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Effect of Flumazenil on Ventilatory Drive during Sedation with Midazolam and Alfentanil

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Background: **Patients who receive a combination of a benzodiazepine and an opioid for conscious sedation are at risk for developing respiratory depression. While flumazenil effectively antagonizes the respiratory depression associated with a benzodiazepine alone, its efficacy in the presence of both a benzodiazepine and an opioid has not been established. This study was designed to determine whether flumazenil can reverse benzodiazepine-induced depression of ventilatory drive in the presence of an opioid.**

Methods: **Twelve healthy volunteers completed this randomized, double-blind, crossover study. Ventilatory responses to carbon dioxide and to isocapnic hypoxia were determined during four treatment phases: (1) baseline, (2) alfentanil infusion; (3) combined midazolam and alfentanil infusions, and (4) combined alfentanil, midazolam, and "study drug" (consisting of either flumazenil or flumazenil vehicle) infusions. Subjects returned 2–6 weeks later to receive the alternate study drug.**

Results: **Alfentanil decreased the slope of the carbon dioxide response curve from 2.14 ± 0.40 to 1.43 ± 0.19 $l \cdot min^{-1} \cdot mmHg^{-1}$ (x ± SE, $P < 0.05$), and decreased the minute ventilation at $P_{ET}CO_2$ = 50 mmHg ($\dot{V}_E50$) from 19.7 ± 1.2 to 14.8 ± 0.9 $l \cdot min^{-1}$ ($P < 0.05$). Midazolam further reduced these variables to 0.87 ± 0.17 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.05$) and 11.7 ± 0.8 $l \cdot min^{-1}$ ($P < 0.05$), respectively. With addition of flumazenil, slope and $\dot{V}_E50$ increased to 1.47 ± 0.37 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.05$) and 16.4 ± 2.0 $l \cdot min^{-1}$ ($P < 0.05$); after placebo, the respective values of 1.02 ± 0.19 $l \cdot min^{-1} \cdot mmHg^{-1}$ and 12.5 ± 1.2 $l \cdot min^{-1}$ did not differ significantly from their values during combined alfentanil and midazolam administration. The effect of flumazenil differed significantly from that of placebo ($P < 0.05$). Both the slope and the displacement of the hypoxic ventilatory response, measured at $P_{ET}CO_2$ = 46 ± 1 mmHg, were affected similarly, with flumazenil showing a significant improvement compared to placebo.**

Conclusions: **Flumazenil effectively reverses the benzodiazepine component of ventilatory depression during combined administration of a benzodiazepine and an opioid. (Key words: Anesthesia: conscious sedation. Antagonists, benzodiazepines: flumazenil. Complications, anoxia: chemically induced; physiopathology. Lungs, hypercapnia: pathophysiology. Lungs, respiration: drug effects. Pharmacology: alfentanil; flumazenil; midazolam.)**

A combination of a benzodiazepine and an opioid is commonly administered to patients undergoing conscious sedation for a variety of diagnostic and therapeutic procedures. The augmentation of benzodiazepine-induced sedation by a concomitantly administered opioid improves patient comfort and enhances surgical conditions.[1,2] However, the potentiation by an opioid of benzodiazepine-induced respiratory depression may lead to hypoxemia, cardiac arrest, and neurologic damage or death.[3]

Flumazenil, a benzodiazepine antagonist, effectively reverses benzodiazepine-induced depression of the ventilatory responses to both carbon dioxide and hypoxemia.[4,5] However, the efficacy of flumazenil in patients who have received an opioid in addition to a benzodiazepine has not been conclusively established. Although flumazenil does not appear to augment opioid-induced ventilatory depression,[6] several investigators have reported a further decrease in ventilatory drive when flumazenil is administered to patients who have previously received both a benzodiazepine and an opioid.[7,8] We performed the current randomized, placebo-controlled, double-blind crossover study to determine the effect of flumazenil on the ventilatory re-

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sponses to carbon dioxide and hypoxemia in volunteers sedated with a combination of a benzodiazepine and an opioid.

