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Flumazenil Antagonism of Midazolam-induced Ventilatory Depression

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Flumazenil, a benzodiazepine antagonist, reliably reverses midazolam-induced sedation; however, its effect on respiratory depression has not been established completely. Twelve healthy volunteers received sufficient midazolam (0.13 ± 0.01 $mg \cdot kg^{-1}$ mean ± SE) to render them unresponsive to verbal command; they then received flumazenil 1.0 mg or placebo (flumazenil vehicle) in a randomized, double-blind fashion. Ventilatory drive was measured before and after administration of midazolam, as well as 3, 30, 60, and 120 min after administration of flumazenil or placebo. Seven to 30 days later, the study was repeated, with subjects receiving placebo or flumazenil (whichever they had not received during their first trial). Midazolam caused significant decreases in the slope of the CO_2 response (−29 ± 5%; $P < 0.005$); minute ventilation ($\dot{V}_E$) at end-tidal CO_2 tension ($P_{ET_{CO_2}}$) = 46 mmHg (−28 ± 4%; $P < 0.001$), and tidal volume at $P_{ET_{CO_2}}$ = 46 mmHg (−44 ± 4%; $P < 0.005$). Three minutes after intravenous administration of flumazenil 1.0 mg, $\dot{V}_E$46 and tidal volume increased to 108 ± 6% and 105 ± 6%, respectively, of their premidazolam values; at the same time after administration of placebo, $\dot{V}_E$46 and tidal volume remained significantly depressed (between groups, $P < 0.005$ for each variable). Thirty minutes later, these variables did not differ between groups, probably because the effects of flumazenil and midazolam were diminishing. Neither flumazenil nor placebo affected the slope of the CO_2 response, which remained significantly ($P < 0.05$) less than premidazolam values for 2 h after both treatments; this variable never differed between groups. By virtue of its ability to reverse some components of midazolam-induced ventilatory depression, flumazenil may help improve resting ventilation in patients who have received midazolam. (Key words: Antagonists: benzodiazepine; flumazenil. Carbon dioxide: ventilatory response. Hypnotics, benzodiazepines: midazolam. Measurement techniques: Read rebreathing method.)

BENZODIAZEPINES significantly depress the ventilatory response to hypercarbia[1–3] and hypoxia.[4,5] Ventilatory depression is especially likely to occur when benzodiazepines are administered in combination with other respiratory depressants (*e.g.*, opioids)[6,7] or to patients with preexisting pulmonary disease.[3]

Despite a number of clinical reports suggesting that physostigmine[8,9] or naloxone[10] may nonspecifically reverse benzodiazepine-induced sedation, neither of these agents has been shown to reliably antagonize benzodiazepine-induced ventilatory depression.[11,12] Flumazenil, a specific benzodiazepine antagonist, reliably reverses benzodiazepine-induced sedation; however, previous studies provide conflicting data regarding its ability to reverse the associated ventilatory depression. Although flumazenil may partially reverse the effect of midazolam on resting end-tidal CO_2 tension ($P_{ET_{CO_2}}$),[13] studies have shown both improvement[13,14] and additional depression of the slope of the ventilatory response to CO_2.§ We designed the current, double-blind, placebo-controlled crossover study to more clearly define the effect of flumazenil on midazolam-induced depression of hypercarbic ventilatory drive. To accurately establish the slope and displacement of the CO_2 response curves, we used a combination of rebreathing and steady-state techniques.[15]

Materials and Methods

Fifteen healthy male volunteers, ranging in age from 22 to 33 yr, with weights ranging from 66 to 95 kg, gave written, informed consent to participate in this study approved by the Institutional Review Board. Prestudy screening with a Collins Eagle II® spirometer revealed that, for all subjects, forced vital capacity (FVC), 1-s forced expiratory volume (FEV_1), and the ratio of FEV_1/FVC were within 15% of the values predicted on the basis of height and age.[16] We excluded people with a history of smoking or of benzodiazepine use during the month preceding the study. Subjects abstained from alcohol for 1 week, from caffeine for 24 h, and from all oral intake for 8 h before each study session.

Throughout each study, we continuously monitored arterial O_2 saturation (Sp_{O_2}; Ohmeda 3700, revision XJ1),[17] ECG, and noninvasive blood pressure (Propaq® 104). Subjects received 0.9% NaCl by the peripheral vein at 100 ml/h. During all respiratory measurements, subjects lay supine, while listening to classical music through in-ear headphones.

