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Benzodiazepine Antagonism Does Not Provoke a Stress Response

Paul F. White, Ph.D., M.D., Audrey Shafer, M.D.,† Walter A. Boyle III, M.D.,‡*
Van A. Doze, B.S.,§ Steven Duncan, M.D.†

Acute anxiety reactions have been reported following antagonism of benzodiazepine-induced sedation. In this study, the level of sedation and anxiety was assessed in 30 patients randomly assigned to receive either saline or flumazenil (a benzodiazepine antagonist) after midazolam sedation according to a double-blind protocol. Carefully titrated doses of flumazenil, 0.8 ± 0.2 mg (mean ± SD), effectively reversed residual midazolam-induced sedation without producing significant changes in the patients' level of anxiety. In addition, plasma epinephrine, norepinephrine, vasopressin, and β-endorphin concentrations were measured in a subset of patients (n = 5) from each group. The levels of these stress hormones did not acutely change following flumazenil (or saline). These results indicate that flumazenil, 0.6–1.0 mg iv, can antagonize midazolam sedation without producing acute anxiety or evidence of a stress response. (Key words: Anesthetic, intravenous: midazolam. Antagonists: benzodiazepine; flumazenil. Anxiety: benzodiazepine. Benzodiazepine: midazolam; sedation. Hormones: β-endorphin; vasopressin (ADH). Sympathetic nervous system: catecholamines.)

BENZODIAZEPINES are widely used during the perioperative period because of their ability to produce sedation, amnesia, and relief of anxiety (anxiolysis).[1] However, oversedation and prolonged recovery following benzodiazepine administration can occur because of the marked variability in individual patient responses to these compounds. Thus, a specific antagonist that could rapidly reverse the residual sedative-amnestic effects of benzodiazepines could have significant clinical utility.

Early clinical studies indicate that flumazenil (Ro 15-1788) effectively antagonizes benzodiazepine-induced sedation.[2–4,¶] However, some investigators reported that the antagonist also precipitated acute anxiety reactions.[4,¶] These reactions were not only unpleasant but could also prove to be harmful in certain situations, particularly in patients with coronary artery disease. This study was designed to examine the ability of flumazenil to reverse the residual CNS-depressant effects of midazolam. We evaluated changes in the patients' levels of both anxiety and sedation as well as plasma stress hormone levels, before and after midazolam sedation and following flumazenil (or saline) administration.

Materials and Methods

Thirty consenting unpremedicated ASA physical status 1–3 outpatients scheduled for minor elective surgical (or diagnostic) procedures under local (or topical) anesthesia with iv sedation were randomly assigned to one of two treatment groups. This double-blind protocol was approved by the local Institutional Review Board. (This investigation was part of a multicenter study sponsored by Hoffmann-La Roche Inc., Nutley, New Jersey.) All subjects were fasted for a minimum of 12 h prior to their scheduled procedure. Patients with a history of illicit drug, excessive alcohol, or recent benzodiazepine use were excluded.

One hour prior to their procedure, patients were asked to assess their level of sedation and anxiety using separate 100-mm linear analog scales (with 0 = awake/alert to 100 = unresponsive/sleeping, and 0 = calm/relaxed to 100 = anxious/nervous, respectively). Immediately after insertion of the iv catheter, peripheral venous blood samples were obtained from the first 15 patients enrolled in the study. Subsequently, plasma samples from the first five patients in each of the treatment groups were analyzed to determine plasma catecholamine (norepinephrine and epinephrine), vasopressin, and β-endorphin concentrations using standardized radioenzymatic (catecholamine) and radioimmune (β-endorphin, vasopressin) assay techniques.[5,6] The lower limit of assay sensitivity and the range of variability for norepinephrine and epinephrine, vasopressin, and β-endorphin were 15 pg/ml and 5–10%, 1 pg/ml and 7–14%, and 8 pg/ml and 10–20%, respectively.

