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Effect of Flumazenil on Recovery after Midazolam and Propofol Sedation

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Background: **Flumazenil, a benzodiazepine antagonist, reverses midazolam-induced sedation and amnesia. We designed a double-blind study to evaluate the effects of flumazenil on patient outcome when flumazenil was used to reverse large or small doses of midazolam as part of standardized monitored anesthesia care.**

Methods: **Ninety-nine healthy consenting women undergoing breast biopsy procedures with local anesthesia were randomly assigned to one of four treatment groups: group 1, propofol–placebo (control); group 2, propofol–flumazenil; group 3, midazolam–placebo; or group 4, midazolam–flumazenil. All patients received intravenous midazolam 2 mg and intravenous fentanyl 50 μg, followed by an infusion of either propofol 25–150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or midazolam 0.5–4 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At the end of the operation, patients were intravenously administered either 10 ml saline (groups 1 and 3) or flumazenil 1 mg in 10 ml saline (groups 2 and 4). Amnesia was assessed by determining recall of pictures shown before and after the procedure. Subjective feelings of sedation, anxiety, clumsiness, and fatigue were evaluated using 100-mm visual analogue scales preoperatively and at 30-min intervals in the recovery room. Cognitive function was assessed using the digit–symbol substitution test at similar intervals. Early recovery was evaluated by the ability of the patients to be transferred directly from the operating room to the step-down unit, as well as by times to ambulation and discharge. A standardized questionnaire and telephone interview were used to assess "resedation" and other postdischarge side effects.**

Results: **Flumazenil (1 mg) enhanced early recovery and picture recall after high-dose (group 4) but not low-dose (group 2) midazolam. Only 32% of patients in group 3 were transferred directly to the step-down unit compared with 85% in group 4 ($P < 0.05$). Flumazenil significantly improved visual analogue scale and digit–symbol substitution test scores at the 30- and 60-min testing intervals ($P < 0.05$). At the 90-min interval, there were no significant differences between groups 3 and 4. Compared with group 3 (84 ± 22 min), patients in groups 1, 2, and 4 were ready for discharge significantly earlier (60 ± 23, 65 ± 21, and 67 ± 27 min, respectively) ($P < 0.05$). However, 33% of the patients in group 4 reported resedation after discharge (*vs.* 0–8% in the other three study groups) ($P < 0.05$).**

Conclusions: **Early recovery after breast biopsy procedures with midazolam sedation and flumazenil reversal is similar to recovery after propofol sedation. However, the beneficial effects of flumazenil were apparent only during the first 60 min after the procedure and resedation after discharge is an important consideration in the outpatient setting. (Key words: Anesthesia, outpatient; Antagonist, benzodiazepine: flumazenil; Anesthetics, intravenous: midazolam, propofol; Monitored anesthesia care, sedation techniques; Recovery testing, visual analogue scales and digit–symbol substitution tests.)**

INTRAVENOUS sedative–hypnotic drugs are commonly used during monitored anesthesia care to enhance patient comfort, maintain cardiorespiratory stability, improve operating conditions, and prevent recall of unpleasant events during the operation. The water-soluble benzodiazepine midazolam (Versed) is the most popular adjuvant§ during local and regional anesthesia because of its sedative, anxiolytic, and amnestic properties. However, recovery of cognitive and psychomotor function after midazolam sedation is more prolonged compared with other sedative–hypnotic medications.[1–4]

Recently, propofol (Diprivan) was approved by the Food and Drug Administration for use as a sedative during monitored anesthesia care. Studies have demonstrated the advantages of propofol over midazolam with respect to early recovery parameters.[2,4–6] However, the availability of a specific benzodiazepine antagonist, flumazenil (Romazicon), should improve midazolam's early recovery profile by rapidly reversing its sedative and amnestic effects.[7–10] Therefore, we designed a randomized, double-blind, placebo-controlled study to evaluate the effect of flumazenil on outcome after midazolam (*vs.* propofol) sedation in outpatients under-

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§ Data on file at Stuart Pharmaceuticals/Zeneca, Wilmington, Delaware (courtesy of Randy Glick). Audit performed on May 14, 1991.

going procedures with local anesthesia as part of a monitored anesthesia care technique.

