Reversal of the Central Effects of Midazolam by Intravenous Flumazenil After General Anesthesia in Outpatients: A Multicenter Double-Blind Clinical Study

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

ABSTRACT

In a US double-blind, multicenter study, flumazenil, a benzodiazepine antagonist, administered postoperatively in a mean intravenous dose of 0.67 mg (range, 0.2 to 1 mg), was superior to placebo in reversing sedation and other central nervous system effects of benzodiazepines in outpatients recovering from general anesthesia induced by midazolam, fentanyl or sufentanil, and nitrous oxide. Within 5 minutes after administration of flumazenil, sedation was reversed in 94% (87 of 93) of flumazenil-treated patients, compared with 13% (6 of 46) of placebo-treated patients. The criterion response (Observer's Assessment of Alertness/Sedation Scale score of 4 or 5) that was achieved at 5 minutes was maintained in 79 (93%) of 85 patients throughout the 180-minute observation period. Psychomotor performance, measured by the Finger-to-Nose Test, was rated as normal at 5 minutes posttreatment for 77% (71 of 92) of flumazenil-treated patients, and 4% (2 of 46) of placebo-treated patients. The reversal of amnesia, as determined by the Picture Recall Test was less consistent. Patients given flumazenil did not experience more pain at the operative site or require more analgesic medication than did those given placebo. Nausea (flumazenil 24%; placebo 15%), dizziness (flumazenil 12%; placebo 2%), and vomiting (flumazenil 10%; placebo 9%) were the most frequent adverse effects in each group. In conclusion, flumazenil provided prompt arousal from benzodiazepine-induced sedation and was well tolerated.

INTRODUCTION

The pharmacologic effects of intravenous (IV) benzodiazepines, such as sedation, psychomotor impairment, and amnesia, make them useful agents as part of a balanced anesthesia regimen to induce or maintain general anesthesia for

*Jerry M. Calkins, M.D., Ph.D., Lovelace Medical Center, Albuquerque NM; Doris A. Chernik, Ph.D., Hoffmann-La Roche Inc., Nutley NJ; Arnold B. Davidson, Ph.D., Hoffmann-La Roche Inc., Nutley NJ; Ray McKenzie, M.D., Magee-Womens Hospital, Pittsburgh PA; Stephen Rupp, M.D., Virginia Mason Hospital, Seattle WA; Earl Sherod, M.D., Utah Valley Medical Center, Provo UT; Judith L. Siegel, Ph.D., Hoffmann-La Roche Inc., Nutley NJ; J. Yung-Fong Sung, M.D., Ambulatory Surgery Center of The Emory Clinic, Atlanta GA.

0149-2918/92/$3.50

various procedures.[1] If persistence of these effects postoperatively delays a desired prompt awakening, an anesthesiologist may choose to restrict the dose of benzodiazepine, thereby limiting the depth of anesthesia that could be achieved.

Flumazenil, an imidazobenzodiazepine that selectively blocks the effects of benzodiazepines by competitive interaction at the benzodiazepine receptor,[2–4] may offer the anesthesiologist greater flexibility in dosing of benzodiazepines used for general anesthesia. In controlled clinical trials,[5–11] flumazenil in doses ≤1 mg IV was more effective than placebo in reversing sedation and psychomotor impairment within the first few minutes after administration. The difference was apparent from the 5-minute assessment through the 60-minute assessment. Thereafter differences were small, as the effects of the benzodiazepines spontaneously waned in placebo-treated patients.

This report presents the results of a single-dose, double-blind, placebo-controlled, multicenter study conducted at 5 study sites in the United States. The objective was to evaluate the effectiveness and safety of intravenous flumazenil in a titrated, 0.2-mg to 1-mg dose in antagonizing residual central depressant effects, especially sedation, after outpatient general anesthesia induced by midazolam and a short-acting opioid (fentanyl or sufentanil) and nitrous oxide.

PATIENTS AND METHODS

Patients

Outpatients who were scheduled for procedures requiring general anesthesia and who met the American Society of Anesthesiologists (ASA) Physical Status Classification 1, 2, or 3 were considered for the study. Each patient gave written informed consent before entry into the study. The Institutional Review Board of each of the 5 centers had approved the protocol.