All patients were administered meperidine, 0.5 mg/kg iv (25–50 mg), 3–5 min prior to initiating sedation with midazolam. An initial dose of midazolam, 2 mg iv, was followed by incremental bolus doses of midazolam, 1–2 mg iv, throughout the procedure to maintain a level of sedation such that the patient was sleeping but immediately responsive to verbal stimulation. No other centrally

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* Professor of Anesthesiology, Director of Clinical Research.
† Clinical Instructor in Anesthesia or Medicine (Pulmonary).
‡ Assistant Professor of Anesthesiology.
§ Medical Student.
Address reprint requests to Dr. White: Department of Anesthesiology, Washington University School of Medicine, Box 8054, 660 South Euclid Avenue, St. Louis, Missouri 63110.

¶ Louis M, Forster A, Suter PM, Gemperle M: Clinical and hemodynamic effects of a specific benzodiazepine antagonist (Ro 15-1788) after open heart surgery (abstract). ANESTHESIOLOGY 61:A61, 1984

active medications were administered during the perioperative period.

On arrival in the recovery room, the sedation and anxiety analog scales were repeated, and a second set of blood samples was obtained from the 15 endocrine study patients for determination of plasma stress hormone concentrations as described previously. Mean arterial pressure (MAP) and heart rate (HR) were recorded at 2–3 min intervals using a noninvasive Dinamap™ hemodynamic monitor. Patients were then given either saline (control) or flumazenil 0.1 mg/ml (total dosage range, 0.6–1.0 mg iv) over 3–5 min. The antagonist (or saline) was administered using a clinical titration method, *i.e.*, a 2-ml initial iv bolus dose followed by 1 ml iv boluses every 60 s until a clinically apparent reversal effect was observed or a total dose of 10 ml was injected. Subsequently, at intervals of 5, 15, 30, 60, 120, and 180 min, the analog scale tests were repeated in all patients. Blood samples for determination of stress hormone levels were again obtained from the 15 endocrine study patients at intervals of 5, 15, 60, and 120 min after reversal. All patients were encouraged to ambulate approximately 60–90 min after receiving flumazenil (or saline). Twenty-four-hour follow-up questionnaires were used to assess the patients' subjective responses to the study medication.

Statistical analysis was performed using the Systat data analysis system.** Continuous variables were analyzed using two-way analysis of variance with repeated measures and the Wilcoxon rank sum test. Descriptive variables were analyzed using chi-square analysis with Fisher's exact test, with between group comparisons performed using Student's *t* test. Data are presented as mean values ± SD, $P < 0.05$ was considered statistically significant.

Results

The two groups of patients were comparable with respect to demographic data (table 1). The preoperative (baseline) hemodynamic variables and levels of sedation and anxiety were similar for the two treatment groups. Baseline plasma norepinephrine and β-endorphin concentrations were also identical. Baseline plasma epinephrine and vasopressin concentrations differed significantly between the two groups; however, the differences were small and the mean hormone levels in both groups were within the normal concentration range.[5,6]

Prior to administration of flumazenil or saline, the sedation scores were increased significantly above baseline in both groups. However, the sedation scores returned to the preoperative (baseline) levels within 15 min after flumazenil administration, while the sedation scores in the control (saline) group remained elevated for up to 120 min (fig. 1). Although the anxiety scores decreased with sedation, they did not increase following either saline or flumazenil (fig. 1). Thus, as compared with the control group, flumazenil (0.84 ± 0.18 mg iv) significantly decreased sedation for 120 min without increasing anxiety.

TABLE 1. Demographic Data and Baseline Values for the Saline (control) and Flumazenil Treatment Groups

	Control	Flumazenil
Number	11	19
Age (yr)	48 ± 15	48 ± 21
Weight (kg)	75 ± 14	60 ± 11
Height (cm)	171 ± 9	166 ± 11
Baseline scores		
Sedation (mm)	12 ± 12	11 ± 18
Anxiety (mm)	36 ± 22	42 ± 36
Baseline hormone levels		
Norepinephrine (pg/ml)	368 ± 230	382 ± 171
Epinephrine (pg/ml)	67 ± 9	30 ± 18†
β-endorphin (pg/ml)	69 ± 14	78 ± 15
Vasopressin (pg/ml)	2.4 ± 1.0	7.1 ± 3.7†
Sedation time* (min)	66 ± 50	42 ± 28
Midazolam dose (mg)	12.6 ± 9.6	11.0 ± 10.2
Meperidine dose (mg)	31 ± 12	31 ± 10

Values are mean ± SD.
* Period of time during which midazolam was administered.
† $P < 0.05$ *versus* control group.