Materials and Methods

Ninety-nine healthy (ASA physical status 1 or 2) women undergoing "deep" breast biopsy procedures using local anesthesia with adjunctive intravenous sedative and analgesic drugs were studied in this institutional review board approved double-blind clinical investigation. After obtaining written informed consent, patients were randomly assigned using a computer-generated random-number sequence to one of four treatment groups:

- Group 1: midazolam 2 mg, propofol infusion, placebo
- Group 2: midazolam 2 mg, propofol infusion, flumazenil
- Group 3: midazolam 2 mg, midazolam infusion, placebo
- Group 4: midazolam 2 mg, midazolam infusion, flumazenil

Patients with a history of acute or chronic sedative or analgesic use, epileptic disorders, or clinically significant preexisting medical diseases were excluded from participating in this study.

In the preoperative holding area, these nonpremedicated patients were asked to complete a series of six 100-mm visual analogue scales[11] to evaluate: (1) sleepiness (0 = wide awake to 100 = almost asleep), (2) fatigue (0 = energetic to 100 = extremely tired), (3) clumsiness (0 = well-coordinated to 100 = extremely clumsy), (4) anxiety (0 = calm and relaxed to 100 = extremely nervous), (5) confusion (0 = none to 100 = totally confused), and (6) pain (0 = none to 100 = worst pain). All patients were shown a picture and told that they would be asked to recall the picture after the operation. Finally, patients completed the digit–symbol substitution test[12] to assess their baseline cognitive function. The test requires that patients match numbers and symbols using a key that is changed each time the test is repeated (to minimize the effects of learning behavior). Patients were encouraged to match as many pairs as possible during the 90-s testing period.

When the patients entered the operating room, a noninvasive blood pressure cuff (Critikon Dinamap, Tampa, FL), electrocardiograph, finger pulse oximeter (Ohmeda Biox, Boulder, CO), and nasal prongs were applied. Supplemental oxygen was administered at a rate of 5 $l \cdot min^{-1}$ using a carbon dioxide sampling nasal cannula (Salter Labs, Arvin, CA). Mean arterial pressure, heart rate, hemoglobin oxygen saturation, and respiratory rate were recorded at 5-min intervals. After obtaining baseline vital sign values, intravenous midazolam 2 mg and intravenous fentanyl 50 μg were administered. After a 3–5–min interval, patients received a loading infusion of either intravenous propofol 300 $\mu g \cdot kg^{-1}$ (groups 1 and 2) or intravenous midazolam 20 $\mu g \cdot kg^{-1}$ (groups 3 and 4) over 1–2 min, followed by an initial maintenance infusion of propofol 75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (groups 1 and 2) or midazolam 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (groups 3 and 4) using a Bard InfusOR pump. The sedative infusion rates were varied by the attending anesthesiologist (PFW) to maintain a stable level of sedation such that the patient was resting comfortably and yet was easily arousable with either verbal or light tactile stimulation. The range of maintenance infusion rates for propofol and midazolam was 25–150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.5–4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively.

If the patient complained of pain or discomfort during the local anesthetic infiltration, intravenous fentanyl in 25-μg bolus doses was administered. No other medications were administered during the maintenance period. Upon completion of the wound closure, the sedative infusions were discontinued, and the study drug (saline 10 ml or flumazenil 1 mg in 10 ml of saline) was administered intravenously in 2-ml incremental doses every 20–30 s. The patients were shown a second picture 3–5 min after administration of the study drug. The attending anesthesiologist (PFW) was asked to guess whether the patient had received the reversal drug (flumazenil) or placebo (saline). Approximately 5 min after the study drug was given, patients were asked to move themselves from the operating room table to a reclining chair. If they were able to transfer themselves unassisted, they were taken directly to the phase 2 step-down unit; patients requiring assistance with the transfer procedure were admitted to the regular postanesthesia care unit (PACU). All subsequent assessments of cognitive function and sedation were performed by a trained research nurse who was unaware of the patients' treatment group and intraoperative events.