Methods

Fourteen healthy volunteers (11 men and 3 women), ranging in age from 23 to 40 years and in weight from 50 to 90 kg, gave written consent to participate in this institutional review board-approved study. Subjects were nonsmokers, and had taken no benzodiazepines for at least 30 days and no caffeine or alcohol for at least 24 h before each study session. Subjects had negative urine drug assays for benzodiazepines and opioids, pulmonary function tests (forced vital capacity, forced expiratory volume in 1 s, forced expiratory volume in 1 s/forced vital capacity) within 15% of age- and height-adjusted normal values, and the women had negative urine pregnancy tests. Each subject was studied on two days, 2–6 weeks apart.

Overall Study Design

After application of electrocardiographic, noninvasive blood pressure and pulse oximetry monitoring equipment, two intravenous cannulas were inserted. The catheter in the left arm served for administration of 0.9% NaCl (100 $ml \cdot h^{-1}$) while the catheter in the right antecubital vein allowed for blood sampling. We then performed baseline measurements of the ventilatory responses to carbon dioxide and hypoxemia (*vide infra*). At the midpoint of these determinations, which lasted approximately 30 min, we obtained blood samples for subsequent determination of plasma midazolam, alfentanil, and flumazenil concentrations.

On each study day, subjects received 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ alfentanil for 5 min, 0.18 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 10 min, followed by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This regimen was chosen to produce a steady-state concentration of 10–20 $ng \cdot ml^{-1}$ within 30 min.[9] Thirty minutes after the beginning of alfentanil administration, we recorded subjects' level of consciousness on a five-point observers' assessment of alertness/sedation scale, ranging from awake and alert to completely unresponsive (table 1). A second set of ventilatory drive determinations assessed the effect of alfentanil, alone, on hypoxic and hypercarbic ventilatory drive.

We then administered 10 $\mu g \cdot kg^{-1}$ midazolam at 1-min intervals until loud, repeated verbal stimulation was necessary to arouse the subjects (observers' assessment of alertness/sedation score = 3). An infusion of midazolam at an hourly dose equal to the initial sedating dose was then initiated.[10] Twenty minutes later, we determined the ventilatory response during combined midazolam and alfentanil infusions.

Subjects then received "study drug," consisting of either 1 mg flumazenil over 10 minutes followed by a flumazenil infusion at a rate of 20 $\mu g \cdot min^{-1}$, or an equal volume of flumazenil vehicle followed by an equivalent infusion of the vehicle. Study drug was supplied in identical, encoded vials, whose content remained unknown until the study was completed. After determination of ventilatory response during combined midazolam, alfentanil, and study drug infusion, all medications were discontinued and subjects were observed for a minimum of 90 min before being driven home. Subjects returned 2–6 weeks later to complete the crossover phase of the study with the alternate study drug.

We collected blood samples in heparinized, glass test tubes. Following centrifugation, we transferred the plasma to scintillation vials and froze them at −20°C until the end of the study. Midazolam, flumazenil, and alfentanil were assayed using high-resolution gas chromatography and mass-selective detection. The coefficients of variation of the assays were 4%, 5%, and 5%, respectively.

Ventilatory Response Determination

Subjects breathed gas mixtures from a face mask incorporated in a to-and-fro breathing system with variable carbon dioxide absorption.[5] A Capnomac Ultima (Datex, Helsinki), calibrated with reference mixtures of 3%, 6%, and 9% CO_2 in oxygen (Linde, North Haven, CT, primary standard grade ± 0.01%) continuously monitored inspired and end-tidal concentrations of carbon dioxide and oxygen, while a Hans Rudolf (Kansas City, MO) #3700 heated pneumotachograph, Validyne differential pressure transducer (Northridge, CA), and electronic integrator determined ventilatory volumes at BTPS. Before each set of measurements, we performed a three-point calibration and linearity check with a Collins #3200 supersyringe (Braintree, MA). An Ohmeda (Boulder, CO) 3700 pulse oximeter with ear probe, set to the fast (3-s) response mode, determined

