test results were analyzed by means of the Mantel-Haenszel Test[16] or the two-sided Fisher's Exact Test.

RESULTS

Of the 172 patients enrolled in the study, 113 patients were randomly assigned to the flumazenil group and 59 patients to the placebo group (Table I). The majority of patients in both groups had gynecologic procedures.

Premedications, such as anticholinergic and antiemetic drugs administered approximately 1 hour before induction of anesthesia, were given to 33% of patients in the flumazenil group and 41% in the placebo group. The medications used during the induction and maintenance of general anesthesia are listed in Table II. The individual doses of opioids or midazolam varied according to the requirements of the patient and the length of the procedure; there were no substantial differences between treatment groups. Muscle relaxants were administered as required, the choice and dosage left to the discretion of the physician. If excessive residual muscle relaxation was present at the end of the procedure, neostigmine (40 to 70 μg/kg) and glycopyrrolate (0.2 mg/1 mg neostigmine) were administered intravenously.

All patients received at least 4 ml of the test drug (Table III). The mean volume dose of placebo (9.8 ml) was larger than that of flumazenil (8.5 ml, equivalent to 0.85 mg).

Postprocedure medications were similar in each treatment group. Analgesics, given primarily for treatment of pain at the operative site, were the most common medications required in each group (flumazenil 34.5%; placebo 35.6%).

Table I. Characteristics of study population.

	Flumazenil (n = 113)	Placebo (n = 59)
Sex		
Male	22 (19%)	5 (8%)
Female	91 (81%)	54 (92%)
Age (yr)		
Mean	34	33
Range	19–65	20–66
Weight (kg)		
Mean	68	68
Range	43–129	46–131
ASA class (no. and %)		
1	76 (67%)	44 (75%)
2	36 (32%)	14 (24%)
3	1 (1%)	1 (1%)
Procedures		
Gynecologic	79 (70%)	42 (71%)
Orthopedic	15 (13%)	9 (15%)
General surgery	12 (11%)	5 (9%)
Genitourinary	3 (3%)	2 (3%)
Ear, nose, throat	2 (2%)	0 (0%)
Neurological	1 (1%)	0 (0%)
Plastic surgery	1 (1%)	1 (2%)

Antiemetics were given to more patients in the flumazenil group (18.6%) than in the placebo group (8.5%).

Efficacy Evaluation

Summaries of the statistical analyses of the efficacy measurements of sedation (OAA/S), psychomotor function (Finger-to-Nose Test), and memory (Picture Recall Test) are presented in Tables IV and V. Eight flumazenil-treated patients and four placebo-treated patients were excluded entirely from the efficacy analyses because of protocol violations that would have interfered with the assessments. Other patients had missing assessments or protocol violations that eliminated them from subsequent analyses, thereby altering the number of patients with data at different times.

Table II. Medications

Flumazenil group
Midazolam
Opioids
Fentanyl
Sufentanil
Inhalant anesthetics
Nitrous oxide
Enflurane
Isoflurane
Muscle relaxants
Nondepolarizing dru
Succinylcholine
Placebo group
Midazolam
Opioids
Fentanyl
Sufentanil
Inhalant anesthetics
Nitrous oxide
Enflurane
Isoflurane
Muscle relaxants
Nondepolarizing dr
Succinylcholine

Sedation (OAA/S)

The mean scores a
of flumazenil or plac
the figure. The mean
line scores in the O
cantly ($P<0.01$) grea
nil group than in the

Table II. Medications used during induction and maintenance of general anesthesia.

	No. (%)	Dose	
		Mean (mg)	Median (mg)
Flumazenil group			
Midazolam	113 (100)	19.3	17.5
Opioids			
Fentanyl	91 (80.5)	0.17	0.16
Sufentanil	21(18.6)	0.03	0.03
Inhalant anesthetics			
Nitrous oxide	113 (100)		
Enflurane	1 (0.9)		
Isoflurane	74 (65.5)		
Muscle relaxants			
Nondepolarizing drugs	108 (95.6)		
Succinylcholine	85 (75.2)		
Placebo group			
Midazolam	59 (100)	18.7	17.5
Opioids			
Fentanyl	48 (81.4)	0.15	0.14
Sufentanil	11 (18.6)	0.03	0.03
Inhalant anesthetics			
Nitrous oxide	59 (100)		
Enflurane	0 (0)		
Isoflurane	42 (71.2)		
Muscle relaxants			
Nondepolarizing drugs	57 (96.6)		
Succinylcholine	46 (78)		

Sedation (OAA/S)

The mean scores after administration of flumazenil or placebo are plotted in the figure. The mean changes from baseline scores in the OAA/S were significantly ($P<0.01$) greater in the flumazenil group than in the placebo group from 5 minutes through 60 minutes (Table IV). By 120 minutes both groups were equally awake.

