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## The Effect of Flumazenil on Midazolam-induced Depression of the Ventilatory Response to Hypoxia during Isohypercarbia

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**Background:** While flumazenil reverses benzodiazepine-induced sedation, its ability to antagonize the ventilatory depressant effects of benzodiazepines has not been fully established. A randomized, double-blind study was conducted to determine whether flumazenil effectively reverses midazolam-induced depression of the hypoxic ventilatory response.

**Methods:** Twelve healthy male volunteers received intravenous midazolam  $0.12 \pm 0.01 \text{ mg} \cdot \text{kg}^{-1}$  followed by either flumazenil 1.0 mg or placebo. Hypoxic ventilatory response was measured using an isocapnic rebreathing technique: as  $\text{Sp}_{\text{O}_2}$  decreased to 70%,  $\dot{V}_E$  and tidal volume were continuously recorded. Hypoxic response determinations were performed before and after midazolam, as well as 3, 30, 60, 120, and 180 min after flumazenil or placebo.

**Results:** After midazolam, the slope of the hypoxic ventilatory response curve ( $\dot{V}_E$  vs.  $\text{Sp}_{\text{O}_2}$ ) decreased to  $0.59 \pm 0.05$  ( $\bar{x} \pm \text{SE}$ ) times its premidazolam baseline; likewise, at  $\text{Sp}_{\text{O}_2} = 90\%$ , minute ventilation ( $\dot{V}_{E90}$ ) and tidal volume (TV90) decreased to  $0.70 \pm 0.04$  and  $0.62 \pm 0.03$  times baseline, respectively. Three minutes after flumazenil, the slope increased to  $1.10 \pm 0.13$  times baseline ( $P < 0.05$  vs. postmidazolam), while following placebo, it was only  $0.81 \pm 0.09$  times baseline ( $P = \text{NS}$  vs. postmidazolam,  $P < 0.05$  between treatments).  $\dot{V}_{E90}$  and TV90, after flumazenil, increased to  $1.45 \pm 0.15$  and  $1.27 \pm 0.09$  times baseline, respectively ( $P < 0.05$  vs. postmidazolam); these increases were significantly greater than the corresponding changes observed after placebo ( $P < 0.05$  between treatments).

**Conclusions:** It was concluded that, after sedation with midazolam, flumazenil causes a greater increase in hypoxic ventilatory response during isohypercarbic conditions than does placebo, and may, therefore, be useful in the treatment of midazolam-induced ventilatory depression. (Key words: Anesthetics, intravenous: midazolam. Antagonists, benzodiazepine: flumazenil. Lungs, ventilation: hypoxic response. Oxygen: hypoxia; ventilatory response.)

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ALTHOUGH flumazenil reliably reverses the sedative effects of benzodiazepines,<sup>1</sup> its ability to reverse benzodiazepine-induced depression of ventilatory control has not been fully established. We recently found that flumazenil effectively reverses the effects of midazolam on the displacement, but not the slope, of the ventilatory response to  $\text{CO}_2$ .<sup>2</sup> In contrast, Mora *et al.* were unable to demonstrate any consistent effect of flumazenil on the hypoxic ventilatory response in patients sedated with diazepam;<sup>3</sup> however, their methodology was subsequently questioned.<sup>4,5</sup> We designed the current double-blind, placebo-controlled study to determine the effect of flumazenil on midazolam-induced depression of the hypoxic ventilatory response.

### Materials and Methods

Twelve healthy, nonsmoking male volunteers, 20–30 yr of age, and weighing 64–93 kg, completed this study, which was approved by our Institutional Review Board; an additional four subjects were excluded before receiving flumazenil or placebo (see below). After obtaining written informed consent, we conducted pre-study screening that included physical examination, complete blood count with differential, serum electrolytes, liver function tests, and pulmonary function tests. Exclusion criteria included renal, hepatic, cardiac, respiratory, or neurologic disease, benzodiazepine use during the month preceding the study, blood test results that deviated from the normal range for our laboratory, and  $\text{FEV}_1$  or  $\text{FVC} < 85\%$  of predicted values. Subjects refrained from alcohol and caffeine use for 24 h, and from all oral intake for 8 h prior to each of the two study sessions.