Upon arrival in the PACU or the phase 2 recovery unit, the patients were shown a third picture (approximately 10 min after the study drug). At 30-min intervals after administration of either flumazenil or

Table 1. Demographic Characteristics and Drug Requirements for the Four Treatment Groups

	Propofol–Placebo	Propofol–Flumazenil	Midazolam–Placebo	Midazolam–Flumazenil
N	24	24	25	26
Age (yr)	45 ± 10	47 ± 12	46 ± 12	45 ± 15
Weight (kg)	60 ± 14	62 ± 13	60 ± 10	58 ± 9
ASA physical status 1/2 (n)	11/13	10/14	13/12	14/12
Duration of sedation (min)	53 ± 20	52 ± 24	50 ± 18	54 ± 36
Fentanyl (μg)	74 ± 28	73 ± 26	78 ± 32	71 ± 39
Midazolam (mg)	2.0	2.0	10.2 ± 3.0	10.9 ± 4.2
Propofol (mg)	335 ± 159	350 ± 198	0	0
Flumazenil (mg)	0	1	0	1
Lidocaine, 0.5% (ml)	16 ± 8	17 ± 12	18 ± 8	21 ± 11

Values are mean ± SD.

saline, the visual analogue scale and digit–symbol substitution test were repeated. In the recovery areas (at 15-min intervals), a research nurse assessed the patient's ability to ambulate without assistance, his/her level of consciousness, and the presence of postoperative side effects (as well as the need for drug treatment). Discharge ("home readiness") required the presence of normal (and stable) vital signs, a level of consciousness similar to their preoperative level, and the ability to ambulate independently. At the time of discharge from the outpatient facility, the patients were asked to recall the three pictures shown during the perioperative period. A short follow-up questionnaire and stamped self-addressed envelope were given to each patient at the time of discharge. In addition, the research nurse also telephoned each patient approximately 24 h after the operation and asked if they had any specific complaints or had experienced an increase in their level of sleepiness after discharge from the ambulatory surgery unit.

The statistical analyses used to compare the four study groups included: Kruskal-Wallis nonparametric analysis of variance for analyzing continuous variables. Evaluation of cognitive and psychomotor function over time was performed using repeated measures of analysis of variance. Discrete variables were analyzed using a Chi-square test. A P value < 0.05 was considered statistically significant. Data are reported as mean values ± SD (in tables 1–3) and ± SEM (in figs. 1 and 2).

Table 2. Picture Recall, Recovery Times, and Overall Effect of Flumazenil on Early Recovery and Resedation after Discharge

	Propofol–Placebo	Propofol–Flumazenil	Midazolam–Placebo	Midazolam–Flumazenil
Preoperative picture recall (%)	92	88	96	92
Postoperative picture recall (%)				
Operating room	42	50	8*	42
PACU	96	92	44*	92
Subjective change after reversal drug (%)	8	0	8	85*
Direct transfer to phase II recovery unit (%)	71	83	32*	85
Recovery times (min, mean ± SD)				
Ambulation	49 ± 25	52 ± 22	67 ± 25*	46 ± 33
"Fit for discharge"	60 ± 23	65 ± 21	84 ± 22*	67 ± 27
Actual discharge	73 ± 27	80 ± 22	103 ± 27*	81 ± 28
Resedation after discharge (%)	0	8	8	33*

PACU = postanesthesia care unit.

* Significantly different from all other treatment groups ($P < 0.05$).