Patients with a history of abuse of benzodiazepines or other drugs were excluded. Patients with clinically significant coronary artery disease, increased intracranial pressure, known or suspected seizure disorder, acute narrow angle glaucoma, or allergy or sensitivity to any of the required medications also were excluded, as were pregnant women. In addition, patients scheduled for major neurosurgery or thoracic, abdominal, or vascular surgery were excluded. Patients with severe pulmonary insufficiency, clinically significant arrhythmia, or clinically significant electrocardiographic abnormalities could be included at the discretion of the investigator.

Patients were randomly assigned to postoperative, double-blind treatment with either flumazenil or placebo in a ratio of 2 flumazenil patients to 1 placebo patient.

METHODS

General anesthesia was induced by the intravenous administration of midazolam and fentanyl or sufentanil and maintained with midazolam and nitrous oxide. Volatile anesthetics, such as isoflurane, were administered to patients as needed, depending on the response to anesthesia. Other opioids were administered when indicated. Baseline evaluations were not

started until the concentration of the volatile anesthetic at the end of the procedure was less than 0.1% at one atmosphere ambient pressure.

The titration method of administering 0.2 mg flumazenil (or 2 ml placebo) at 1-minute intervals, not exceeding 1 mg of flumazenil or 10 ml of placebo, was used to enable the physician to control the extent of reversal. Test-drug administration was terminated when the patient reached a criterion response corresponding to slightly drowsy or fully alert.

Assessments of sedation and psychomotor performance were performed prestudy (before the procedure and before any medications were administered), baseline (at the end of the procedure and before administration of flumazenil or placebo), and posttreatment (after the administration of flumazenil or placebo) at 5, 15, 30, 60, 120, and 180 minutes from the start of test-drug administration. Memory was evaluated at 180 minutes, based on the ability of patients to recall pictures previously shown at each assessment from prestudy through 60 minutes posttreatment. The Physician's Global Rating of effectiveness was made at the 5-minute posttreatment assessment.

Efficacy Evaluations

Observer's Assessment of Alertness/Sedation

The Observer's Assessment of Alertness/Sedation (OAA/S),[12] a 5-point rating scale, was used to quantify the patient's level of sedation. The score at each assessment period was based on an appraisal in each of four categories: responsiveness, speech, facial expression, and appearance of the eyes. An OAA/S score of 1 indicated a patient who was deeply sedated; a score of 5 indicated a patient who was awake and alert. The OAA/S Scale was used to determine when the patient had reached the criterion level of arousal for stopping test drug administration (either 4 or 5 on the OAA/S) determined by the physician.

Because prompt reversal of sedation was considered the most important clinical effect of flumazenil in the postoperative setting, the change from baseline in the OAA/S score at 5 minutes posttreatment was selected as the primary efficacy variable. The 5-minute observation, completed within 5 minutes of the start of the test medication, provided an immediate evaluation of efficacy.

Finger-to-Nose Test

Psychomotor impairment was scored with the Finger-to-Nose Test[13] comprising a 5-point scale with 4 = normal, 3 = mild impairment, 2 = moderate impairment, 1 = severe impairment, 0 = too sedated to complete the task. The percentage of patients who exhibited complete reversal of psychomotor impairment (score of 3 or 4) at the 5-minute assessment was determined.

Picture Recall Test

The Picture Recall Test[14] provided a measure of the reversal of amnesia that had been induced by midazolam. Each patient was shown pictures of familiar items (eg, dollar bill, chair, bird), one each at the prestudy assessment and at each assessment time through 60 minutes. At the 180-minute assessment, the pa-

tient was asked to recall, in any order, the pictures that had been shown.

Physician's Global Efficacy Rating

The Physician's Global Efficacy Rating[15] was completed at the 5-minute assessment. Reversal of benzodiazepine effects was rated on a 4-point scale: 4 = excellent, 3 = good, 2 = moderate, and 1 = insufficient.

Safety Evaluations

All patients were observed for adverse effects throughout the entire 180-minute assessment period. Vital signs (arterial blood pressure, heart rate, and respiration rate) were measured at each assessment through 180 minutes.