Table 1. Observer's Assessment of Alertness/Sedation

Score	Responsiveness	Speech	Facial Expression	Eyes
5	Responds readily	Normal	Normal	Clear, no ptosis
4	Lethargic response	Mild slowing	Mild relaxation	Glazed or mild ptosis (<50%)
3	Responds only when called loudly	Slurred or prominent slowing	Slack jaw	Marked ptosis (>50%)
2	Responds only to prodding or shaking	Few recognizable words		
1	Unresponsive			

The composite score is the lowest achieved in each of the categories.

arterial oxygen saturation.[11] Ventilatory variables, gas tensions, and arterial oxygen saturation were sampled at 30 Hz by a 12-bit analog-to-digital convertor, and stored on computer for subsequent analysis.

To fully characterize the ventilatory responses to both carbon dioxide and hypoxemia, each set of ventilatory response determinations consisted of four components: (1) Steady-state ventilation at $P_{ET}CO_2 \approx 46$ mmHg with $F_{I_{O_2}} > 50\%$; (2) Hypoxic ventilatory response at $P_{ET}CO_2 \approx 46$ mmHg. (3) Steady-state ventilation at $P_{ET}CO_2 \approx 55$ mmHg; (4) Hypoxic ventilatory response at $P_{ET}CO_2 \approx 55$ mmHg. To maintain a balanced design, the sequence of carbon dioxide tensions was reversed for alternate subjects; however, for a given subject, the sequence of carbon dioxide tensions was the same on both study days.

Steady-state determinations were performed by allowing subjects to breathe a mixture of carbon dioxide in oxygen ($F_{I_{O_2}} > 0.5$) for 6 min; carbon dioxide absorption was manually controlled to maintain $P_{ET}CO_2 \approx 46 \pm 1$ mmHg. After this equilibration period, minute ventilation, tidal volume, respiratory rate, and $P_{ET}CO_2$ were recorded for 30 breaths. We then rapidly decreased the $F_{I_{O_2}}$ to 0.21 while maintaining a constant $P_{ET}CO_2$. After an additional 2 min of equilibration, we terminated oxygen inflow and substituted an equivalent flow of nitrogen while maintaining a constant $P_{ET}CO_2$. The computer continuously recorded ventilatory variables, carbon dioxide tension, and oxygen saturation as the latter decreased from its normoxic value (96–100%) to 70%. Because of the shape of the oxyhemoglobin dissociation curve, it generally took only 2 or 3 minutes for oxygen saturations to fall from 90% to 70%, making it unlikely that hypoxic ventilatory decline significantly contaminated our results. Subjects were then allowed a 10-min recovery period, during which blood samples were obtained, before the sequence of ventilatory determinations was repeated at the alternate carbon dioxide tension.

Data Analysis

Because of breath-to-breath variability in respiratory variables, 5-breath average values of $\dot{V}_E$, tidal volume, $P_{ET}CO_2$, Sp_{O_2}, and were used throughout the analysis. To determine the steady-state ventilatory response to carbon dioxide we used 12 of these 5-breath averages as data points for the linear regression of $\dot{V}_E$ *versus* $P_{ET}CO_2$: Six of these points have $P_{ET}CO_2 \approx 46$ mmHg, while the other six have $P_{ET}CO_2 \approx 55$ mmHg. The tidal volume response to carbon dioxide was computed in a corresponding manner. Computed values of $\dot{V}_E$ and tidal volume at $P_{ET}CO_2 = 50$ mmHg ($\dot{V}_E50$, V_T50) indicated the displacement of the carbon dioxide response. The ventilatory response to isocapnic hypoxemia was determined at both low (≈46 mmHg) and high (≈55 mmHg) carbon dioxide tensions by linear regression of $\dot{V}_E$ *versus* SpO_2. Values of $\dot{V}_E$ at $Sa_{O_2} = 90\%$ ($\dot{V}_E90$) indicated the displacement of the hypoxic ventilatory response.

The effects of alfentanil and combined alfentanil/midazolam infusions on ventilatory variables were assessed using two-way analysis of variance followed by Tukey's adjusted *t* tests. Differences between the effects of flumazenil and placebo were analyzed using 3-way analysis of variance. Awareness scores were analyzed using Bonferroni-corrected Wilcoxon rank sum tests. Values are given as $\bar{x} \pm SE$, with $P < 0.05$ indicating significance.