Overall Study Design

Each subject participated on two study days; on each of these days, we first determined baseline values for the

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§ Mora CT, Torjman M, DiGiorgio K: Sedative and ventilatory effects of midazolam and flumazenil (abstract). ANESTHESIOLOGY 67: A534, 1987.

slope and displacement of the CO_2 ventilatory response curve (see below). We then administered midazolam, 0.01 $mg \cdot kg^{-1}$ intravenously (iv), over 10 s at the beginning of each minute. At the end of each minute, we asked subjects to repeat the phrase "The quick brown fox jumps over the lazy dog" and determined their level of consciousness on the 5-point scale summarized in table 1. Midazolam administration continued until subjects reached a consciousness score of 1; people who did not reach this level after receiving 0.2 $mg \cdot kg^{-1}$ midazolam (over 20 min) were eliminated from the study.

Two minutes after subjects reached a sedation score of 1, we performed "postmidazolam" ventilatory response determinations. Immediately after these measurements, we administered flumazenil 1.0 mg or an equal volume (10 ml) of placebo (flumazenil vehicle) iv over 5 min, as determined by a randomization table. To ensure the double-blind nature of the study, the manufacturer packaged flumazenil and placebo in identical ampules, identified only by subject and day numbers (*e.g.*, subject 4, day 2); thus, the contents of the ampules remained unknown to the investigators until the entire study was completed. Three, 30, 60, and 120 min after the last dose of the study drug, we determined "post study drug" ventilatory responses.

Between ventilatory response determinations, subjects breathed O_2 (2 l/min) through a nasal cannula; for safety, Sp_{O_2} was monitored continuously. Subjects remained in the laboratory until they were fully awake, at which time they were escorted home. Seven to 30 days later, subjects underwent the identical testing procedure, this time receiving the study drug (placebo or flumazenil) that had not been used during the previous trial.

Ventilatory Response Determination

The circuit shown in figure 1 enabled us to determine the slope and displacement of the hypercarbic ventilatory response curve. A Hans Rudolf #3700 heated pneumotachograph, along with a Validyne® DP45 differential pressure transducer, carrier demodulator, and integrator, determined ventilatory volumes at BTPS; we performed a 3-point volume calibration and linearity check before each set of measurements with a Collins #3200 "supersyringe." An Instrumentation Laboratories IL282 CO_2 analyzer, calibrated at three CO_2 tensions with Linde primary standard-grade mixtures of CO_2 in O_2 (±0.01%), monitored $P_{ET_{CO_2}}$ continuously. A Commodore® 8032 microcomputer and Connecticut Microcomputer AIM-16® analog-to-digital converter recorded breath-by-breath values of $P_{ET_{CO_2}}$, tidal volume, and minute ventilation. The measured resistance of the breathing circuit was approximately 0.03 $cmH_2O \cdot l^{-1} \cdot min$ at a flow rate of 100 $l \cdot min^{-1}$. The variable-speed blower and CO_2 absorber (soda lime) enabled us to control $P_{ET_{CO_2}}$s precisely during steady-state determinations; during Read rebreathing tests (see below), this portion of the circuit was clamped.

Each ventilatory response measurement consisted of two parts: a Read rebreathing test,[18,¶] to determine the slope, and a "steady-state" test,[19] performed at a constant $P_{ET_{CO_2}}$, to determine the displacement of the CO_2 ventilatory response curve. For the rebreathing tests, we clamped off the CO_2 absorber and circulator (fig. 1) and filled the rebreathing bag with 7% CO_2 in O_2.

After taking three deep breaths from the circuit, subjects continued to breathe normally through the facemask for 4 min, by which time $P_{ET_{CO_2}}$ exceeded 60 mmHg. The computer determined the least-squares slope of the ventilatory response curve from five-breath averages[20] of $P_{ET_{CO_2}}$ and minute ventilation ($\dot{V}_E$).