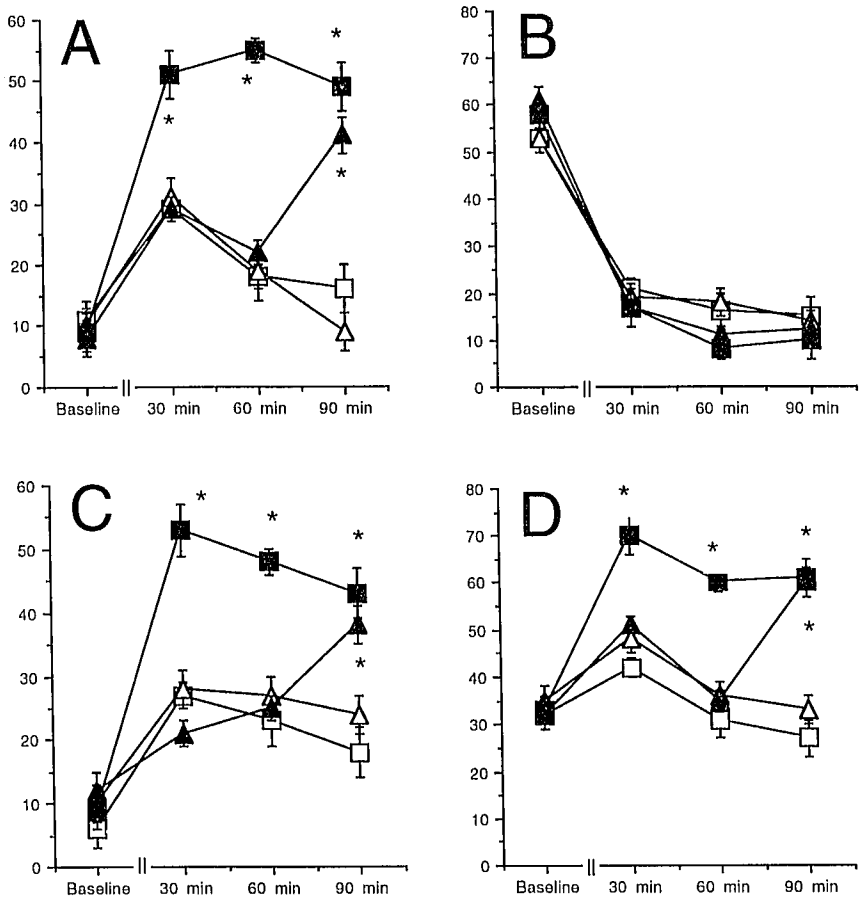

Fig. 1. Visual analogue scales (VAS) for (*A*) sedation or sleepiness (0 = wide awake to 100 = almost asleep), (*B*) anxiety (0 = calm to 100 = extremely nervous), (*C*) clumsiness (0 = none to 100 = maximal), and (*D*) fatigue (0 = energetic to 100 = extremely tired). Baseline values for each variable were similar in all four groups: group 1 (open squares) propofol–placebo, group 2 (open triangles) propofol–flumazenil, group 3 (filled squares) midazolam–placebo, and group 4 (filled triangles) midazolam–flumazenil. Values (means ± SEM) were obtained preoperatively (baseline) and postoperatively at 30-min intervals in the postanesthesia care unit. Baseline values were similar in all four treatment groups. *Significant difference from propofol–placebo (control) group, $P < 0.05$.

Results

The four study groups were similar with respect to demographic variables (table 1). The average maintenance infusion rates of propofol (groups 1 and 2) and midazolam (groups 3 and 4) were comparable in the placebo and flumazenil treatment groups (propofol 105 and 108 $\mu g \cdot kg^{-1} \cdot min^{-1}$; midazolam 2.7 and 2.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively). Adjunctive opioid and local anesthetic dosages were also similar in all four treatment groups (table 1). The drug infusion rates used were adequate to achieve and maintain the desired level of sedation in all subjects.

Propofol produced more pain on injection than midazolam (46–50% *vs.* 8%). Hemodynamic (mean arterial pressure and heart rate) and respiratory (respiratory rate and hemoglobin oxygen saturation) variables were similar in all four treatment groups (data not shown). Intravenous flumazenil, 1 mg, was not associated with a clinically significant change in the hemodynamic parameters (*i.e.*, change in mean arterial pressure or heart rate exceeding 15% of the values recorded at the time the reversal drug was administered). However, the blinded observer could accurately predict when flumazenil had been administered to patients receiving the midazolam infusion (groups 3 and 4), but not in patients receiving the propofol infusion after a 2 mg "premedicant" dose of midazolam (groups 1 and 2) (table 2). In addition, there was no significant difference in the percentage of patients reporting anxiety in the early postoperative period between the flumazenil and placebo-treated patients (8% *vs.* 0%). However, picture recall in the early postoperative period was improved in the midazolam-sedated patients receiving flumazenil compared with those receiving saline (table 2). Finally, administration of flumazenil after midazolam sedation facilitated transfer from the operating room table to a reclining chair and increased direct admissions to the step-down (phase 2) recovery unit (table 2). However, one third of the high-dose mid-