Results

Because they failed to complete the study, data from two male subjects were eliminated from the analysis.

One of these subjects became agitated during determination of hypoxic ventilatory response with simultaneous alfentanil and midazolam, before administration of the study drug. The other refused to return on the second study day for personal reasons. None of the subjects experienced any sequelae as a result of his or her participation in the study.

As expected on the basis of the study design, subjects' level of consciousness during baseline, alfentanil, and the combination of midazolam and alfentanil did not differ between placebo and flumazenil trials (table 2). With flumazenil, awareness scores increased significantly, whereas placebo had no effect.

The initial dose of midazolam required to achieve an awareness score of 3 did not differ between flumazenil (66.7 ± 6.3 $\mu g \cdot kg^{-1}$) and placebo (72.5 ± 6.1 $\mu g \cdot kg^{-1}$) trials. Plasma midazolam concentrations increased from 78.6 ± 5.9 $ng \cdot ml^{-1}$ during midazolam/alfentanil measurements to 94.0 ± 7.2 ng/ml during study drug measurements ($P < 0.001$). Alfentanil concentrations were 9.5 ± 0.6, 9.1 ± 0.5, and 9.6 ± 0.6 $ng \cdot ml^{-1}$ during the alfentanil, alfentanil/midazolam, and study drug phases, respectively (P = NS). Plasma flumazenil concentrations were 13.4 ± 2.0 $\mu g \cdot ml^{-1}$ during flumazenil trials.

Before administration of study drug, respiratory variables did not differ significantly between flumazenil and placebo trials. Alfentanil decreased the slope of the carbon dioxide response curve from 2.14 ± 0.40 to 1.43 ± 0.19 $l \cdot min^{-1} \cdot mmHg^{-1}$, and caused a rightward shift as demonstrated by a decrease in $\dot{V}_E50$ from 19.7 ± 1.2 to 14.8 ± 0.9 $l \cdot min^{-1}$ ($P < 0.05$ for both variables, figs. 1 and 2). Concomitant midazolam administration further decreased both of these variables as compared to their values during alfentanil alone (to 0.87 ± 0.17 $l \cdot min^{-1} \cdot mmHg^{-1}$ and 11.7 ± 0.8 $l \cdot min^{-1}$, respectively, $P < 0.05$). When flumazenil was added to midazolam and alfentanil, slope increased to 1.47 ± 0.37 $l \cdot min^{-1} \cdot mmHg^{-1}$ and $\dot{V}_E50$ increased to 16.4 ± 2.0 $l \cdot min^{-1}$ ($P < 0.05$ for both variables compared to values obtained during the same trials immediately before flumazenil administration). However, both variables remained less than baseline ($P < 0.05$). During placebo administration, neither slope nor $\dot{V}_E50$ changed significantly; as a result, the *increase* in both slope and $\dot{V}_E50$ associated with flumazenil administration was greater ($P < 0.05$) than that associated with placebo.

Alfentanil's effect on $\dot{V}_E50$ resulted from a decrease in both tidal volume (V_T50) and respiratory rate ($P < 0.05$ for both variables, table 2). Concomitant administration of midazolam further decreased tidal volume ($P < 0.05$) but had no effect on respiratory rate. Addition of flumazenil increased V_T50 ($P < 0.05$), and the change associated with flumazenil was greater ($P < 0.05$) than that associated with placebo. Nonetheless, V_T50 remained significantly lower than baseline. Respiratory rate was unaffected by either flumazenil or placebo infusion.