After inserting a 20-G catheter in a hand vein, we started an intravenous infusion of lactated Ringer's so-

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lution at  $100 \text{ ml} \cdot \text{hr}^{-1}$  and affixed pulse oximeter (Ohmeda 3700®, ear probe), ECG, and noninvasive blood pressure (Propaq® 104) monitors. To minimize external auditory stimulation during respiratory measurements, subjects listened to soft symphonic music through headphones.

After determining baseline values for the slope and displacement of the hypoxic ventilatory response curve (see below), we began midazolam administration: at the beginning of each minute, subjects received midazolam,  $0.01 \text{ mg} \cdot \text{kg}^{-1}$ , by rapid ( $<1 \text{ s}$ ) intravenous injection; 50 s after each midazolam injection, we assessed the subjects' level of consciousness by grading their response to a standard verbal command. Midazolam administration and assessment of sedation continued until the subjects' levels of consciousness reached a score of 2 (table 1). Subjects who had not attained this level of sedation after receiving midazolam  $0.2 \text{ mg} \cdot \text{kg}^{-1}$  were excluded from further participation in the study. We began a postmidazolam hypoxic ventilatory response determination 3 min after the last dose of midazolam.

Immediately after the postmidazolam ventilatory measurements, each subject received flumazenil 1.0 mg or an equal volume (10 ml) of placebo (vehicle only) intravenously over 5 min, as determined by a randomization table. Flumazenil and placebo were packaged identically by the manufacturer, in ampules identified only by the subject and day numbers (e.g., subject 2, day 1), thus ensuring the double-blind nature of the study. The actual contents of the ampules were revealed to the investigators only after completion of the study. We repeated the hypoxic ventilatory response determinations 3, 30, 60, 120, and 180 min after study drug administration.

After the study, subjects remained in the laboratory until they were fully awake, at which time they were escorted home. Seven to 26 days later, subjects returned to repeat the entire testing procedure, this time with the study drug (placebo or flumazenil) not administered previously.

**Table 1. Definition of Awareness Scores**

Score	Definition
4	Awake and alert
3	Relaxed, lethargic response to name
2	Spontaneous eye closure, responds only to loud voice
1	Responds only to prodding/shaking
0	Unresponsive

We measured isocapnic hypoxic ventilatory response using an isocapnic rebreathing technique. Subjects breathed a mixture of  $\text{O}_2$  (21%) and  $\text{N}_2$  through a face mask incorporated in a closed, to-and-fro circuit with variable  $\text{CO}_2$  absorption.<sup>2</sup> The measured resistance of the circuit is approximately  $0.03 \text{ cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{min}$  at a flow rate of  $100 \text{ l} \cdot \text{min}^{-1}$ ; its internal volume, including the rebreathing bag, is approximately 5.5 L. An Instrumentation Laboratories IL200®  $\text{CO}_2$  analyzer, calibrated with three reference mixtures of  $\text{CO}_2$  in  $\text{O}_2$  (Linde® primary standard grade  $\pm 0.01\%$ ) continuously measured  $\text{CO}_2$  tensions at the mask; by varying the flow through the  $\text{CO}_2$  absorber, we kept  $\text{PET}_{\text{CO}_2}$  constant  $\pm 1 \text{ mmHg}$  despite changes in subjects' ventilation. We set the oximeter to its fast response mode and used an ear sensor; we have previously shown that, under these conditions, the Ohmeda® 3700 reliably reflects arterial oxygenation during rapid desaturation.<sup>6</sup> A Hans Rudolph® #3700 heated pneumotachograph, along with a Validyne® DP45 differential pressure transducer and electronic integrator, determined ventilatory volumes at BTPS. Before each set of measurements, we performed a three-point volume calibration and linearity check with a Collins® #3200 "supersyringe." An AIMT Medspect® mass spectrometer monitored circuit  $\text{O}_2$  concentration, and a computer recorded breath-by-breath values for  $\text{Sp}_{\text{O}_2}$ ,  $\text{PET}_{\text{CO}_2}$ , TV, and  $\dot{V}_{\text{E}}$  via an analog-to-digital converter.