As soon as the rebreathing test was complete, we unclamped the CO_2 absorber circuit and adjusted the absorber gas flow to maintain a $P_{ET_{CO_2}}$ of 46 ± 1 mmHg. A low flow of O_2 (≈300 $ml \cdot min^{-1}$) from the gas machine met the subjects' metabolic requirements while keeping the volume of the rebreathing bag constant. After subjects equilibrated at this steady-state CO_2 tension for 6 min, we determined 20-breath averages for $\dot{V}_E$ ($\dot{V}_E46$) and tidal volume (TV46). Upon completion of the steady-state measurement, subjects breathed room air with supplemental O_2 through a nasal cannula until the next rebreathing test. Less than 15 min was required to perform a complete ventilatory response determination (rebreathing plus steady state).

Statistical Analysis

Ventilatory drive may vary significantly from day to day[21]; therefore, before performing statistical analyses, we expressed all respiratory variables (slope, $\dot{V}_E46$, and TV46) as fractions of that day's corresponding premidazolam control value. Two-way analysis of variance

Table 1. Scoring for Level of Consciousness

Score	Description
4	Awake and alert
3	Slight ptosis (<50%) of eyelids Mild slowing or slurring of speech
2	Marked ptosis (>50%) or closure of eyes Responds with slurred speech only after name called loudly or repeatedly
1	Eyes closed Responds with few recognizable words only after mild prodding or shaking
0	Asleep Does not respond to mild prodding or shaking

¶ Read DJC: A clinical method for assessing the ventilatory response to carbon dioxide. Australasian Ann Med 16:20–32, 1967.

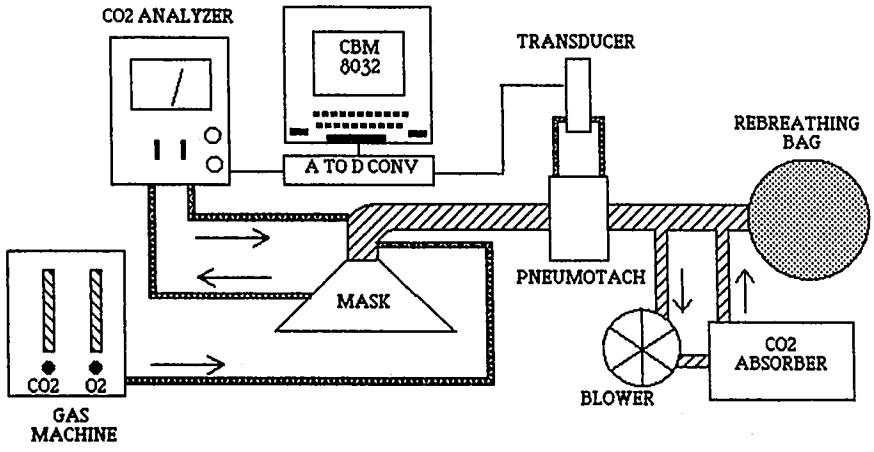

FIG. 1. Circuit for CO_2 response determinations. The hoses leading to the blower and CO_2 absorber were clamped during Read rebreathing tests. Adjustment of the flow through the absorber allowed a constant end-tidal CO_2 tension to be maintained for the steady-state tests.

(ANOVA), followed by Dunnett's test for multiple comparisons with a control, determined the significance of changes in ventilatory variables within each treatment group.[22] To perform within-group comparisons of the changes in ventilatory control associated with flumazenil and placebo, we used two-way ANOVA. Three-way ANOVA (treatment × subject × time) and Bonferroni-corrected *t* tests determined the significance of between-group differences 3, 30, 60, and 120 min after administration of the study drug. The Bonferroni-corrected Kruskal-Wallis analysis of variance was used to compare the awareness scores between groups, whereas the corrected Wilcoxon signed-ranks tests were used to compare scores at different times within groups. Parametric data are shown as mean ± SE, whereas median values are shown for nonparametric data. Throughout the analysis, a P value less than 0.05 indicated significance.

Results

Of the 15 subjects who entered the study, 12 completed the protocol; 2 were eliminated because they did not reach a sedation score of 1 (table 1) after administration of a total midazolam dose of 0.2 $mg \cdot kg^{-1}$, whereas a third subject became agitated during the postmidazolam determination of hypercarbic ventilatory drive. For the remaining subjects, the midazolam dose necessary to achieve a sedation score of 1 was 0.13 ± 0.01 $mg \cdot kg^{-1}$ (mean ± SE), before both the flumazenil and the placebo trials. All subjects were hemodynamically stable throughout the study sequence; heart rates and blood pressures always remained within 20% of baseline (table 2).