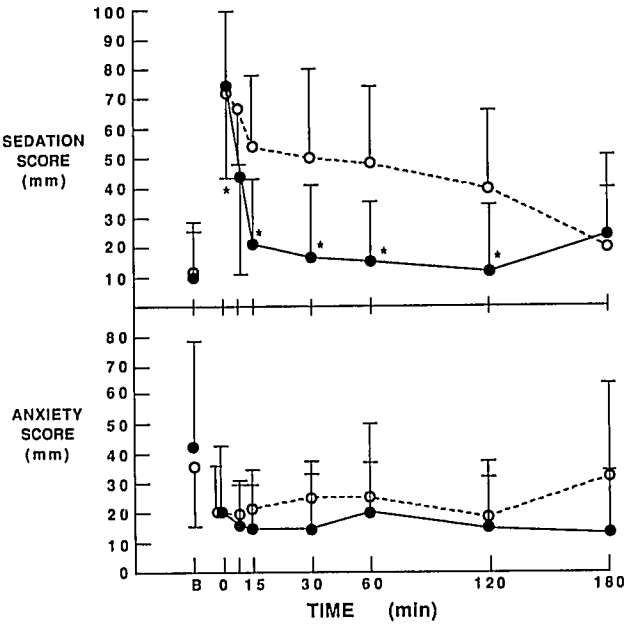

FIG. 1. Levels of sedation and anxiety immediately before (B) and at the conclusion of midazolam sedation (O); and as a function of time following treatment with either saline (control, O----O) or flumazenil (● —— ●). Data represents mean values ± S.D. Asterisks indicate significant differences between the two treatment groups, $P < 0.05$.

** Wilkinson L: Systat: The System for Statistics. Evanston, Illinois, Systat, Inc., 1986

TABLE 2. Changes in the Level of Catecholamines (norepinephrine and epinephrine) and Vasopressin in the Saline (control) and Flumazenil Treatment Groups

Treatment Group	Time before (0) and after Reversal (min)				
	0	5	15	60	120*
Norepinephrine (pg/ml)					
Control (n = 5)	230 ± 126	201 ± 114	186 ± 91	182 ± 89	242 ± 138
Flumazenil (n = 5)	327 ± 101	302 ± 106	353 ± 108	324 ± 107	412 ± 196
Epinephrine (pg/ml)					
Control (n = 5)	73 ± 76	67 ± 58	53 ± 17	63 ± 21	158 ± 122
Flumazenil (n = 5)	49 ± 55	43 ± 32	47 ± 37	33 ± 23	89 ± 39
Vasopressin (pg/ml)					
Control (n = 5)	3.7 ± 2.9	2.5 ± 1.9	2.3 ± 1.6	1.8 ± 1.1	1.6 ± 1.2
Flumazenil (n = 5)	6.2 ± 4.3	7.0 ± 4.4	6.8 ± 4.3	6.8 ± 3.9	6.2 ± 3.8

Values are mean ± SD.

* Blood samples obtained after ambulation.

There were no statistically significant changes in MAP or HR following treatment in either group. Furthermore, in the endocrine study patients, there were no acute changes in plasma catecholamine or vasopressin concentrations during the study period (table 2). Similarly, plasma β-endorphin concentrations 5–10 min after flumazenil antagonism (73 ± 13 pg/ml) were unchanged from the preoperative baseline (78 ± 15 pg/ml) and post-midazolam (71 ± 12 pg/ml) levels. On the follow-up questionnaire, none of the patients reported feeling uncomfortable or acutely anxious after administration of the study drug. All of the flumazenil-treated patients stated that they would be willing to receive the reversal medication again in the future.

