Impact of flumazenil on recovery after outpatient endoscopy: a placebo-controlled trial

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Background: **Flumazenil is an imidazobenzodiazepine that blocks the central effects of benzodiazepines by competitive interaction at the receptor level. In this study we assessed the impact of flumazenil use on postsedation observation time in outpatients undergoing endoscopy.**
Methods: **Sixty outpatients received midazolam for conscious sedation and were randomized after endoscopy to receive intravenous flumazenil (0.1 mg/mL) or placebo until awake or a total of 10 mL was given. All patients were assessed using various psychomotor and cognitive tests at baseline and at 5, 15, 30, 45 and 60 minutes after flumazenil or placebo was administered.**
Results: **The two groups were similar in age, gender, midazolam dose (mg/kg), vital signs, and baseline parameters. The average dose of flumazenil given was 0.41 mg. Sedation scores returned to presedation levels earlier in the flumazenil group, with significant differences compared to placebo at 5 minutes (84.6% vs. 24.2%), 15 minutes (88.5% vs. 57.6%) and 30 minutes (96.2% vs. 66.7%). Other parameters tested were not significantly different for patients receiving placebo compared to those given flumazenil. Sedation scores returned to baseline earlier than other psychomotor and cognitive tests in both groups. Flumazenil reduced the mean observation time from 23.5 minutes to 8.3 minutes ($p < 0.0005$), a difference of 15.2 minutes (64.7%) based on sedation score.**
Conclusions: **Flumazenil significantly reduces postsedation observation time. Actual cost savings will vary depending on staff and facility capacity, patient volume, flumazenil cost, and unit cost of observation time. (Gastrointest Endosc 1999;49:573-9.)**

Most gastrointestinal procedures today are being performed on an outpatient basis, with the use of benzodiazepines to enhance the comfort and efficiency of these procedures. The goal is to achieve a subjective level of amnesia and anxiolysis, balanced against safety and rapid recovery time.

Midazolam is a benzodiazepine that has a peak effect at 1.5 to 2.5 minutes, an elimination half-life of 1.2 to 4 hours and a rapid clearance (6.4 to 11.1 mL/min/kg).[1] Its amnestic response is 70%, with up to 90% of patients showing an impairment in test of memory shortly after the procedure. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline Trieger competency) usually return to baseline within 2 hours but recovery may take up to 6 hours in some cases.[2]

Flumazenil is an imidazobenzodiazepine that reverses benzodiazepine sedating effects by competitive inhibition of the benzodiazepine receptor. Because of a short elimination half-life (53 minutes), a partial return of central nervous system depression has been shown to occur.[3] Several authors have investigated the use of flumazenil as a benzodiazepine antagonist. Jensen et al.[4] found a significant decrease in sedation and improvement in orientation to time and place. These findings were confirmed by several other studies.[5-8] Dodgson et al.[9] found a significant improvement in psychomotor performance with the use of flumazenil, whereas Gjorup et al.[3] did not. Saletin et al.[10] studied patients undergoing outpatient colonoscopy and Rosario and Costa[11] studied patients undergoing upper endoscopy; both reported a shortening of the recovery period with flumazenil.

Received July 14, 1998. For revision September 1, 1998. Accepted October 8, 1998.

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Supported in part by a grant from Roche Laboratories.

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0016-5107/99/$8.00 + 0 **37/1/95033**

It has been suggested that routine administration of flumazenil will decrease the cost of outpatient endoscopy by reducing postsedation observation time (recovery time). Although flumazenil is clearly indicated in cases of benzodiazepine oversedation, its routine use in outpatient endoscopy is not widespread. This is likely due to the relatively high cost of the medication and concern regarding the possibility of resedation because of its short half-life. This prospective, double-blind, placebo-controlled trial was designed to assess the efficacy of flumazenil for reversing the effects of midazolam and to determine the impact of flumazenil use on postsedation observation time.

PATIENTS AND METHODS

Adult patients at least 18 years of age scheduled for outpatient EGD were recruited for this double-blind, placebo-controlled trial. The study was approved by our institutional review board. Patients were excluded from the study if any one of the following was present: evidence of significant renal, hepatic, cardiac, respiratory or psychiatric disease; history of adverse reaction to benzodiazepines; history of dependency on benzodiazepines (daily use); chronic use of antidepressants; continuing use of alcohol by an alcoholic patient; and pregnant or nursing women.