As required by the study design, awareness scores decreased significantly after administration of midazolam (fig. 2; $P < 0.01$). Within 3 min after administration of flumazenil, the median awareness scores no longer differed significantly from their premidazolam baseline values. However, 2 h later, the level of consciousness was again significantly ($P < 0.05$) less than that before midazolam. Three, 30, and 60 min after administration of placebo, awareness scores remained significantly less than before administration of midazolam ($P < 0.05$). These awareness scores also were significantly less than those observed at the corresponding times after administration of flumazenil ($P < 0.005$ at 3 and 30 min; $P < 0.05$ at 60 min). Awareness scores 120 min after administration of placebo did not differ from those observed at the same time after administration of flumazenil. Three hours after administration of flumazenil or placebo, subjects were fully awake.

Baseline premidazolam values of respiratory variables did not differ between flumazenil and placebo trials. Midazolam reduced the slope of the CO_2 ventilatory response from 1.90 ± 0.16 to 1.43 ± 0.18 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.005$) in flumazenil trials and from 1.89 ± 0.16 to 1.25 ± 0.11 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.005$) in placebo

TABLE 2. Effects of Flumazenil *versus* Placebo on Blood Pressure and Heart Rate in Subjects Sedated with Midazolam

	Placebo		Flumazenil	
	Before	After	Before	After
Heart rate (beats per min)	68 ± 2	66 ± 3	65 ± 2	60 ± 2
Systolic blood pressure (mmHg)	114 ± 2	109 ± 3	111 ± 3	108 ± 2
Diastolic blood pressure (mmHg)	67 ± 2	61 ± 2	62 ± 3	63 ± 2

Values are mean ± SE.

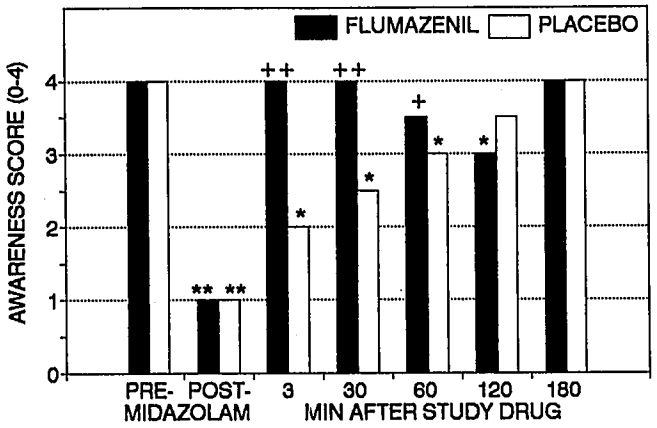

FIG. 2. Median level of consciousness pre- and postmidazolam as well as 3, 30, 60, 120, and 180 min after flumazenil or placebo. Consciousness scores, ranging from 0 (completely unresponsive) to 4 (fully awake) are defined in table 1. (*$P < 0.05$ *vs.* premidazolam; **$P < 0.01$ *vs.* premidazolam; †$P < 0.05$ *vs.* placebo; and ++$P < 0.005$ *vs.* placebo.)

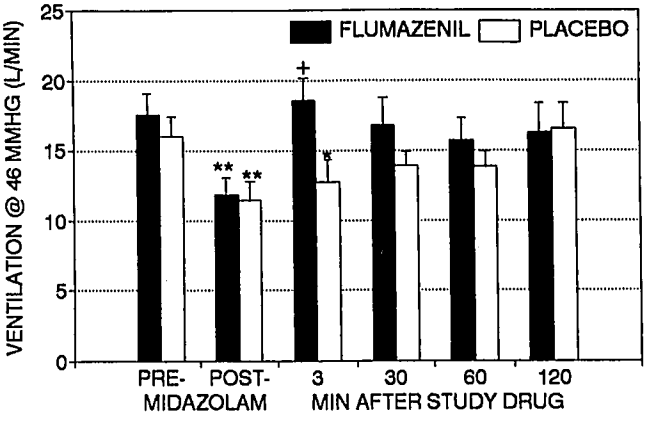

FIG. 4. Minute ventilation (liters per minute) at PET_{CO_2}; = 46 mmHg pre- and postmidazolam as well as 3, 30, 60, and 120 min after flumazenil or placebo. (*$P < 0.01$ *vs.* premidazolam; **$P < 0.001$ *vs.* premidazolam; and †$P < 0.005$ between groups.)