Discussion

The results from this study indicate that flumazenil (0.6–1.0 mg iv), a specific benzodiazepine antagonist, is capable of antagonizing midazolam-induced sedation without acutely increasing MAP, HR, or anxiety levels in patients undergoing minor diagnostic and therapeutic procedures. In addition, in this small series, flumazenil did not produce significant changes in the plasma norepinephrine, epinephrine, β-endorphin, or vasopressin levels. Thus, flumazenil is capable of antagonizing midazolam-induced sedation without producing acute anxiety reactions or neurohumoral evidence of a stress response.

Our findings regarding the ability of flumazenil to antagonize midazolam sedation without producing significant changes in MAP and HR are in agreement with other results presented at a recent meeting.[7,8] In one of these reports, antagonism of midazolam-induced sedation and amnesia was not associated with significant changes in hemodynamic variables or serum catecholamine levels following regional anesthesia.[7] It was also reported that incremental doses of flumazenil, 0.3 mg iv, produced "a smooth recovery without major adverse circulatory reactions" in patients with coronary artery disease who had received a benzodiazepine for sedation during cardiac catheterization.[8]

However, our data conflict with earlier animal†† and human studies.[4,¶] In the clinical studies,[4,¶] flumazenil antagonism precipitated clinically significant acute anxiety reactions in 20–50% of the treated patients. In addition, increases in plasma catecholamine levels have also been reported following flumazenil administration.[9,10,††] Although the reasons for the differences between our results and those reported previously are not completely clear, the earlier investigations utilized significantly higher doses of flumazenil (0.1 mg/kg) than were administered in our study (0.01 mg/kg). Thus, although flumazenil can safely and effectively reverse excessive sedation following administration of a benzodiazepine agonist, these studies suggest that careful titration of the antagonist may be necessary to produce the desired clinical effect without producing untoward psychologic sequelae and acute stress reactions.

Another possible explanation for the differences between our findings and those of previous investigators[4,¶] may relate to the different surgical populations studied. When flumazenil was administered to antagonize the residual effects of benzodiazepines used as adjuvants during cardiac surgery,¶ the stress and anxiety associated with the procedure, as well as enhanced awareness of surgical pain, may have contributed to the adverse psychologic reactions reported. Indeed, a recent editorial suggested that rapid emergence from general anesthesia may be undesirable because of acute awareness of pain.[11] Although flumazenil antagonism of benzodiazepine supplemented general anesthesia for laparoscopy did not result in an increased incidence of complaints of pain,[12] adequate pain control may be important to avoid adverse sequelae following flumazenil antagonism after more stressful surgical

†† Glisson SN, Falinski BA: Reversal of midazolam's effect on autonomic responses in dogs by the benzodiazepine antagonist Ro 15-1788 (abstract). ANESTHESIOLOGY 61:A324, 1984

procedures. Thus, the clinical and endocrine responses to flumazenil antagonism of benzodiazepine-induced sedation following major surgical procedures may differ from the response to flumazenil when it was used to antagonize sedation after relatively minor procedures.

To meet the criteria for entry into this study, the multicenter protocol design required that we maintain a state of sedation such that the patient was lethargic and drowsy but responsive to verbal stimulation throughout the entire procedure. Despite this restriction, some patients in the saline group experienced rapid (spontaneous) awakening after arriving in the postanesthesia care unit, which appeared identical to the recovery pattern noted after flumazenil administration. Thus, careful titration of midazolam (*e.g.*, decreasing the dosage at the end of the procedure) should obviate the need for an antagonist in most patients receiving benzodiazepine sedation. In addition, the short elimination half-life of flumazenil (0.7–1.8 h)[10] might contribute to a recurrence of sedation after discharge from the recovery facility when it is used to antagonize benzodiazepine actions on the CNS in the outpatient setting.

In conclusion, this clinical study demonstrates that a titrated dose of flumazenil can rapidly reverse midazolam-induced sedation following minor procedures without provoking anxiety reactions or undesirable neuroendocrine responses.

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