After baseline tests were completed, midazolam was given intravenously in 1 mg increments until the desired level of consciousness was achieved as determined by the endoscopist. By consensus, the appropriate end point of conscious sedation was considered to have been achieved if the patient was sedated but still arousable and the endoscopist was able to safely perform the procedure with minimal or no observable patient discomfort. Immediately after the procedure, each patient was randomized to receive either 2 mL flumazenil (equivalent to 0.2 mg) or placebo (normal saline) intravenously in a double-blind fashion. A random bivariate distribution table was generated within SPSS 7.0 (SPSS Inc., Chicago, Ill.), to which each of the two treatments was randomly assigned. If the desired level of alertness was not achieved after the initial dose, additional flumazenil or placebo was administered in 1 mL increments, each given over 1 minute, until the effects of sedation were reversed or a total of 10 mL (1.0 mg flumazenil) had been given. The blinded investigator dispensed all medications, evaluated each patient's level of consciousness at baseline and before and after reversal with the study medication, and administered all tests. The time and total amount of flumazenil or placebo given were recorded along with any adverse effects.

Vital signs, oxygen saturation, and electrocardiography were monitored throughout the procedure and at baseline, 5, 15, 30, 45 and 60 minutes after sedation. The sedation score and selected psychomotor and cognitive function tests were administered at each of these time intervals. Each patient's presedation test score was used to define return to normal or baseline value.

Selection of tests

Benzodiazepines may affect cognitive and psychomotor performance in multiple ways. It is therefore necessary to use a battery of simple and reproducible tests that can measure a wide spectrum of mental function. The combination of tests selected for this study was designed to evaluate the effects of midazolam on cognitive function, motor performance, perceptual speed, memory and sedation, as well as the efficacy of flumazenil to reverse these effects.[1,2,4,7-9,11-15] A brief description of each test follows.

Paired-word association test

This test evaluates cognitive function and short-term memory. The test is administered in two parts. In the first part, the examiner tells the patient three pairs of words that are associated closely to each other (e.g., knife-fork, east-west, hand-foot). Then the examiner offers the first word of each pair and the patient is asked to respond appropriately with the associated word. The three word-pairs are offered to the patient in random order three times each. In the second part of the test, three pairs of words that have no association to each other are offered as described previously, and then patient recall is tested. The patient receives 1 point for every correct pairing. A total score, from 0 to 18, is obtained by adding the scores in both parts of the test.

Trieger dot-joining test

This is a test of psychomotor performance, adapted by Trieger from the Bender Motor Gestalt test.[15] A series of dots is placed in the form of a three-sided square and a transversely placed bell-shaped curve, with the two figures common at one dot. The patient is asked to connect the dots. Their ability to do so is a measure of fine motor coordination, perception of size and shape relations and judgment. The first test administered is used as the baseline for the patient. Scoring is based on the number of dots missed, the error magnitude in millimeters, presence of extraneous lines, and the experimenter's subjective evaluations of the drawing based on accuracy in length, number of curves, smoothness, extraneous deviations, location, and degree of intersection.

Number connection test

This test is used to assess psychomotor skills and is similar to the Trieger dot-joining test. However, the number connection test requires more judgment and visual coordination. A series of dots is placed randomly on a page with numbers alongside several of the dots. The patient is asked to connect the dots according to ascending numeric order. The score is based on time taken to complete the test and the number of dots missed or inappropriately connected.

Color stimulation test

This is a test of perceptual speed and hand-eye coordination. The patient is provided with a panel of lights consisting of various colors. A particular color of light is illuminated at random and the patient is instructed to strike

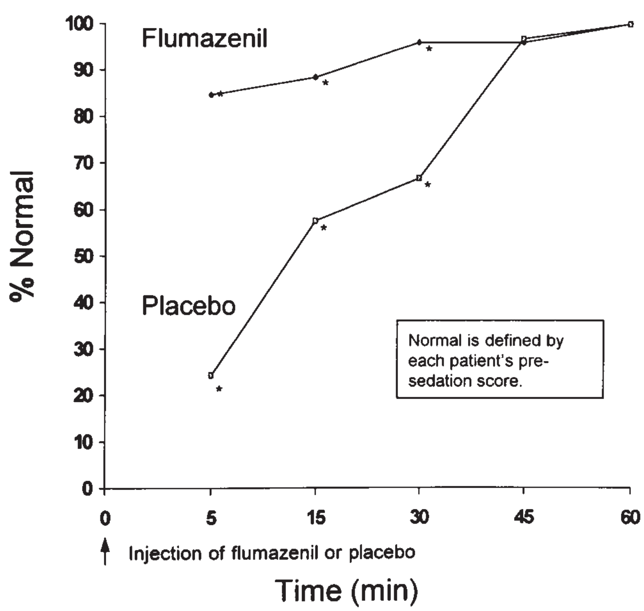

Figure 1. Proportion of patients with a normal sedation score after reversal with flumazenil vs. placebo was significantly different at 5, 15, and 30 minutes, $*p < 0.009$.