On a given study day, we performed all hypoxic ventilatory response determinations at the same  $\text{CO}_2$  tension; each day's target  $\text{PET}_{\text{CO}_2}$  (46–48 mmHg) was 6 mmHg above the resting  $\text{P}_{\text{ET}}\text{CO}_2$  before midazolam administration. This ensured that each series of measurements was performed against a constant background of hypercarbia. To ensure equilibration of medullary centers, subjects breathed 21%  $\text{O}_2$  in  $\text{N}_2$ , with  $\text{PET}_{\text{CO}_2}$  held constant, for 8 min before each hypoxic response determination. During equilibration, we adjusted  $\text{O}_2$  and  $\text{N}_2$  delivery to maintain an  $\text{Fi}_{\text{O}_2}$  of 21% and constant volume of the rebreathing bag. At the end of the equilibration period, we stopped the  $\text{O}_2$  inflow and began data collection as subjects' metabolism decreased the circuit  $\text{O}_2$  concentration. We adjusted  $\text{N}_2$  inflow to maintain constant rebreathing bag volume and varied  $\text{CO}_2$  absorber flow to maintain constant  $\text{PET}_{\text{CO}_2}$  despite changes in ventilation. When  $\text{Sp}_{\text{O}_2}$  reached 70%, usually within 4–5 min after discontinuation of  $\text{O}_2$  inflow, we terminated data collection and allowed the subjects to breathe 100%  $\text{O}_2$  for 30 s.

## HYPOXIC RESPONSE AFTER MIDAZOLAM AND FLUMAZENIL

For each hypoxic response determination, the computer generated 5-breath averages of minute ventilation, tidal volume, and  $Sp_{O_2}$ , and computed the least squares regressions of  $\dot{V}_E$  and TV *versus*  $Sp_{O_2}$ . From the regressions, we computed  $\dot{V}_{E90}$  and TV90 ( $\dot{V}_E$  and TV at 90%  $O_2$  saturation) as indices of the displacement of the ventilatory response curve. Because of the known day-to-day variability in hypoxic ventilatory response,<sup>7</sup> we expressed all values as fractions of the corresponding premidazolam baseline determinations before statistical analysis.

Two-way ANOVA followed by Dunnett's test determined the significance of changes from baseline in flumazenil and placebo trials, while two-way ANOVA and single degree of freedom tests compared the effect of placebo *versus* flumazenil at each time after study drug injection (Systat®). To determine whether the immediate effect of flumazenil on hypoxic ventilatory response differed from that of placebo, we computed the change in slope, TV90, and  $\dot{V}_{E90}$ , between "postmidazolam" and "3-min poststudy drug" determinations; paired *t* tests compared these changes between flumazenil and placebo trials. Nonparametric data were analyzed using Bonferroni-corrected Kruskal-Wallis tests between treatments, and Bonferroni-corrected Wilcoxon rank sums tests within treatments. Parametric data are shown as means  $\pm$  SE, while nonparametric results are expressed as medians, with  $P < 0.05$  indicating significance throughout the analysis.

## Results

None of the subjects suffered any sequelae as a result of his participation in the study. Two volunteers were excluded because of elevated prestudy serum bilirubin concentration, while two others were eliminated before receiving study drug (flumazenil or placebo) because they failed to reach a sedation score of 2 (table 1) after receiving  $0.2 \text{ mg} \cdot \text{kg}^{-1}$  midazolam. The following results are based on the twelve subjects who completed the entire protocol.

The midazolam dose required to attain a sedation score of 2 ranged from 0.06 to  $0.2 \text{ mg} \cdot \text{kg}^{-1}$ , with a mean of  $0.11 \pm 0.01 \text{ mg} \cdot \text{kg}^{-1}$  ( $\bar{x} \pm \text{SE}$ ) in flumazenil trials and  $0.12 \pm 0.01 \text{ mg} \cdot \text{kg}^{-1}$  in placebo trials. Within 3 min after flumazenil, awareness scores increased to baseline (fig. 1), and were significantly greater than the scores observed at the same time after placebo ( $P < 0.05$ ). Thirty minutes later, awareness scores re-