trials; the reduction in slope did not differ significantly between groups (fig. 3). After administration of either flumazenil or placebo, there was a slight, nonsignificant increase in the slope of the CO_2 response curve. This increase did not differ between treatments, and the slope measured 3 min after administration of each study drug remained significantly ($P < 0.01$) less than the corresponding premidazolam control value. During the subsequent 2 h, the slope never differed significantly between treatments; 120 min after administration of the study drug, slopes in both study groups remained significantly less than those before administration of midazolam ($P < 0.05$).

Midazolam also caused a rightward shift of the ventilatory response curve, as reflected by $\dot{V}_E$ at a PET_{CO_2} of 46 mmHg ($\dot{V}_E46$). In flumazenil trials, $\dot{V}_E46$ decreased from 17.55 ± 1.47 to 11.83 ± 0.79 $l \cdot min^{-1}$ ($P < 0.001$), whereas in placebo trials, $\dot{V}_E46$ decreased from 16.06 ± 1.26 to 11.48 ± 0.79 ($P < 0.001$; fig. 4). These changes did not differ significantly between treatments. Three minutes after administration of flumazenil, $\dot{V}_E46$ returned to 18.56 ± 1.45 $l \cdot min^{-1}$ (108 ± 6% of its baseline value); in contrast, 3 min after administration of placebo, $\dot{V}_E46$ was 12.75 ± 0.99 $l \cdot min^{-1}$ (81 ± 5% of its baseline; $P < 0.005$ between groups). However, within 30 min after administration of the study drug, the difference in $\dot{V}_E46$ between flumazenil and placebo was no longer significant.

Figure 5 demonstrates that the effect of midazolam on $\dot{V}_E46$ primarily resulted from a change in tidal volume (TV46). In flumazenil trials, midazolam caused TV46 to decrease from 1,041 ± 99 to 642 ± 33 ml ($P < 0.005$);

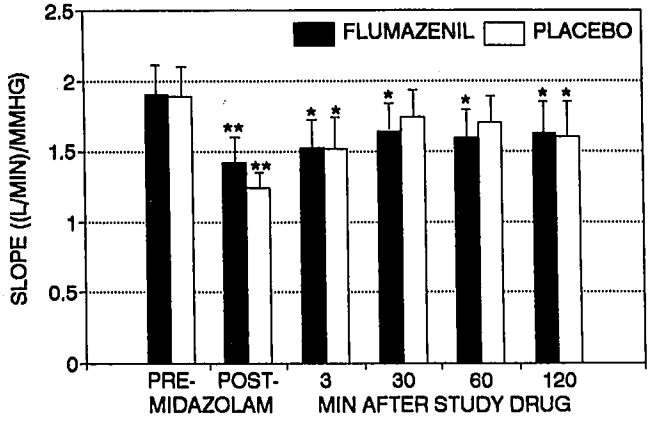

FIG. 3. Slope of the CO_2 response curve (liters per minute per mmHg) pre- and postmidazolam as well as 3, 30, 60, and 120 min after flumazenil or placebo. There were no significant differences between groups. (*$P < 0.05$ *vs.* premidazolam, and **$P < 0.005$ *vs.* premidazolam.)

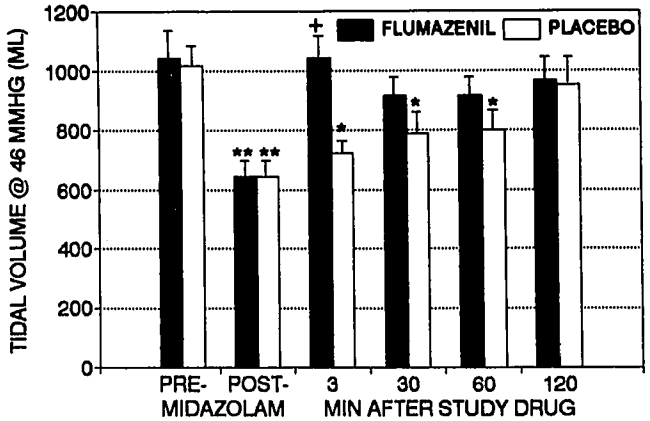

FIG. 5. Tidal volume (milliliters) at PET_{CO_2}; = 46 mmHg pre- and postmidazolam as well as 3, 30, 60, and 120 min after flumazenil or placebo. (*$P < 0.01$ *vs.* premidazolam; **$P < 0.005$ *vs.* premidazolam; and †$P < 10^{-4}$ between groups.