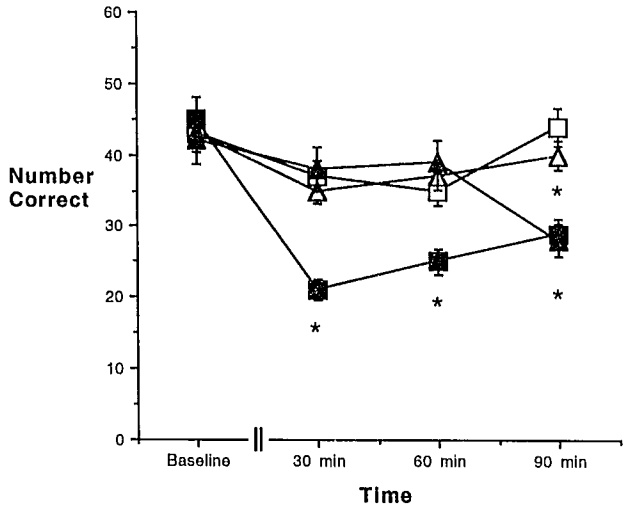

Fig. 2. Digit-symbol substitution test (DSST) results for the four treatment groups: group 1 (open squares) propofol–placebo, group 2 (open triangles) propofol–flumazenil, group 3 (filled squares) midazolam–placebo, and group 4 (filled triangles) midazolam–flumazenil. Values (means ± SEM) were obtained preoperatively (baseline) and postoperatively at 30-min intervals in the postanesthesia care unit. Baseline values were similar for all four groups. *Significant difference from propofol–placebo (control) group, $P < 0.05$.

azolam group who received flumazenil (group 4) reported "resedation" (*i.e.*, a feeling of increased sleepiness after discharge from the PACU) compared with only 0–8% in the other three treatment groups.

Flumazenil significantly improved recovery from the subjective effects of high-dose midazolam (group 4) during the first 60 min in the PACU (fig. 1). In fact, early recovery from flumazenil-reversed midazolam sedation was similar to recovery after propofol sedation (table 2 and fig. 1). However, at the 90-min testing interval, there were no significant differences between the midazolam–placebo and midazolam–flumazenil treatment groups. Similar findings were noted with respect to flumazenil's effects on cognitive function (fig. 2). No differences were found between the four groups with respect to the visual analogue scale confusion and pain scores in the early postoperative period (data not reported). Times from the end of the procedure until the patients were able to ambulate, were judged suitable for discharge, and were actually discharged from the PACU were significantly longer in the midazolam–placebo group (*vs.* the other three treatment groups). Finally, in the propofol-sedated patients receiving 2 mg intravenous midazolam before the infiltration of the local anesthetic solution, 1 mg intravenous flumazenil had no effect on any of the recovery parameters (table 2 and figs. 1 and 2).

All the patients were contacted by telephone after discharge; however, only 50% returned their written questionnaire. The results of the follow-up telephone survey and patient questionnaire revealed that a significantly larger number of patients in the midazolam–flumazenil group (*vs.* the other three groups) reported resedation after discharge from the outpatient facility (table 2). Overall, patient satisfaction was equally high in all four treatment groups (table 3), with over 90% of patients in each group reporting that they would like to receive the same medications for a future operation.

Discussion

Sedative medications are frequently administered during local anesthesia to enhance patient comfort and thereby improve operating conditions during surgery. Although midazolam remains the most popular sedative, the use of propofol for sedation has been increasing because of its more favorable early recovery profile.[2–4] The availability of the specific benzodiazepine antagonist flumazenil (which can rapidly and effectively reverse benzodiazepine-induced sedation and amnesia), appears to facilitate early recovery after midazolam sedation.[7–16] We have found that if residual midazolam sedation was reversed with 1 mg intravenous flumazenil, the early recovery profile was similar to propofol.

In this clinical investigation, routine use of flumazenil at the end of surgery was not associated with an increase in undesirable postoperative side effects. Other clinical studies involving outpatients undergoing dental surgery, endoscopic procedures, and minor ambulatory surgery have also reported that flumazenil facilitated early recovery without producing adverse side effects.[2–4,15–17] When small incremental doses of flumazenil (0.2-mg intravenous boluses) are administered, effective reversal of benzodiazepine-induced sedation and amnesia can be achieved without increasing anxiety levels or eliciting an acute stress response.[7] However, the short duration of flumazenil's reversal effects (<90 min) and the resultant high incidence of resedation (33%) may be a concern when it is administered to patients undergoing ambulatory procedures.