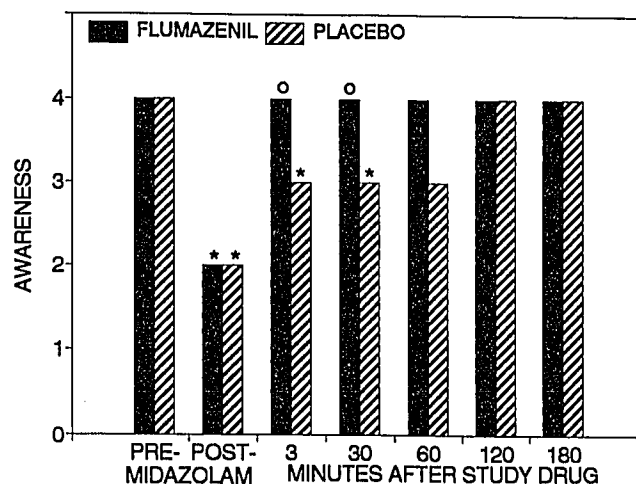


Fig. 1. Awareness scores (as defined in table 1) before and after midazolam, as well as 3, 30, 60, 120, and 180 min after flumazenil or placebo. \* $P < 0.05$  *versus* premidazolam value for same treatment. <sup>o</sup> $P < 0.05$  *versus* same time following placebo.

mained higher after flumazenil than after placebo ( $P < 0.05$ ); however, by 60 min after study drug administration, awareness scores did not differ between groups.

Baseline hypoxic ventilatory response slopes before placebo trials ( $1.45 \pm 0.35 \text{ l} \cdot \text{min}^{-1} \cdot \%Sp_{O_2}^{-1}$ ) did not differ significantly from those before flumazenil trials ( $1.04 \pm 0.14 \text{ l} \cdot \text{min}^{-1} \cdot \%Sp_{O_2}^{-1}$ ). In the placebo trials, the slope decreased to  $0.65 \pm 0.06$  times its baseline value following midazolam ( $P < 0.05$  *vs.* premidazolam, fig. 2); similarly, slope decreased to  $0.53 \pm 0.09$  times baseline in flumazenil trials ( $P < 0.05$  *vs.* premidazolam;  $P = \text{NS}$  *vs.* placebo trials). Three minutes after study drug administration, slope increased by  $0.57 \pm 0.13$  times baseline ( $P < 0.05$ ) in flumazenil trials, although it increased only  $0.16 \pm 0.08$  times baseline in placebo trials ( $P = \text{NS}$ ); furthermore, the increase following flumazenil was significantly ( $P < 0.05$ ) greater than that associated with the waning effects of midazolam in placebo trials. Repeated measures ANOVA revealed that, when all poststudy drug determinations were considered, slopes were significantly higher after flumazenil than after placebo ( $P < 0.05$ ); however, *post hoc* testing could not attribute this difference to any particular observation times. The mean slope of the regression of  $PER_{CO_2}$  *versus*  $Sp_{O_2}$  did not differ significantly from 0.00 during any measurement period, implying a constant hypercarbic stimulus during each hypoxic response measurement.

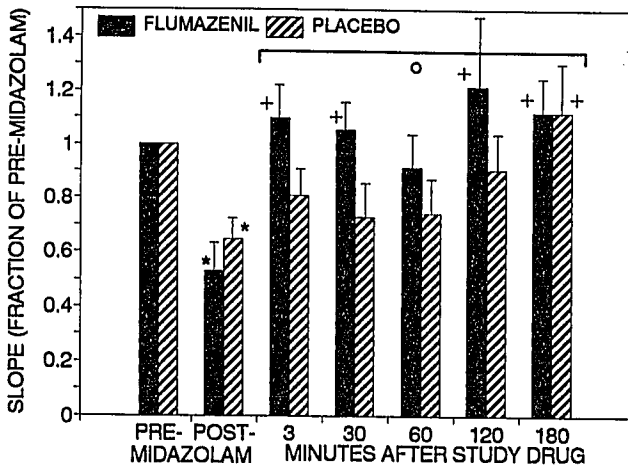


Fig. 2. Slope of hypoxic ventilatory response, expressed as fractions of premidazolam control values. Observation times are the same as in figure 1. \* $P < 0.05$  versus premidazolam value for same treatment. † $P < 0.05$  versus postmidazolam value for same treatment. ° $P < 0.05$  for flumazenil versus placebo by repeated measures ANOVA; the difference could not be attributed to an individual time point (see text).