Analysis of Data

Patients whose OAA/S score was >3 at the baseline assessment were not eligible for the study. Patients who had a protocol violation that would invalidate the efficacy ratings (eg, use of potentially sedating medication during the recovery phase) were removed from the analysis from the time of the violation onward. However, no patients were excluded from the evaluations of safety.

The change from baseline scores or the actual categorical data were analyzed, as appropriate, using an analysis of variance to compare differences between treatment groups and within each treatment group. 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]

RESULTS

Of the 142 patients enrolled in the study, 95 were randomly assigned to flumazenil and 47 to placebo (Table I). Women outnumbered men 4 to 1, principally because of the predominance of gynecologic procedures.

The medications used to induce and maintain general anesthesia are summarized in Table II. The doses of each medication were adjusted to the patient's need and response, as well as the duration of the procedure. Postoperatively, analgesics and antiemetics were the most frequently used medications. Thirty percent of patients in the flumazenil group and 36% of patients in the placebo group were given analgesics, primarily for relief of pain at the operative site.

Flumazenil-treated patients received a mean dose of 6.7 ml (0.67 mg), whereas the placebo-treated patients received a mean dose of 9.8 ml; 94% of the placebo-treated patients received the maximum dose allowed, compared with 23% of the flumazenil-treated patients (Table III).

Efficacy Evaluation Results

Two flumazenil patients were excluded entirely from the statistical analyses because they had received incorrect doses of test drug, and one placebo

Table I. Demographic characteristics.

	Flumazenil (n=95)	Placebo (n=47)
Sex (Male/Female)	19/76	9/38
Age (yr)		
Mean	44	48
Range	18–78	18–72
Weight (kg)		
Mean	68	71
Range	45–119	50–118
ASA Class (n)		
1	55	21
2	39	25
3	1	1
Procedures (n/%)		
Gynecologic	42/44%	21/45%
General surgery	28/29%	13/28%
Genitourinary	15/16%	7/15%
Orthopedic	10/11%	6/13%

patient was excluded because intravenous lidocaine had been administered during the procedure. All treated patients were included in the safety analysis.

Results of the efficacy evaluations at each assessment time are summarized in Tables IV and V. The different numbers of patients at different time points were due to missing assessments or termination of patients for protocol violations.

Sedation (OAA/S)

The mean scores after administration of flumazenil or placebo are plotted in the figure. Patients given flumazenil were significantly ($P<0.01$) more alert than those given placebo from the 5-minute through the 30-minute assessments, according to the analysis of the mean change from baseline scores of OAA/S (Table IV). By the 60-minute assessment, spontaneous waning of the sedative effect of midazolam was evident, and the differences were no longer statistically significant.

Response Rate. Eighty-seven (94%) flumazenil-treated patients, compared with 6 (13%) placebo-treated patients, achieved the criterion level of awakening (OAA/S score of 4 or 5) at the 5-minute assessment. An additional 3 (3%) patients in the flumazenil group and 13 (28%) patients in the placebo group be-

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

	n (%)	Mean Dose (mg)	Median Dose (mg)
Flumazenil Group			
Midazolam	95 (100)	13.1	12.5
Opioids			
Fentanyl	82 (86)	0.13	0.10
Sufentanil	13 (14)	0.008	0.01
Anesthetics			
Nitrous oxide	95 (100)	—	—
Isoflurane	95 (100)	—	—
Local/regional	2 (2)	—	—
Placebo Group			
Midazolam	47 (100)	12.6	12.5
Opioids			
Fentanyl	82 (86)	0.15	0.10
Sufentanil	8 (17)	0.009	0.008
Anesthetics			
Nitrous oxide	47 (100)	—	—
Isoflurane	43 (82)	—	—
Local/regional	4 (9)	—	—

came more alert but did not attain a criterion score.

Three (3%) of the flumazenil-treated patients and 27 (59%) of the placebo-treated patients had no change in the OAA/S score at the 5-minute assessment. All such nonresponding patients had received the maximum dose of test drug. All but one of these patients recovered during the course of the 180-minute observation period. One patient in the flumazenil group, whose baseline OAA/S score was 1, was still partially sedated (OAA/S score of 3) at the end of the observation period.