in placebo trials, the corresponding change was from 1,017 ± 67 to 642 ± 38 ml ($P < 0.005$). Flumazenil-induced improvement in $\dot{V}_E46$ was accompanied by a corresponding increase in TV46. Thus, 3 min after administration of flumazenil, TV46 increased to 1,044 ± 54 ml (105 ± 6% of its premidazolam value); this change differed significantly from the increase to 723 ± 36 ml (74 ± 6% of the premidazolam value) observed after administration of the placebo ($P < 10^{-4}$ between groups).

Discussion

The design of the current study approximates those clinical situations in which a single 1-mg dose of flumazenil is used to reverse the sedation produced by midazolam, in the absence of opioids. Midazolam administration ended when subjects were sedated to a level adequate for most endoscopic procedures (sedation score of 1; table 1). Fifteen minutes later, subjects received flumazenil or placebo; the fact that the blood concentration of midazolam is decreasing at this time accounts for our observation that awareness scores tended to increase after administration of placebo (fig. 2). Despite this potentially confounding effect, subjects were significantly more alert for 60 min after administration of flumazenil than after administration of placebo. We also confirmed previous observations that resedation may occur after administration of flumazenil[23,24]; 120 min after administration of flumazenil, awareness scores were significantly less than those before administration of midazolam. This finding is compatible with known differences in the pharmacokinetics of midazolam and flumazenil: in young volunteers, the elimination half-life of midazolam is 1.5–3.0 h, whereas that of flumazenil is 0.7–1.3 h.[25]

Previous studies of the combined effects of midazolam and flumazenil on the slope of the CO_2 ventilatory response curve have yielded conflicting results. Mora *et al.*§ could not demonstrate a decrease in the CO_2 response curve slope after infusion of midazolam 0.37 $mg \cdot kg^{-1}$; however, after administration of flumazenil 1.0 mg, they observed a 30% decrease in slope, which lasted for at least 60 min. In contrast, Dailland *et al.*[14] observed a 40% decrease in slope after administration of midazolam 0.3 $mg \cdot kg^{-1}$ and fentanyl 1 $\mu g \cdot kg^{-1}$; when compared with placebo, flumazenil caused a significant increase in CO_2 response slope. The current results confirm the significant effect of midazolam on the slope of the CO_2 ventilatory response curve[2,3]; however, in contrast to the findings of Dailland *et al.*,[14] we observed that the slope remained significantly lower than its premidazolam value for 120 min after administration of flumazenil.

It appears, therefore, that flumazenil 1.0 mg iv may not effectively antagonize the effect of midazolam on the slope of the CO_2 response. Perhaps a larger dose of flumazenil would be more effective in this regard. Alternatively, flumazenil could be acting as a partial agonist at those centers that control the sensitivity (as opposed to the "set point") of hypercarbic ventilatory drive. However, Forster *et al.* found that, when given alone, flumazenil 0.1 $mg \cdot kg^{-1}$ has no effect on resting ventilatory variables.** Furthermore, because slope never differed significantly between treatments in the current study, it appears unlikely that flumazenil caused additional depression of ventilatory drive in volunteers sedated with midazolam.

The current study also confirms previous findings that, in addition to its effect on slope, midazolam causes a significant rightward shift in the CO_2 ventilatory response curve.[3,13,26] However, Barakat *et al.*[13] found that flumazenil 1.0 mg iv did not significantly reverse the effect of midazolam on this variable, whereas Suttmann *et al.*[26] found that flumazenil 0.1 $mg \cdot kg^{-1}$ caused only a transient, partial reversal of this effect. In contrast, we found that flumazenil 1.0 mg iv completely antagonized the effect of midazolam on the displacement of the CO_2 response curve, as demonstrated by a return of $\dot{V}_E46$ to its premidazolam value.