Baseline minute ventilation at  $Sp_{O_2} = 90\%$  ( $\dot{V}_{E90}$ ) before placebo trials ( $19.67 \pm 2.49 \text{ l} \cdot \text{min}^{-1}$ ) did not differ significantly from that measured before flumazenil trials ( $17.51 \pm 1.82 \text{ l} \cdot \text{min}^{-1}$ ). After midazolam,  $\dot{V}_{E90}$  decreased to  $0.72 \pm 0.05$  times baseline in the placebo trials, while it decreased to  $0.68 \pm 0.07$  times baseline in the flumazenil trials ( $P < 0.05$  vs. premidazolam in each group,  $P = \text{NS}$  between groups, fig. 3). Three minutes after flumazenil,  $\dot{V}_{E90}$  increased to

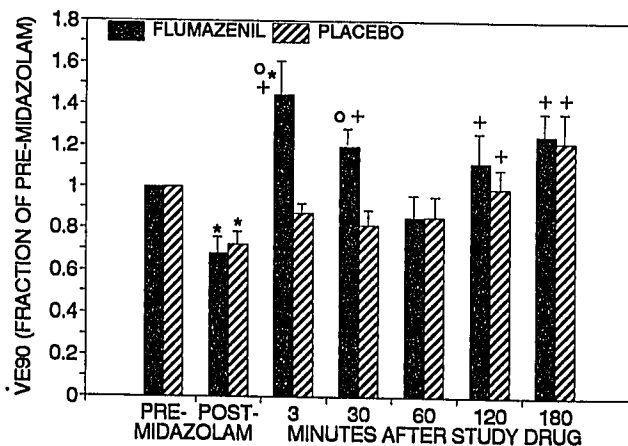


Fig. 3. Minute ventilation at  $Sp_{O_2} = 90\%$  ( $\dot{V}_{E90}$ ) expressed as fractions of the corresponding premidazolam values. Observation times are the same as in figure 1. \* $P < 0.05$  versus premidazolam value for same treatment. † $P < 0.05$  versus postmidazolam value for same treatment. ° $P < 0.05$  versus same time following placebo.

$1.45 \pm 0.15$  times its premidazolam value ( $P < 0.05$  vs. premidazolam;  $P < 0.05$  vs. postmidazolam), while at the same time after placebo it increased to  $0.87 \pm 0.05$  times baseline ( $P = \text{NS}$  vs. postmidazolam;  $P < 0.05$  placebo vs. flumazenil). ANOVA revealed that  $\dot{V}_{E90}$  was greater after flumazenil than after placebo ( $P < 0.05$ ); *post hoc* testing revealed significant between-treatment differences at 3 min ( $P < 0.05$ ) and 30 min ( $P < 0.05$ ) after study drug. Mean ventilatory response curves before and after midazolam, as well as 3 min after study drug, are shown in figure 4.

Changes in  $\dot{V}_{E90}$  resulted primarily from changes in tidal volume (fig. 5). Initial tidal volumes at  $Sp_{O_2} = 90\%$  ( $TV_{90}$ ) were  $1237 \pm 95 \text{ ml}$  in placebo trials and  $1186 \pm 108 \text{ ml}$  in flumazenil trials ( $P = \text{NS}$  be-

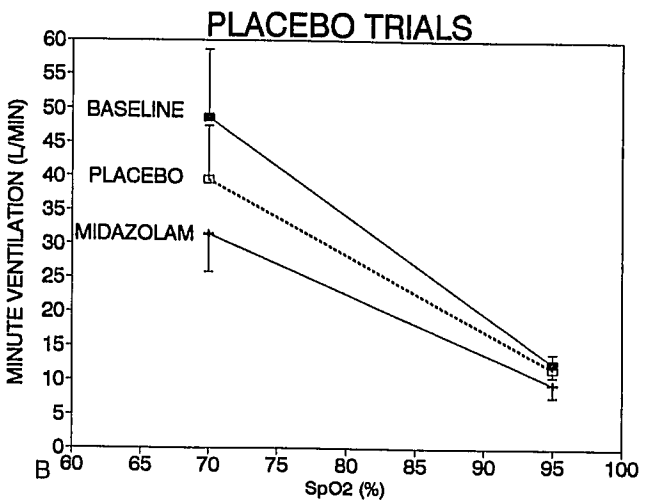
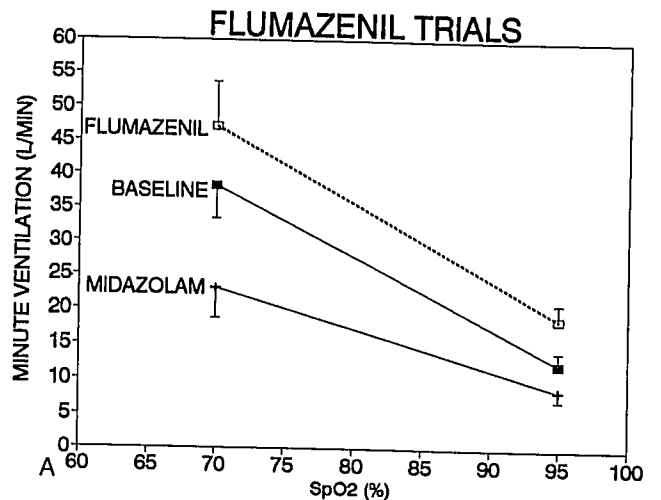