Mean values for $P_{ET}CO_2$ ranged from 46.0 to 46.8 mmHg during determination of hypoxic ventilatory response at low carbon dioxide tension; they did not differ significantly among the time periods of the study or between flumazenil and placebo trials. Alfentanil decreased both the slope (from 0.73 ± 0.11 to 0.51 ± 0.07 $l \cdot min^{-1} \cdot \%Sp_{O_2}{}^{-1}$) and $\dot{V}_E90$ (from 14.0 ± 1.2 to 10.8 ± 0.8 $l \cdot min^{-1}$, $P < 0.05$). Midazolam further decreased the slope to 0.26 ± 0.03 $l \cdot min^{-1} \cdot \%Sp_{O_2}{}^{-1}$ ($P < 0.05$); the corresponding decrease in $\dot{V}_E90$ to 9.1 ± 0.6 $l \cdot min^{-1}$ did not achieve significance. After flumazenil administration, the slope increased to 0.41 ± 0.10 $l \cdot min^{-1} \cdot \%Sp_{O_2}{}^{-1}$ ($P < 0.05$ *vs.* value during midazolam and alfentanil) and $\dot{V}_E90$ increased to 10.9 ± 1.5 $l \cdot min^{-1}$ ($P < 0.05$). In contrast, placebo did not affect these variables, which remained significantly lower than during alfentanil, alone. However, the difference between the effects of flumazenil and placebo on these variables did not achieve statistical significance.

During determination of hypoxic ventilatory responses at elevated carbon dioxide tension, mean values for $P_{ET}CO_2$ ranged from 55.0 to 55.6 mmHg. Alfentanil decreased both the slope (from 1.79 ± 0.27 to 1.44 ± 0.23 $l \cdot min^{-1} \cdot \%Sp_{O_2}{}^{-1}$ $P < 0.05$) and $\dot{V}_E90$ (from 36.0 ± 2.0 to 27.3 ± 1.9 $l \cdot min^{-1}$, $P < 0.05$). Addition of midazolam was associated with a further decrease in these variables to 0.78 ± 0.12 $l \cdot min^{-1} \cdot \%Sp_{O_2}{}^{-1}$ and 18.4 ± 1.4 $l \cdot min^{-1}$, respectively ($P < 0.05$ for both variables). During flumazenil slope increased to 1.05 ± 0.26 $l \cdot min^{-1} \cdot \%Sp_{O_2}{}^{-1}$ ($P < 0.05$ compared to its value during combined midazolam and alfentanil infusions), although it still remained lower than during alfentanil alone. Slope was not affected significantly by placebo. However, a significant difference between the effects of flumazenil and placebo on this variable could not be demonstrated. Additionally, flumazenil increased $\dot{V}_E90$ to 25.6 ± 3.6 $l \cdot min^{-1}$ ($P < 0.05$) so that this variable no longer differed from its value during alfentanil, alone. The change in V_E90 with fluma-

Table 2. Effect of Alfentanil, Midazolam + Alfentanil, and Flumazenil or Placebo on Level of Consciousness and Ventilatory Drive

	Baseline*	Alfentanil*	Midazolam + Alfentanil*	Flumazenil	Placebo
N	24	24	24	12	12
Awareness score (range)	5 (5)	4† (4–5)	3†,‡ (2–3)	5‡,§,¶ (4–5)	3†,‡ (2–4)
CO_2 slope ($L \cdot min^{-1} \cdot mmHg^{-1}$)	2.14 (0.40)	1.43† (0.19)	0.87†,‡ (0.17)	1.47†,§,¶ (0.37)	1.02† (0.19)
$\dot{V}_E50$ ($L \cdot min^{-1}$)	19.7 (1.2)	14.8† (0.9)	11.7†,‡ (0.8)	16.4†,§,¶ (2.0)	12.5†,‡ (1.2)
Tidal volume at PET_{CO_2} = 50 mmHg (ml)	1151 (57)	937† (49)	737†,‡ (39)	1001†,§,¶ (95)	807†,‡ (87)
Respiratory rate at PET_{CO_2} = 50 mmHg ($breaths \cdot min^{-1}$)	17.2 (0.8)	15.8† (0.6)	15.7† (0.5)	16.0† (0.6)	15.6† (0.7)
Hypoxic slope at $PET_{CO_2} \approx 46$ mmHg ($L \cdot min^{-1} \cdot \% Sp_{O_2}^{-1}$)	0.73 (0.11)	0.51† (0.07)	0.26†,‡ (0.03)	0.41†,§ (0.10)	0.26†,‡ (0.07)
$\dot{V}_E90$ at $PET_{CO_2} \approx 46$ mmHg ($L \cdot min^{-1}$)	14.0 (1.2)	10.8† (0.8)	9.1† (0.6)	10.9†,§ (1.5)	9.3†,‡ (0.8)
Hypoxic slope at $PET_{CO_2} \approx 55$ mmHg ($L \cdot min^{-1} \cdot \% Sp_{O_2}^{-1}$)	1.79 (0.27)	1.44† (0.23)	0.78†,‡ (0.12)	1.05†,‡,§ (0.26)	0.99†,‡ (0.24)
$\dot{V}_E90$ at $PET_{CO_2} \approx 55$ mmHg ($L \cdot min^{-1}$)	36.0 (2.0)	27.3† (1.9)	18.4†,‡ (1.4)	25.6†,§,¶ (3.6)	19.0†,‡ (1.8)