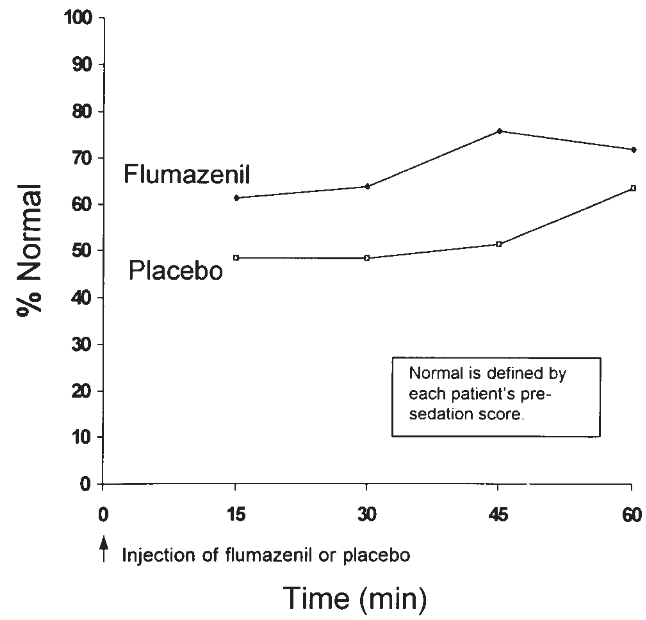

Figure 2. Proportion of patients with a normal number connection test score after reversal with flumazenil vs. placebo was not significantly different.

the corresponding color. A series of lights is illuminated when there is a correct response, and the score is based on reaction time and the total number of correct "hits" made by the patient. The maximum score is 6.

Sedation score

This scoring system is based on assessment of alertness, orientation to time and place, and cooperation and collaboration (Table 1). The patient is given a numeric score with a maximum score of 7 being considered as awake and alert.

Statistics

Sample size was calculated to provide 80% power for the detection of a statistically significant difference between treatment groups at an α level of 0.05, assuming clinical success proportions of 85% for flumazenil and 50% for placebo; the minimum sample size required was 27 subjects per treatment group. The chi-square test and Fisher exact test were used to assess the independence of proportions of the sedation scores, psychomotor tests, and cognitive tests between the study groups. The Student t test was used to assess the difference between the means of the observation time and other baseline variables. The chi-square test and Fisher exact test were used to compare the test scores of the patients who had a low flumazenil/midazolam ratio and those patients who had a high ratio.

RESULTS

A total of 60 patients were enrolled in this study; 1 patient subsequently withdrew from the study and was excluded from analysis. Twenty-six patients were randomized to flumazenil and 33 patients to placebo. There were no significant differences between the two groups with regard to age, gender, midazolam dose, blood pressure, heart rate, oxygen saturation, mean procedure time, and baseline scores for sedation score, number connection test, color stimulation test, Trieger (dot-joining) test and paired-word association test (Table 2). The average dose of placebo or flumazenil required to reverse the effects of midazolam was 7.7 mL versus 4.1 mL (0.41 mg), respectively, $p = 0.0005$. No adverse medication effects were observed in either group.

There was a rapid clinical response to administration of flumazenil in sedated patients. Eighty percent of patients who received flumazenil returned to their normal (baseline) sedation scores at 5 minutes. In contrast, only 20% of those patients who received placebo returned to normal at this same time point. The sedation scores are shown in Figure 1, where significant differences between the two groups were observed at 5, 15 and 30 minutes ($p < 0.009$). By the end of the observation period (60 minutes), all patients in both groups had returned to their baseline values.

Recovery of psychomotor function was assessed using the number connection test (Fig. 2) and the color stimulation test (Fig. 3). At each time point measured, the results were not significantly different between the flumazenil group and the placebo group.