Of the 105 flumazenil-treated patients, 79 (75%) achieved the criterion reversal of sedation at 5 minutes, in contrast to 8 (14%) placebo-treated patients. Twenty-two (21%) flumazenil-treated patients

Table III. Distribution of test drug doses.

Dose (ml)	Flumazenil (n = 113) No.	%	Placebo (n = 59) No.	%
4	6	5	0	0
6	23	20	1	2
8	21	19	3	5
10	63	56	55	93
Mean	8.5 ml		9.8 ml	
	0.85 mg		—	
Median	10 ml		10 ml	
	1 mg		—	

and 24 (44%) placebo-treated patients had an improved OAA/S score at 5 minutes but did not attain a score of ≥4. A complete lack of response was evident in 4 (4%) flumazenil patients and 23 (42%) placebo patients. All of the nonresponders had received the maximum dose of flumazenil or placebo, and all spontaneously recovered by the 180-minute assessment.

Sixty (76%) of the 79 flumazenil patients who were alert at 5 minutes maintained their level of wakefulness throughout the 180-minute observation period. Resedation, defined as any reduction in the OAA/S score after a patient had attained a score of 4 or 5 at the 5-minute assessment, was observed in 18 (23%) patients, of whom 3 reverted to the baseline level of sedation by the 15-minute assessment.

Psychomotor Function (Finger-to-Nose Test)

Flumazenil was significantly ($P<0.01$) more effective than placebo in reversing psychomotor impairment from the 5-minute through 60-minute assessments (Table IV). At the 5-minute assessment, 79 (75%) of the 105 flumazenil-treated patients had normal or near-normal psychomotor performance (score of 3 or 4), whereas only 8 (15%) of the 55 placebo-treated patients attained this level of performance. The placebo group did not achieve normal psychomotor functioning levels for 120 minutes or longer.

Memory (Picture Recall Test)

Although midazolam-induced amnesia was incompletely reversed, the difference in change scores was significantly ($P<0.01$) greater in the flumazenil group than in the placebo group at the 5-, 15-, and 30-minute assessments (Table V). No patient in the placebo group, compared with 37% of patients in the flumazenil group, correctly recalled the picture shown at the 5-minute assessment. Little change in picture recall was evident until the 60-minute assessment, when the pictures shown were correctly

Table IV. Efficacy res
Nose Test.*

OAA/S (5 = alert)
Baseline (mean score)
5 min
15 min
30 min
60 min
120 min
180 min
Finger-to-Nose Test (4 =
Baseline (mean score)
5 min
15 min
30 min
60 min
120 min
180 min

*Mean baseline values and
with 1 representing deep sl
1 to 4, with 1 representing
sedated to perform test). A
score to the baseline score; e
†Estimated mean change fr
‡$P<0.01$: Statistical signifi

recalled by 46% of
flumazenil group and
the placebo group.

Physician's Global Eff

Global efficacy wa
excellent for 83 (79%)
patients and 10 (18%)
tients (Table VI). The

Placebo (n = 59)
%
0
2
5
93
9.8 ml
—
10 ml
—

irment from the 5-
-minute assessments
5-minute assessment,
)5 flumazenil-treated
or near-normal psy-
ıce (score of 3 or 4),
%) of the 55 placebo-
ined this level of per-
cebo group did not
:homotor functioning
tes or longer.

ecall Test)

lam-induced amnesia
reversed, the differ-
res was significantly
the flumazenil group
group at the 5-, 15-,
essments (Table V).
placebo group, com-
patients in the flu-
ectly recalled the pic-
5-minute assessment.
cture recall was evi-
-minute assessment,
:hown were correctly

Table IV. Efficacy results: Observer's Assessment of Alertness/Sedation and Finger-to-Nose Test.*

	Flumazenil		Placebo	
	N	Mean Change†	N	Mean Change†
OAA/S (5 = alert)				
Baseline (mean score)	105	2.0	55	2.0
5 min	105	1.9‡	55	0.69
15 min	102	2.1‡	54	1.1
30 min	97	2.1‡	54	1.4
60 min	88	2.2‡	48	1.6
120 min	75	2.3	45	2.2
180 min	73	2.7	39	2.7
Finger-to-Nose Test (4 = normal)				
Baseline (mean score)	105	0.55	55	0.53
5 min	105	2.3‡	55	0.66
15 min	102	2.7‡	54	1.1
30 min	97	2.7‡	54	1.5
60 min	87	2.8‡	48	2.2
120 min	75	2.9	45	2.8
180 min	73	3.3	39	3.2