The level of consciousness is shown as median (range) and ventilatory variables are shown as mean (SE).

* Pooled values for placebo and flumazenil trials.

† $P < 0.05$ *versus* Baseline.

‡ $P < 0.05$ *versus* alfentanil.

§ $P < 0.05$ *versus* midazolam + alfentanil.

¶ $P < 0.05$, change from midazolam + alfentanil with flumazenil *versus* change from midazolam + alfentanil with placebo.

zenil was greater than that observed during placebo ($P < 0.05$).

Discussion

Opioids potentiate the respiratory depressant effects of benzodiazepines; during benzodiazepine sedation, addition of an opioid markedly increases the risk of hypoxemia.[3] Hypoventilation during conscious sedation can often be corrected by verbally encouraging patients to breathe deeply or by performing basic airway maneuvers such as a jaw thrust; hypoxemia may be alleviated by supplemental oxygen.[12] Positive pressure ventilation, with or without tracheal intubation, is recommended if these measures prove inadequate. In addition, the availability of a rapid, reliable, pharmacologic means for reversing benzodiazepine-induced ventilatory depression in these patients could provide an additional margin of safety.

While flumazenil reliably reverses benzodiazepine-induced sedation after general anesthesia,[13] conscious sedation,[14] and multiple drug overdoses, its effect on the associated ventilatory depression is more controversial. In laboratory studies of volunteers sedated solely with midazolam, flumazenil has been shown to effectively reverse depression of the ventilatory responses to carbon dioxide[5,15] and isocarbic hypoxia.[4] However, in clinical studies, spontaneous ventilation has been reported to increase,[13] decrease,[7,8] or remain unaffected[14,16,17] after administration of flumazenil to sedated patients. The ventilatory depressant effects of the opioids are known to potentiate those of the benzodiazepines; therefore, if even slight benzodiazepine-induced respiratory depression remains after flumazenil administration, the benzodiazepine-opioid interaction could explain the apparent failure to reverse ventilatory depression.