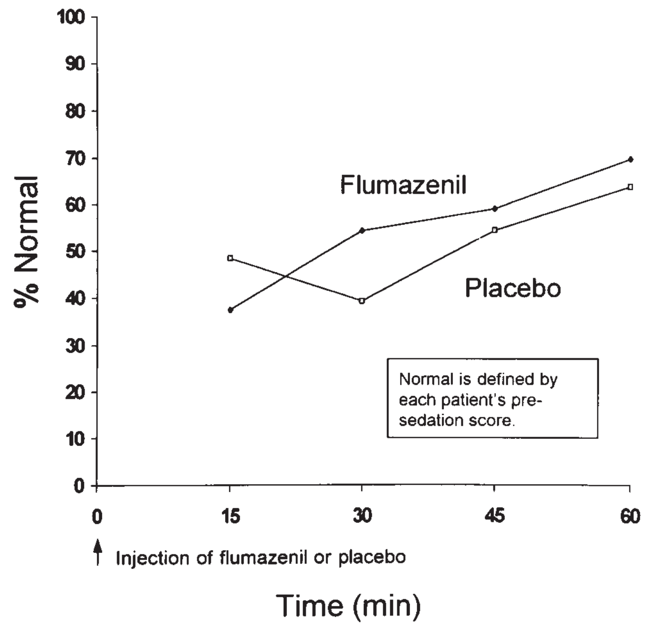

Figure 3. Proportion of patients with a normal color stimulation test score after reversal with flumazenil vs. placebo was not significantly different.

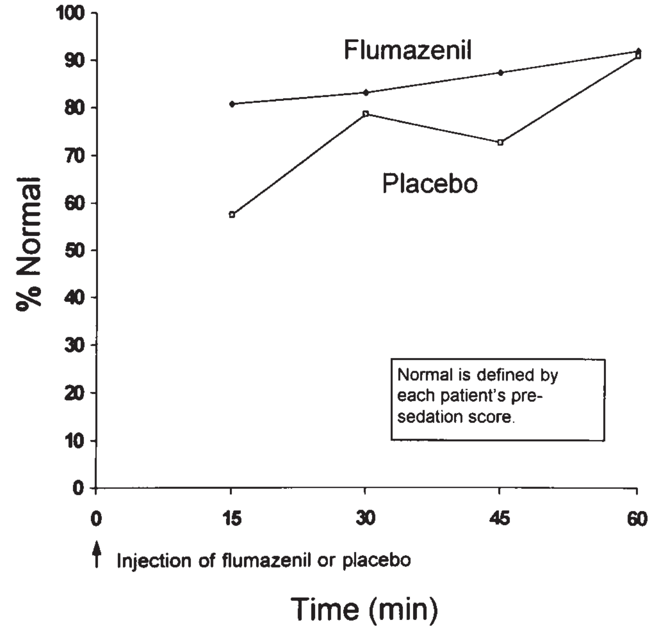

Figure 5. Proportion of patients with a normal paired-word association test score after reversal with flumazenil vs. placebo was not significantly different.

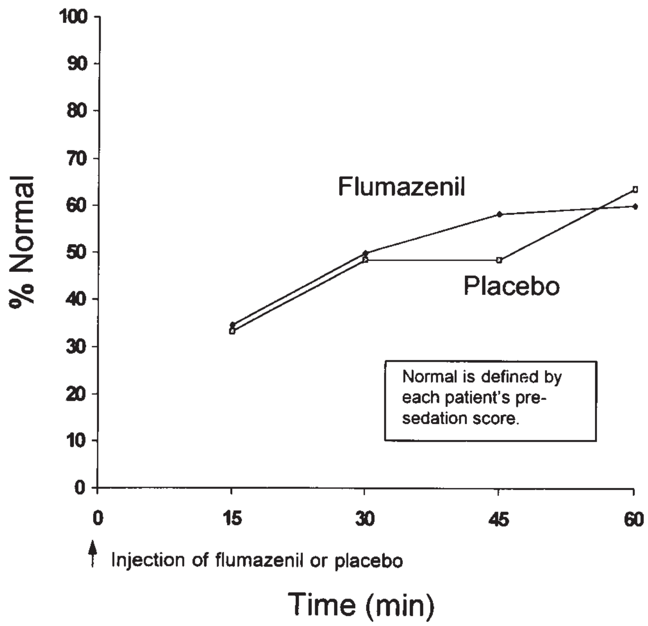

Figure 4. Proportion of patients with a normal Trieger test score after reversal with flumazenil vs. placebo was not significantly different.