A preliminary examination of the data indicated no meaningful effect of any of the demographic characteristics on the reversal of sedation. However, the small numbers of patients in some categories limited the statistical conclusions that could be drawn. Of special interest was the similarity of response of patients over 65 years to that of younger patients.

Resedation Rate. Resedation was defined as any reduction in the OAA/S score after a patient had attained a criterion score at the 5-minute assessment. Of the 87 flumazenil-treated patients who were alert at 5 minutes, 79 (93%)

Table III. Distribution of test drug doses.

Flumazenil (n = 95)			Placebo (n = 47)		
Dose (mg)	No.	%	Dose (ml)	No.	%
0.2	1	1	2	0	0
0.4	22	23	4	1	2
0.6	38	40	6	0	0
0.8	12	13	8	2	4
1	22	23	10	44	94

Table IV. Efficacy results: OAA/S and Finger-to-Nose Test.*

	Flumazenil		Placebo	
	n	Mean Change†	n	Mean Change†
OAA/S (5 = alert)				
Baseline	93	1.3	46	1.3
5 min	93	2.9‡	46	0.7
15 min	85	3.1‡	46	1.4
30 min	82	3.3‡	42	2.3
60 min	72	3.3	39	3.0
120 min	68	3.5	32	3.4
180 min	66	3.6	30	3.7
Finger-to-Nose Test (4 = normal)				
Baseline	93	0.2	46	0.2
5 min	92	2.7‡	46	0.5
15 min	84	3.2‡	45	1.2
30 min	81	3.4‡	42	1.9
60 min	71	3.5‡	39	3.0
120 min	68	3.7§	32	3.4
180 min	66	3.8	30	3.7

*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).

†The mean change score can be added to the baseline score to give an approximation of the actual mean score; eg, the OAA/S score in the flumazenil group at 5 minutes is 1.3 + 2.9, or 4.2.

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

Table V. Efficacy results: Picture Recall Test.*

	Flumazenil			Placebo		
	Total	Recalled		Total	Recalled	
	n	n	%	n	n	%
Prestudy	93	87	93.6	46	43	93.5
Baseline	12	2	16.7	5	0	0.0
5 min	89	34	38.2†	22	0	0.0
15 min	84	35	41.7†	30	2	6.7
30 min	81	37	45.7†	37	6	16.2
60 min	72	34	47.2‡	37	10	27.0

*Memory was evaluated at 180 minutes based on recall of pictures shown at prestudy through 60-minute assessment periods.
†$P<0.01$; ‡$P<0.05$: Statistical significance of between-treatment comparison (two-sided Mantel-Haenszel Test).

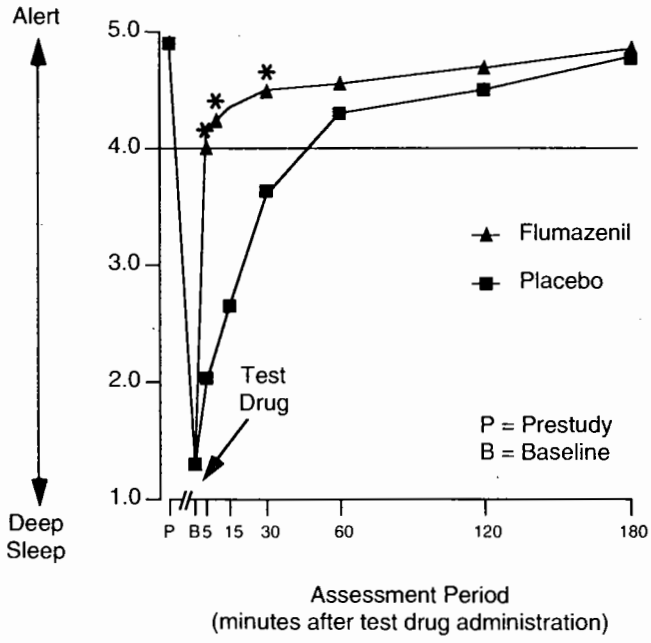

Figure. Mean scores on the Observer's Assessment of Alertness/Sedation Scale. *$P<0.01$, between-treatment comparisons of changes from baseline.

remained so throughout the 180-minute observation period. The 6 placebo-treated patients who were alert at the 5-minute observation also remained alert for the rest of the study period.