The recurrence of midazolam's central effects was apparent 90 min after administering the reversal agent on both subjective (visual analogue scale) and objective

Table 3. Results of Postoperative Patient Questionnaires Regarding the Perioperative Experience

	Propofol–Placebo	Propofol–Flumazenil	Midazolam–Placebo	Midazolam–Flumazenil
Nervous about sugery				
None	67	67	68	65
Mild	25	25	24	19
Moderate	4	8	4	12
Severe	4	0	4	4
Concerned about MAC technique				
None	67	54	68	65
A little	29	38	28	27
A lot	4	8	4	8
Pain on injection of sedative medication	46*	50*	8	8
Recall local anesthetic infiltration	25	13	16	15
Anxious in the PACU	0	8	0	8
Nauseated in the PACU	4	4	8	8
Confused in the PACU	4	8	4	4
No complaints	100	100	100	96

Values are percentages.

PACU = post anesthesia care unit.

* Significantly different from midazolam groups, $P < 0.05$.

(digit–symbol substitution test) tests. Flumazenil's short duration of action is a result of its rapid elimination from the body (with an elimination half-life of only 60 min.[18,19]) Although the use of flumazenil contributed to an earlier discharge of patients from the ambulatory surgery facility, it can be argued that their discharge may have been premature given the high incidence of resedation. The similar intraoperative conditions and early recovery profiles suggest that the midazolam–flumazenil and propofol techniques are equally acceptable during monitored anesthesia care. However, the comparative costs‖ for the midazolam–flumazenil ($68.67) and propofol ($27.80) techniques indicates a clear cost savings associated with the propofol technique. Moreover, the short duration of flumazenil's reversal effect and the high incidence of resedation further reduces the value of *routine* flumazenil administration in this outpatient population. In the ambulatory setting, the possibility of prematurely discharging patients in whom sedation had been reversed by flumazenil and who might later experience a recurrence of the benzodiazepine's central effects is a major concern.[20]

To achieve and maintain comparable levels of sedation with midazolam and propofol throughout the intraoperative period, we used continuous variable-rate infusions of the two sedative drugs.[2] Analogous to previous studies comparing intermittent bolus doses and continuous infusions of intravenous anesthetics and analgesics,[21] continuous infusions of midazolam# and propofol[4,22] appear to decrease their acute cardiovascular and respiratory depressant effects and may contribute to improved recovery profiles. Because the intraoperative cardiorespiratory and sedative conditions were comparable in all four treatment groups, the differences in the recovery times appear to reflect differences in the pharmacokinetic and pharmacodynamic profiles of the study medications.

This study can be criticized because all patients received at least 2 mg midazolam. However, previous studies involving outpatients receiving small doses of midazolam (2–5 mg) before propofol sedation[23] or anesthesia[24] did not demonstrate delayed recovery. The sedative and amnestic effects of 2 mg intravenous midazolam had apparently dissipated by the end of these

‖ Cost to the pharmacy at the Zale-Lipshy University Hospital in Dallas, Texas

Mora CT, Torjman M, White PF: Unpublished data.

breast biopsy procedures. As expected, the beneficial effects of flumazenil were influenced by the dose of the agonist drug. These data suggest that flumazenil is unlikely to prove efficacious in patients receiving premedicant or coinduction doses of midazolam (*i.e.*, 2–5 mg). Our study also may be criticized for the administration of a standard 1-mg dose of flumazenil. However, the dose of flumazenil was based on the manufacturer's recommendations and the finding that larger doses (> 1 mg) do not improve the recovery profile after ambulatory surgery.** It is possible that the administration of a second dose of flumazenil (0.5–1 mg, intravenously or intramuscularly) before discharge from the day-surgery unit would have prevented the occurrence of postdischarge resedation. Finally, it should be kept in mind that our study population comprised healthy ASA 1 or 2 patients undergoing extensive (deep) breast biopsy procedures and that these findings may not be applicable to other patient populations or clinical settings. The amount of sedative–analgesic medication administered to these young, healthy women might prove to be excessive in older, debilitated patients undergoing similar ambulatory procedures.

In conclusion, flumazenil-reversed midazolam sedation is associated with an early recovery profile similar to that of propofol sedation. However, the midazolam–flumazenil technique is more expensive and compares less favorably to propofol for ambulatory procedures where early discharge is desirable. The use of flumazenil to reverse midazolam-induced sedation and amnesia may lead to a recurrence of sedation after discharge from the ambulatory center. Future studies are needed to define clinical situations (such as procedures outside the operating room) where the use of flumazenil may well prove to be cost-effective.

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