Table 1.
Sedation score: patients with a total score of 7 were considered awake and alert

		Score
Assessment of alertness		
Patient sedated, not arousable	0	____
Patient sedated but arousable	1	____
Patient drowsy	2	____
Patient awake	3	____
Orientation for time and place		
Not evaluable	0	____
Partially oriented	1	____
Fully oriented	2	____
Cooperation and collaboration		
Not evaluable	0	____
Execution by imitation	1	____
Execution of verbal order	2	____
Total score		____

Recovery of cognitive function was assessed using the Trieger test (Fig. 4) and the paired-word association test (Fig. 5). At each time point measured, there was no significant difference between the flumazenil group and the placebo group. However, at the end of the study period, 91.5% of all patients (both groups combined) had returned to baseline scores for the paired-word association test, whereas only about 62.7% of all patients had returned to baseline scores for the Trieger test.

For each individual patient in either group, the sedation score returned to baseline earlier than the psychomotor or cognitive tests. Furthermore, at the end of the study period the proportion of patients in the flumazenil group who had returned to their baseline scores varied depending on the test used: 100.0% for the sedation score, 72.0% for the number connec-

Table 2.
Baseline characteristics of the flumazenil group and placebo group

	Flumazenil (n = 26)	Placebo (n = 33)	Statistical test	Level of significance
Age (yr) (mean ± SD)	62.0 ± 15.7	57.9 ± 17.7	*t* test	0.36
Gender (M/F)	11/15	13/20	Chi-square	0.82
Midazolam (mean ± SD)	4.9 ± 2.2	5.6 ± 2.1	*t* test	0.17
Blood pressure (mm Hg)				
Systolic	137 ± 18	140 ± 27	*t* test	0.67
Diastolic	78 ± 15	86 ± 15		0.04
Heart rate (beats/min)	78 ± 14	79 ± 16	*t* test	0.87
Oxygen saturation (%)	96.1 ± 2.1	96.3 ± 2.2	*t* test	0.76
Sedation score	100%	100%	No test	—
Number connection test (errors)	1.4 ± 1.8	1.2 ± 1.0	*t* test	0.54
Trieger test (errors)	2.9 + 3.6	3.6 + 3.0	*t* test	0.47
Color stimulation test (correct answers)	5.8 ± 1.6	5.2 ± 1.9	*t* test	0.18
Paired-word association test (correct answers)	16.6 ± 1.2	15.9 ± 2.0	*t* test	0.08
Mean procedure time (min)	14.6 ± 8.1	14.7 ± 5.7	*t* test	0.76

Mean procedure time, Time from start of endoscopy procedure to injection of flumazenil or placebo.

tion test, 60.0% for the Trieger test, 69.6% for the color stimulation test, and 92.0% for the paired-word association test; a similar trend was seen in the placebo group: 100.0% for the sedation score, 63.6% for the number connection test, 63.6% for the Trieger test, 63.6% for the color stimulation test, and 90.9% for the paired-word association test. Thus, despite the use of flumazenil, residual sedation effects could be demonstrated for up to 1 hour after endoscopy.

Additional analyses were performed to compare the test scores of the patients who had a low flumazenil/midazolam ratio (0.02 to 0.08) and those patients who had a high ratio (0.1 to 0.33). No significant differences were detectable between the two groups in terms of either the sedation score or the results of the other cognitive and psychomotor tests.

The potential cost savings associated with flumazenil use can be estimated if its impact on postsedation observation time is calculated. Observation time in this study was defined as the time required to return to the patient's presedation score after injection of flumazenil or placebo. If the sedation score is used as the basis for discharge, flumazenil use would reduce the mean observation time from 23.5 minutes to 8.3 minutes ($p < 0.0005$), or a reduction of 15.2 minutes (64.7%). Cost-benefit analyses of routine reversal with flumazenil based on sedation score are shown in Table 3. Cost assumptions were based on local institutional costs prorated as follows: acquisition cost of flumazenil at $74.40 per 10 mL multidose vial (1 mg/10 mL) and recovery room cost at $116 per hour.