In assessing the combined effects of benzodiazepines

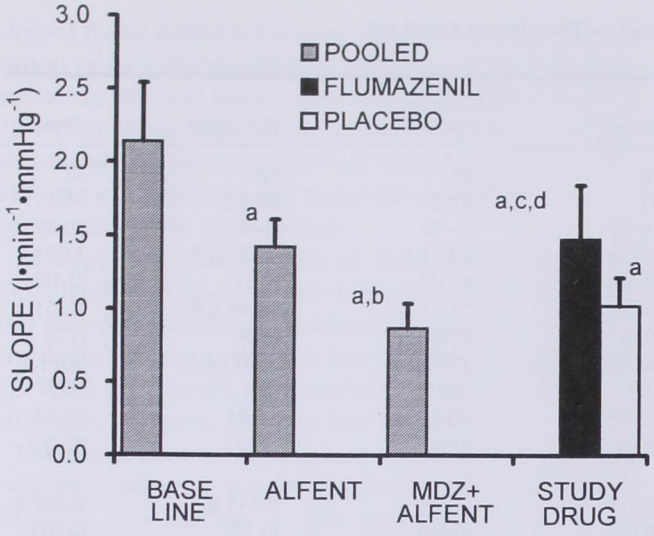

Fig. 1. Slope of carbon dioxide response curves ($\bar{x} \pm SE$). Because they did not differ between flumazenil and placebo trials, pooled values are shown for the baseline, alfentanil, and midazolam/alfentanil determinations. (*A*) $P < 0.05$ *versus* baseline. (*B*) $P < 0.05$ *versus* alfent. (*C*) $P < 0.05$ *versus* mdz + alfent. (*D*) $P < 0.05$ change from mdz + alfent with flumazenil *versus* change from mdz + alfent with placebo.

and opioids on ventilatory control, the choice of opioid dose was critical: If too little were administered, there would be insufficient opioid-induced ventilatory depression. In contrast, if the opioid dose were too large, it would be impossible to demonstrate either additional respiratory depression from a subsequently administered benzodiazepine or reversal of this effect by flumazenil. We used a low-dose alfentanil infusion to maintain a constant background of opioid-induced ventilatory depression against which to determine the relative ventilatory effects of midazolam and flumazenil. Because of its rapid onset and relatively small volume of distribution, a stable plasma concentration of alfentanil was easily achieved using a relatively simple, three-stage infusion scheme. Although the alfentanil concentrations during this study ($\approx$10 ng·ml^{-1}) are much lower then than those commonly encountered during nitric oxide/alfentanil anesthesia and only slightly affected subjects' level of consciousness, they were sufficient to cause a statistically and clinically significant decrease in indices of both hypercarbic and hypoxic ventilatory drive.

By administering midazolam to a fixed clinical endpoint, we were able to maximize the likelihood of demonstrating midazolam augmentation of alfentanil-induced ventilatory depression, while maintaining a level of subject responsiveness commensurate with conscious sedation. Although the subsequent midazolam infusion resulted in modest increases in plasma midazolam concentrations between the midazolam and study drug ventilatory drive determinations, levels of consciousness and respiratory variables after placebo administration did not differ from those observed immediately after midazolam administration, suggesting that a steady-state of sedation had been achieved. Furthermore, increasing midazolam concentrations would reduce, rather than increase, the likelihood of our finding that flumazenil was effective.

Benzodiazepines and opioids act on distinct receptors; there is no reason to expect that flumazenil should reverse opioid-induced ventilatory depression. Therefore, even with complete reversal of the benzodiazepine by an ideal antagonist, the opioid component of respiratory depression would be expected to persist. In the current study, we observed that during flumazenil, ventilatory variables returned to values that were similar to those observed during alfentanil, alone. Because plasma alfentanil concentrations were maintained during the flumazenil determinations, this was the maximum improvement that we could expect to observe after antagonism of the benzodiazepine. In addition, while alfentanil caused respirations to slow, midazolam did not further decrease this variable. Thus, as we ob-

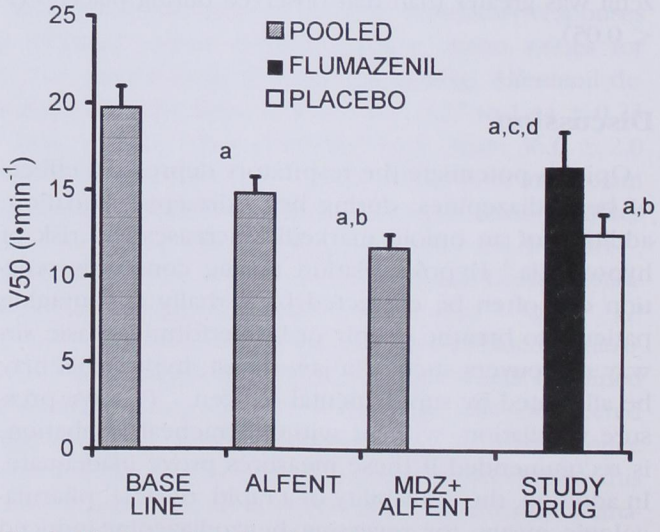

Fig. 2. Displacement of carbon dioxide response curves, expressed as V_E50, the minute ventilation at $P_{ET}CO_2$ = 50 mmHg. See legend to figure 1 for clarification of definitions.

served, reversal of the respiratory effects of midazolam would not be expected to cause an increase in respiratory rate.