Six (7%) of the flumazenil patients experienced resedation, as represented by a lower OAA/S score after the initial response. No flumazenil-treated patient became resedated to the level that existed at baseline.

Finger-to-Nose Test

At the 5-minute assessment, 71 (77%) flumazenil-treated patients had normal or near-normal psychomotor performance, compared with 2 (4%) placebo-treated patients. Flumazenil was significantly more effective than placebo in reversing psychomotor impairment from the 5-minute through 60-minute assessments ($P<0.01$) and through the 120-minute assessment ($P<0.05$), according to the analysis of the change from baseline scores (Table IV). The placebo group did not achieve normal psychomotor function until the 60-minute assessment or later.

Picture Recall Test

Flumazenil partially reversed benzodiazepine-induced amnesia. Thirty-eight percent of flumazenil-treated patients versus 0% of placebo-treated patients correctly recalled the picture shown at the 5-minute assessment. Recall of pictures shown at the 5-minute through 30-minute assessments was significantly ($P<0.01$) greater in the flumazenil group than in the placebo group (Table V). However, the percentage of patients who correctly recalled the pictures shown at any assessment after the prestudy assessment did not approach the 94% recall of the picture shown prestudy.

Physician's Global Efficacy Rating

At the 5-minute assessment, 78 (85%) of 92 flumazenil patients had global effectiveness ratings of good or excellent compared with 5 (11%) of 46 placebo patients with a rating of good (Table VI). Expression of these ratings by their numerical equivalents resulted in a mean global score of 3.3 for the flumazenil group versus 1.3 for the placebo group ($P<0.01$).

Table VI. Physician's global assessment.

	Flumazenil (n=92)		Placebo (n=46)	
Global Assessment	No.	%	No.	%
Excellent	44	48	0	0
Good	34	37	5	11
Moderate	8	9	3	7
Insufficient	6	7	38	83

Safety Evaluation Results

All 142 patients given flumazenil or placebo were included in evaluations of safety. Thirty-seven (39%) of 95 flumazenil patients and 7 (15%) of 47 placebo patients reported one or more adverse effects judged to be remotely or possibly related to the test medication; none was considered probably related. Only one, a report of fatigue in a patient given flumazenil, was rated severe. None of the effects were considered serious or potentially serious. Fifteen (16%) of the flumazenil patients and 3 (6%) of the placebo patients were treated for adverse effects.

Adverse experiences reported by patients in either treatment group and considered remotely or possibly related to test-drug administration are listed in Table VII. Nausea, dizziness, and vomiting were the most frequently reported adverse experiences in both groups.

The use of flumazenil to reverse benzodiazepine-induced sedation was not associated with a greater frequency of operative-site pain than was reported in the placebo group, 23 (24%) and 15 (32%) patients, respectively. Furthermore, 15 (32%) placebo patients, compared with 23 (24%) flumazenil patients required medication for the pain.

There were no serious changes in vital sign measurements posttreatment and no clinically meaningful differences in vital sign measurements between the flumazenil and the placebo treatment groups.

DISCUSSION

In the past, drugs such as physostigmine[17,18] and aminophylline[19,20] were used to antagonize the sedative effects of benzodiazepines, but their lack of consistent efficacy limited their use. Unlike these drugs, flumazenil acts at the benzodiazepine receptor complex to selectively block the effects of benzodiazepines.[2–4] The results of this study show that flumazenil, administered postoperatively in doses up to 1 mg intravenously, promptly antagonizes the central depressant effects of midazolam, especially sedation and psychomotor impairment, in most patients. Placebo-treated patients usually did not attain a similar level of alertness and psychomotor function until ≥60 minutes after administration.