Table 3.
Cost-benefit analysis of reversal with flumazenil based on sedation score

	Sedation score	
	Flumazenil (n = 26)	Placebo (n = 33)
Recovery time (min)		
Mean	8.3 ± 11.0*	23.5 ± 16.6*
Range	5-60	5-60
Median	5.0	15.0
Room fee	$417.21	$1499.30
Flumazenil used (mL)	107	—
Flumazenil cost	$507.18	—
Total cost	$924.39	$1499.30
Per patient cost	$35.55	$45.43

Recovery time, Time required to return to patient's presedation score after injection of flumazenil or placebo.
*$p < 0.0005$.

DISCUSSION

Flumazenil is an imidazobenzodiazepine that has a high affinity for benzodiazepine receptors. It has no sedative properties and by competing with midazolam for the same benzodiazepine receptor sites, it may reverse their central sedative effects.[16] Clinicians should be aware of the contraindications to use of flumazenil. Seizure activity has been reported in high risk populations such as patients with concurrent major sedative-hypnotic drug withdrawal, known seizure disorders controlled with benzodiazepines, recent therapy with repeated doses of parenteral benzodiazepines, and serious cyclic antidepressant poisoning. Caution is indicated for patients with known panic disorders, severe liver disease or patients with head trauma. Flumazenil use should be avoided in pregnant patients. Because the half-life of midazolam (2 hours) is longer than the half-life of flumazenil (53 minutes), there has been some concern regarding a possible resedating effect, as reported by Knudsen et al.[17]

Reversal of sedation effects as measured by the sedation score were significantly different between the flumazenil group and the placebo group at 5, 10, 15 and 30 minutes. On the other hand, the results of the psychomotor and cognitive tests were not significantly different between the two groups at each time interval up to 60 minutes. Rosario and Costa[11] reported significant differences between flumazenil and placebo groups in the performance of the Trieger, Number Connector, and Digit Symbol tests at 30 minutes after sedation but not at 60 minutes. Birkenfeld at al.[7] reported that flumazenil shortened the time required to perform the Number Connector Test to 108% of baseline versus 160% for patients who received placebo. The average dose of midazolam used in the latter study was 8 mg, which was higher than the mean dose used in our study (4.9 mg). Pearson et al.[12] reported that patients receiving flumazenil were able to complete the Trieger Dot-Joining Test faster than those in the placebo group. They also reported that amnesia was retained for the endoscopic procedure but not for events occurring after administration of flumazenil.

In this study only 2 of every 3 patients regained their baseline psychomotor and cognitive functions at the end of the study (60 minutes) regardless of whether they received flumazenil, indicating the presence of residual sedative effects that were not detected by using the sedation score alone. A notable exception was the paired-word association test in which 91.5% of patients returned to baseline values at 60 minutes, whereas with the Trieger test only 62.7% returned to baseline. Because both of these tests are designed to measure cognitive function, we hypothesize that recovery of verbal function (paired-word association test) occurs more rapidly than visual function (Trieger test) after conscious sedation.

Full return of psychomotor and cognitive functions consistently lagged behind the sedation score for individual patients in both groups. Thus, the patient may feel subjectively normal but remain physically and mentally impaired. Therefore, regardless of flumazenil use, the patient should not be permitted to operate heavy machinery, drive a motorized vehicle, or engage in legal decision making after conscious sedation.

Using the sedation score as the clinical criterion for discharge, flumazenil use reduced the observation time by 15 minutes to an average of 8 minutes. This is a 65% reduction in observation time, which could result in significant cost savings in some high volume outpatient endoscopy centers. On the other hand, it could be argued that even in a highly efficient endoscopy center, a patient who is fully awake at the end of the procedure cannot be discharged in such a short period of time. Given the latter limitation, the potential for cost savings would be institution dependent.

The results of this study can be used by each facility to perform their own cost-benefit analyses. Whether routine flumazenil use after sedation proves to be cost-effective for a facility depends on multiple factors that tend to vary among institutions. These include staff and facility capacity, patient volume, the acquisition cost of flumazenil, the unit cost of observation time, and the criteria for discharge used. This study has quantified the impact of routine flumazenil use on postsedation observation time in endoscopy outpatients without significant hepatic, renal or cardiopulmonary compromise. Because clearance of flumazenil occurs primarily by hepatic metabolism and is dependent on hepatic blood flow, additional studies are needed to determine the impact of flumazenil reversal on postsedation observation time in patients with cirrhosis and portal hypertension.

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