The current results suggest that factors other than the addition of an opioid, *per se,* resulted in previous investigators' failure to demonstrate reversal of benzodiazepine-induced ventilatory depression by flumazenil. For example, the inability of Mora *et al.*[7] to demonstrate a flumazenil-induced improvement in hypoxic ventilatory response was probably related to their failure to measure both the displacement and slope of the hypoxic response curves.[18] In a second study, these investigators were unable to demonstrate consistent respiratory depression after fentanyl and midazolam administration, despite mean plasma midazolam concentrations in excess of 300 $ng \cdot ml^{-1}$; therefore, it is not surprising that they failed to demonstrate consistent reversal of ventilatory depression by flumazenil.[19] Weinbrum *et al.* did not separately assess opioid-induced ventilatory depression before midazolam administration; thus, they attributed their negative findings to residual opioid-induced ventilatory depression rather than to ineffectiveness of flumazenil, *per se.*[17] Carter *et al.* concluded that in patients sedated with midazolam alone, flumazenil did not significantly affect V_E or Sp_{O_2}.[14] However, they did not measure P_aCO_2 or $P_{ET}CO_2$ concurrently with V_E and their data show that flumazenil returned Sa_{O_2} to within 0.4% of its baseline value.

Tolksdorf *et al.* found that after anesthesia with midazolam, fentanyl, and nitrous oxide patients who received flumazenil (0.3–0.5 mg) were more alert but more likely to become hypoxemic ($SaO_2 < 90\%$) in the recovery room than patients who received placebo.[8] Although the authors attributed their observation to an interaction between flumazenil and fentanyl, the relatively low dose of flumazenil and the 10-min interval between administration of flumazenil and the beginning of recovery room measurements may have allowed a "rebound" effect to occur. Subsequently, these authors found that in the presence of an opioid alone, flumazenil was associated with greater increases in $P_{ET}CO_2$ and decreases in Sa_{O_2} than was placebo.[20] Other investigators, however, have been unable to demonstrate any respiratory depressant effect of flumazenil either when administered alone[21] or in combination with fentanyl.[6] The current study suggests that during sedation with benzodiazepines and low-dose opioids, any potentiation of opioid-induced ventilatory depression by flumazenil is outweighed by the reversal of benzodiazepine-induced ventilatory depression.

Demonstration of a statistically significant improvement in ventilatory drive after flumazenil administration does not imply that all subjects improved: small decreases in a few subjects could have been overshadowed by large increases in the remaining volunteers, allowing the mean value to show a significant increase. However, we observed that after flumazenil administration, there was evidence of improved central ventilatory drive in all 12 of our subjects: in 11, the slope of the carbon dioxide response increased. The slight decrement observed in the remaining subject resulted from a profound, flumazenil-induced *increase* in her V_E at $P_{ET}CO_2 = 46$ mmHg (from 8 to 26 $l \cdot min^{-1}$); thus, it would have been difficult for her to further increase her ventilation in response to a carbon dioxide challenge.

The uniform improvement in ventilatory drive and awareness scores observed in the current study suggests that flumazenil may be an appropriate adjunct to oxygen and positive pressure ventilation for patients who become hypoxemic and/or unresponsive during conscious sedation. Besides reversing the benzodiazepine component of the ventilatory depression, flumazenil will enable patients to respond to verbal commands to take a deep breath. If flumazenil is ineffective, the likelihood of opioid-induced ventilatory depression should be entertained and administration of naloxone considered. In an emergency, flumazenil may be administered as rapidly as 0.5 $mg \cdot min^{-1}$.[22] However, the current data do not address the speed with which reversal of ventilatory depression will occur under these circumstances.

The authors conclude that in the presence of concomitant opioid-induced depression of ventilatory drive, flumazenil effectively reverses the benzodiazepine-component of ventilatory depression during conscious sedation.

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