*Mean baseline values and mean posttreatment changes from baseline. The OAA/S is scored from 1 to 5, with 1 representing deep sleep and 5 representing full awakening. 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). An approximate actual mean score can be obtained by adding the mean change score to the baseline score; eg, OAA/S flumazenil group: at 5 minutes, the mean score is approximately 3.9.
†Estimated mean change from baseline.
‡$P<0.01$: Statistical significance of between-group comparison of mean changes (two-sided F-test).

recalled by 46% of patients in the flumazenil group and 30% of patients in the placebo group.

Physician's Global Efficacy Rating

Global efficacy was judged good or excellent for 83 (79%) flumazenil-treated patients and 10 (18%) placebo-treated patients (Table VI). The mean global score was 3.1 for the flumazenil group versus 1.5 for the placebo group ($P<0.01$).

Safety Evaluation Results

All 172 patients were included in evaluations of safety. Fifty-six (50%) of 113 flumazenil patients experienced 86 adverse effects and 18 (31%) of 59 placebo patients experienced 27 adverse

effects considered remotely, possibly, or probably related to the test medication. Six (3 cases of vomiting, 2 of nausea, and 1 of insomnia) in the flumazenil group and 1 (shivering) in the placebo group were judged to be severe; the remainder were mild or moderate. None were considered serious or potentially

Table V. Efficacy results: Picture Recall Test* (percent correctly recalled).

	Flumazenil			Placebo		
	Total	Recalled		Total	Recalled	
	N	N	%	N	N	%
Prestudy	100	86	86.0	52	49	94.2
Baseline	45	2	4.4	24	0	0.0
5 min	99	37	37.4†	42	0	0.0
15 min	98	32	32.7†	48	1	2.1
30 min	93	38	40.9†	50	4	8.0
60 min	84	39	46.4	46	14	30.4

*Memory was evaluated at 180 minutes based on recall of pictures shown at prestudy through 60-minute assessment periods.
†$P<0.01$: Statistical significance of between-treatment comparison (two-sided Mantel-Haenszel Test).

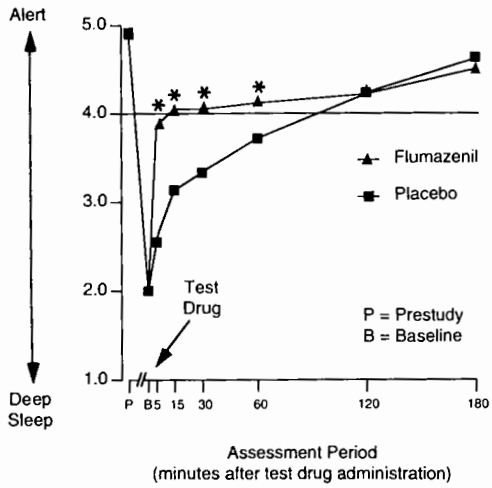

Figure. Mean scores on the Observer's Assessment of Alertness/Sedation Scale. *$P<0.01$, between-treatment comparisons of changes from baseline.

serious. Eighteen (16%) nil patients and six (10% patients were treated for

Probably, possibly, or adverse effects reporte either treatment group a VII. Gastrointestinal co and vomiting), followed counted for the most groups.

Table VI. Physician's G

Global Assessment
4 (excellent)
3 (good)
2 (moderate)
1 (insufficient)
Mean score ± SE

*$P<0.01$: Statistical significa

Table VII. Treatment-re ment group.

Adverse Experiences
Nausea
Vomiting
Dizziness
Pain at operative site
Abnormal crying
Injection-site reaction
Hypertension
Headache
Shivering

ing) in the placebo
o be severe; the re-
or moderate. None
rious or potentially

ecalled).

Placebo	
Recalled	
N	%
49	94.2
0	0.0
0	0.0
1	2.1
4	8.0
14	30.4

estudy through 60-minute

antel-Haenszel Test).

tness/Sedation Scale.
om baseline.

serious. Eighteen (16%) of the flumazenil patients and six (10%) of the placebo patients were treated for adverse effects.

Probably, possibly, or remotely related adverse effects reported by patients in either treatment group are listed in Table VII. Gastrointestinal complaints (nausea and vomiting), followed by dizziness, accounted for the most reports in both groups.