The difference between our results and those of the previous studies may be related to the way in which displacement was measured. Barakat *et al.*[13] used Read rebreathing test results to determine both the slope and the displacement of the CO_2 response curve. As discussed below, rebreathing tests may be less sensitive than steady-state measurements to the effects of pharmacologic interventions on CO_2 response curve displacement.[27] On the other hand, the data of Suttmann *et al.* are based on a "semiquantitative method" that used resting ventilation with room air as an indication of CO_2 response curve displacement.[26] Because O_2 tensions were allowed to change (Pa_{O_2} decreased after administration of midazolam), the interaction between hypoxic and hypercarbic ventilatory drives may have affected their results.

We designed the current study to avoid these shortcomings and obtain measurements as rapidly as possible; this was necessary because the effects of midazolam and flumazenil were expected to change relatively quickly during the experiment. Thus, "gold-standard" steady-state determinations of the CO_2 response, which may take as long as 30 min to perform, were inappropriate. In contrast, a Read rebreathing test takes only 4–5 min to complete, making it ideal for these types of studies. The assumption underlying the Read rebreathing technique is

** Forster A, Crettenand G, Morel DR: Absence of ventilatory agonist or inverse agonist effects of a overdose of RO15-1788, a specific benzodiazepine antagonist (abstract). ANESTHESIOLOGY 67:A144, 1987.

that, during a single rebreathing test, the difference between end-tidal and medullary CO_2 tensions is constant. Therefore, CO_2 response slopes obtained by the Read rebreathing method are comparable to those obtained by steady-state methods.¶ Because of the end-tidal to medullary gradient, curves obtained by the Read method tend to be displaced to the right (*i.e.*, toward higher CO_2 tensions) by 6–13 mmHg,[18] as compared with their steady-state counterparts; furthermore, this displacement may not remain constant when repeated Read rebreathing tests are performed, particularly if some pharmacologic intervention has taken place.[27] We avoided this potential source of error by determining CO_2 response curve displacement from a single steady-state point, measured after subjects had equilibrated to a constant CO_2 tension of 46 ± 1 mmHg for 6 min; we chose this CO_2 tension to minimize discomfort to our subjects, while avoiding the nonlinear portion of the CO_2 response. By using hyperoxic gas mixtures (fractional inspired O_2 concentration > 50%) during both rebreathing and steady-state tests, we eliminated the potentially confounding effect of hypoxic ventilatory drive.

Our finding that the primary effect of midazolam was to decrease tidal volume confirms previously reported data. With a Pa_{CO_2} of 46 mmHg, Alexander *et al.* found a 50% decrease in tidal volume within 2 min after administration of midazolam 0.1 $mg \cdot kg^{-1}$ iv.[28] Similarly, Berggren *et al.* found that midazolam and diazepam significantly reduced resting tidal volume.[29] This propensity to decrease tidal volume may help explain the relatively high incidence of hypoxemia that accompanies the use of midazolam[30]: For a given $\dot{V}_E$, the effective alveolar ventilation of unintubated patients tends to decrease with decreasing tidal volumes.[31,32] Because flumazenil completely antagonized the effect of midazolam on tidal volume, it may prove to be especially useful in treating midazolam-induced hypoxemia.

Previously published reports suggest that the current results may not be applicable to patients who have received both a benzodiazepine and an opiate. Weinbrum and Geller found that, after patients were sedated with benzodiazepines alone, those who received flumazenil had higher room-air Sp_{O_2}s than those who received placebo; in contrast, flumazenil had no effect on the Sp_{O_2} of patients who were sedated with a combination of opiates and benzodiazepines. Furthermore, Tolksdorf *et al.* found that, after patients received general anesthesia with midazolam, fentanyl, and N_2O, they were more likely to become hypoxic if they received flumazenil than if they received a placebo.[33] However, the effect of flumazenil on the slope and displacement of the ventilatory response to CO_2 under these circumstances has not been established conclusively.

In summary, we found that flumazenil 1.0 mg iv rapidly and completely reversed the sedation produced by midazolam 0.13 mg/kg. Flumazenil did not antagonize the depressant effect of midazolam on the slope of the CO_2 response. However, flumazenil completely reversed the effect of midazolam on $\dot{V}_E46$ and TV46. These results suggest that iv flumazenil may effectively treat some components of midazolam-induced ventilatory depression.

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