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

	Flumazenil (n=95)		Placebo (n=47)	
Adverse Experiences	No.	%	No.	%
Nausea	23	24	7	15
Dizziness	11	12	1	2
Vomiting	10	10	4	9
Abnormal crying	2	2	0	0

The demographic characteristics of the patients enrolled in this study were generally similar to those reported in a recent prospective study of more than 17,000 healthy patients who had been administered general anesthesia at university-affiliated hospitals.[21] One difference is the larger proportion of younger women in the present study owing to the preponderance of gynecologic procedures performed. However, none of the demographic characteristics, including sex or age, appeared to influence the response to flumazenil.

The possibility was considered that some of the flumazenil-treated patients who were alert at 5 minutes might subsequently experience residual sedation because flumazenil has a shorter elimination half-life ($t_{1/2} = 0.86$ to 1.2 hr)[4] than does midazolam ($t_{1/2} = 1.2$ to 12.3 hr). This occurred less often than was expected. Most (93%) patients who were awake and alert 5 minutes after administration of flumazenil remained so for the entire 180-minute observation period. By that time, most of the sedative effects of midazolam had worn off in both treatment groups. Nevertheless, because the possibility of residual sedation exists, practitioners are advised not to consider reversal of sedation with flumazenil as a substitute for adequate postprocedure monitoring.

Flumazenil, at the doses tested, did not consistently reverse midazolam-induced amnesia. Earlier reports[2–4] indicate that doses higher than the 1-mg recommended dose may be required to achieve complete recovery of memory. Accordingly, practitioners should not expect patients to remember verbal discharge instructions conveyed in the postoperative period; they should provide the patient with written instructions or entrust them to a responsible family member.

CONCLUSION

The results of this study show flumazenil to be an effective benzodiazepine antagonist after outpatient procedures in which midazolam has been used, along with a short-acting opioid and nitrous oxide, for the induction or maintenance of general anesthesia. Titrated doses of 0.4 to 1 mg of flumazenil, administered in 0.2-mg increments, achieved a controlled awakening in most patients with few drug-related side effects.

ACKNOWLEDGMENTS

The principal investigators acknowledge the participation of Carol A. Stephenson, R.N., Virginia Mason Hospital, Seattle WA, in the performance of this study.

REFERENCES

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

2. Dunton AW, Schwam E, Pitman V, et al. US clinical pharmacology studies. *Eur J Anaesthesiol* 1988; 2:81–95.

3. Amrein R, Hetzel W, Hartman D, Lorscheid TF. Clinical pharmacology of flumazenil. *Eur J Anaesthesiol* 1988; 2:65–80.

4. Klotz U. Drug interactions and clinical pharmacokinetics of flumazenil. *Eur J Anaesthesiol* 1988; 2:103–108.

5. 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.

6. Kaukinen S, Kataja J, Kaukinen L. Antagonism of benzodiazepine-fentanyl anaesthesia with flumazenil. *Can J Anaesth* 1990; 37:40–45.

7. Lauven PM, Kulka PJ. Anaesthesia techniques for midazolam and flumazenil: An overview. *Acta Anaesthesiol Scand* 1990; 34(Suppl 92):84–89.

8. Rupp SM, Stephenson CA. Flumazenil versus placebo in antagonism of midazolam-based general anesthesia for outpatient surgery. *Anesth Analg* 1990; 70:S340.

9. 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.

10. Klausen NO, Juhl O, Sorensen J, et al. Flumazenil in total intravenous anaesthesia using midazolam and fentanyl. *Acta Anaesthesiol Scand* 1988; 32:409–412.

11. 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.

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 and 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. Avant GR, Speeg KU, Freemon FR, et al. Physostigmine reversal of diazepam-induced hypnosis. *Ann Intern Med* 1979; 91:53–55.

18. Garber JG, Ominsky AJ, Orkin FK, Quinn P. Physostigmine-atropine solution fails to reverse diazepam sedation. *Anesth Analg* 1980; 59:58–60.

19. Hoegholm A, Steptoe P, Fogh B, et al. Benzodiazepine antagonism by aminophylline. *Acta Anaesthesiol Scand* 1989; 33:164–166.

20. Gurel A, Elevil M, Hamulu A. Aminophylline reverses flunitrazepam sedation. *Anesth Analg* 1987; 66:333–336.

21. Forrest JB, Rehder K, Goldsmith CH, et al. Multicenter study of general anesthesia. *Anesthesiology* 1990; 72:252–261.