Pain at the operative site, irrespective of its attribution to the test drug, was reported in 26 (23%) flumazenil patients and 8 (14%) placebo patients. Twenty (18%) flumazenil-treated patients and 7 (12%) placebo-treated patients required analgesics for postoperative pain.

Vital signs were measured at each assessment period, with no serious post-treatment changes in either group.

Table VI. Physician's Global Assessment.

	Flumazenil (n = 105)		Placebo (n = 55)	
Global Assessment	No.	%	No.	%
4 (excellent)	44	42	3	6
3 (good)	39	37	7	13
2 (moderate)	15	14	6	11
1 (insufficient)	7	7	39	71
Mean score ± SE	3.1 ± 0.09*		1.5 ± 0.13	

*$P<0.01$: Statistical significance of between-treatment comparison.

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

	Flumazenil (n = 113)		Placebo (n = 59)	
Adverse Experiences	No.	%	No.	%
Nausea	24	21	5	9
Vomiting	22	20	8	14
Dizziness	12	11	4	7
Pain at operative site	7	6	1	2
Abnormal crying	3	3	0	0
Injection-site reaction	2	2	1	2
Hypertension	2	2	0	0
Headache	2	2	0	0
Shivering	0	0	2	3

DISCUSSION

Results of studies conducted with physostigmine[17,18] and aminophylline[19,20] to antagonize benzodiazepine effects have shown that these drugs have variable effectiveness and delayed time of onset. In contrast, the results of this study show that postoperative administration of flumazenil (up to 1 mg intravenous) reversed sedation and psychomotor impairment within 5 minutes in most patients.

The possibility of resedation after the 5-minute assessment period was anticipated because of the shorter elimination half-life ($t_{1/2}$ = 0.86 to 1.2 hr) of flumazenil[5] compared with that of midazolam ($t_{1/2}$ = 1.2 to 12.3 hr). However, most of the patients (76%) alert at 5 minutes maintained their level of wakefulness throughout the 180-minute observation period. Eighteen percent of patients experienced some loss of alertness; 3% of these patients became resedated to the baseline level of sedation. Despite the reversal of sedation by flumazenil, adequate postoperative monitoring is still essential since some patients may experience resedation.

Whereas sedation and psychomotor impairment were completely or almost completely reversed by flumazenil in most patients, amnesia was only partially reversed. Some studies[5,21,22] suggest that larger doses may be necessary for the reversal of amnesia. In normal volunteers given various benzodiazepines, 3 mg of flumazenil was more effective in reversing memory loss than was 0.7 mg or 1.4 mg.[5] It should be noted, however, that the doses of flumazenil used in this study were titrated to a criterion reversal of sedation, as determined by the OAA/S Scale, and not to reversal of psychomotor impairment or amnesia. Inasmuch as the maximum recommended dose of flumazenil is 1 mg, which may not consistently reverse amnesia, physicians should provide written instructions to the patient at discharge.

CONCLUSION

The results of this study confirm the effectiveness and safety of flumazenil in antagonizing the central nervous system (CNS) effects of midazolam used to induce and maintain general anesthesia in conjunction with a short-acting opioid and nitrous oxide in outpatients undergoing various procedures. Controlled awakening to a level considered satisfactory by the physician was achieved in most patients with flumazenil titrated to the point of reversal of sedation or a maximum of 1 mg given intravenously (0.2 mg flumazenil or 2 ml placebo) at 1-minute intervals. There were few drug-related adverse effects, none of which were considered serious.

ACKNOWLEDGMENTS

The principal investigators acknowledge the participation of the following associates in the performance of this study: T. Simpson, M.D., M. Hauch, M.D., and R. Mallampati, M.D., Brigham & Women's Hospital, Boston MA.

REFERENCES

1. Corssen G, Reves JG, Stanley TH. *Intravenous anesthesia and analgesia.* Philadelphia: Lea and Febiger, 1988: 219–255.

2. Amrein R, Hetzel W. I Dormicum (midazolan (flumazenil). *Acta An* 1990; 34(Suppl 92):6–1

3. Klotz U, Ziegler G, R macokinetics of the se azepine antagonist RO *Eur J Pharmacol* 1984;

4. Haefely WE. The stor flumazenil (Anexate). *A Belg* 1989; 40:3–9.

5. Dunton AW, Schwam al. US clinical pharm *Eur J Anaesthesiol* 19 95.

6. Ochs MW, Tucker M Anderson JA. The effe mazenil in reversing t amnesia produced by i azolam. *J Oral Maxill* 48:240–245.

7. Pearson RC, McCloy Bardhan KD. Midazola in gastroenterology. *A Scand* 1990; 34(Suppl

8. Lauven PM, Kulka PJ. niques for midazolam An overview. *Acta An* 1990; 34(Suppl 92):84–

9. Philip BK, Simpson T Mallampati SR. Fluma dation after midazolam anesthesia in ambulat tients. *Anesth Analg* 19

10. Weinbrum A, Geller E effects of reversing mi with flumazenil in the sence of narcotics. *A Scand* 1990; 34(Suppl

11. Klausen NO, Juhl O, S Flumazenil in total in thesia using midazola *Acta Anaesthesiol Scan* 412.

azenil used in this study
criterion reversal of se-
mined by the OAA/S
to reversal of psycho-
t or amnesia. Inasmuch
recommended dose of
ıg, which may not con-
amnesia, physicians
ritten instructions to the
ge.

his study confirm the
safety of flumazenil in
central nervous system
midazolam used to in-
n general anesthesia in
a short-acting opioid
e in outpatients under-
procedures. Controlled
vel considered satisfac-
ician was achieved in
h flumazenil titrated to
ersal of sedation or a
ng given intravenously
nil or 2 ml placebo) at
s. There were few drug-
effects, none of which
serious.

MENTS

estigators acknowledge
of the following asso-
ormance of this study:
D., M. Hauch, M.D.,
ıti, M.D., Brigham &
l, Boston MA.

ea and Febiger, 1988:

2. Amrein R, Hetzel W. Pharmacology of Dormicum (midazolam) and Anexate (flumazenil). *Acta Anaesthesiol Scand* 1990; 34(Suppl 92):6–15.
3. Klotz U, Ziegler G, Reiman IW. Pharmacokinetics of the selective benzodiazepine antagonist RO 15-1788 in man. *Eur J Pharmacol* 1984; 27:115–117.
4. Haefely WE. The story and activity of flumazenil (Anexate). *Acta Anaesthesiol Belg* 1989; 40:3–9.
5. Dunton AW, Schwam E, Pitman V, et al. US clinical pharmacology studies. *Eur J Anaesthesiol* 1988; 2(Suppl):81–95.
6. 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.
7. Pearson RC, McCloy RF, Morris P, Bardhan KD. Midazolam and flumazenil in gastroenterology. *Acta Anaesthesiol Scand* 1990; 34(Suppl 92):21–24.
8. Lauven PM, Kulka PJ. Anaesthesia techniques for midazolam and flumazenil: An overview. *Acta Anaesthesiol Scand* 1990; 34(Suppl 92):84–89.
9. Philip BK, Simpson TH, Hauch MA, Mallampati SR. Flumazenil reverses sedation after midazolam-induced general anesthesia in ambulatory surgery patients. *Anesth Analg* 1990; 71:371–376.
10. 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(Suppl 92):65–69.
11. Klausen NO, Juhl O, Sorensen J, et al. Flumazenil in total intravenous anaesthesia using midazolam and fentanyl. *Acta Anaesthesiol Scand* 1988; 32:409–412.
12. 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.
13. DeJong RN, editor. *The neurological examination*, 4th ed. Philadelphia: Harper & Row, 1979:396–397.
14. Dundee JW, George KA. The amnesic action of diazepam, flunitrazepam, and lorazepam in man. *Acta Anaesthesiol Belg* 1976; 27:3–11.
15. Spilker B. *Guide to clinical studies and developing protocols*. New York: Raven Press, 1985:120–121.
16. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; 22:719–748.
17. Garber JG, Ominsky AJ, Orkin FK, Quinn P. Physostigmine-atropine solution fails to reverse diazepam sedation. *Anesth Analg* 1980; 59:58–60.
18. Nilsson E, Himberg J-J. Physostigmine for postoperative somnolence after diazepam-nitrous oxide anesthesia. *Acta Anaesthesiol Scand* 1982; 26:9–14.
19. Arvidsson S, Neimand D, Martinell S, et al. Aminophylline reversal of diazepam sedation. *Anesthesia* 1984; 39:806–809.
20. Hoegholm A, Steptoe P, Fogh B, et al. Benzodiazepine antagonism by aminophylline. *Acta Anaesthesiol Scand* 1989; 33:164–166.
21. Amrein R, Hetzel W, Hartman D, Lorscheid TF. Clinical pharmacology of flumazenil. *Eur J Anaesthesiol* 1988; 2:65–80.
22. Klotz U. Drug interactions and clinical pharmacokinetics of flumazenil. *Eur J Anaesthesiol* 1988; 2:103–108.