Fig. 4. Mean hypoxic ventilatory response curves before midazolam (baseline), after midazolam, and 3 min after flumazenil (A) or placebo (B) administration.

## HYPOXIC RESPONSE AFTER MIDAZOLAM AND FLUMAZENIL

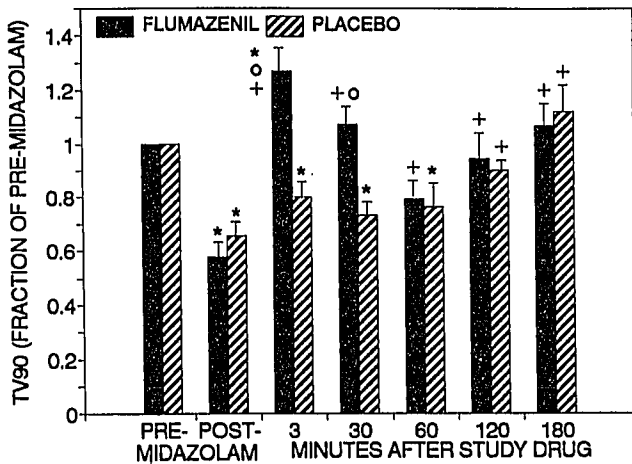


Fig. 5. Tidal volume at  $Sp_{O_2} = 90\%$  (TV90) expressed as fractions of the corresponding premidazolam values. Observation times are the same as in figure 1. \* $P < 0.05$  versus premidazolam value for same treatment. † $P < 0.05$  versus postmidazolam value for same treatment. ° $P < 0.05$  versus same time following placebo.

tween groups). In placebo trials, TV90 decreased to  $0.66 \pm 0.04$  times baseline after midazolam ( $P < 0.05$  vs. premidazolam); this did not differ from the decrease to  $0.58 \pm 0.04$  times baseline in flumazenil trials ( $P < 0.05$  vs. premidazolam). The increase in TV90 to  $1.27 \pm 0.09$  times baseline after flumazenil ( $P < 0.05$  vs. premidazolam;  $P < 0.05$  vs. postmidazolam) was significantly greater than the increase to  $0.8 \pm 0.05$  times baseline after placebo ( $P = NS$  vs. postmidazolam,  $P < 0.05$ , flumazenil vs. placebo). ANOVA established that TV90 was greater after flumazenil than after placebo ( $P < 0.05$ ); *post hoc* testing revealed that this could be attributed to significant between-treatment differences at 3 min ( $P < 0.05$ ) and 30 min ( $P < 0.05$ ) after study drug administration.

## Discussion

Depression of hypoxic ventilatory control after sedative doses of benzodiazepines has been described previously. Alexander *et al.* reported a 53% decrease in the hypoxic ventilatory response slope and a 30% decrease in  $\dot{V}_E$  at  $Sp_{O_2} = 90\%$  ( $\dot{V}_{E90}$ ) after midazolam  $0.1 \text{ mg} \cdot \text{kg}^{-1}$  intravenous.<sup>8</sup> Similarly, Lakshminarayan *et al.* found that diazepam  $10 \text{ mg}$  intramuscularly depresses hypoxic ventilatory response slope by 40%.<sup>9</sup> Mora *et al.*<sup>3</sup> also observed depression of the hypoxic ventilatory response after diazepam; however, they suggested that tolerance to this effect might develop if the duration of administration exceeded 1 h. The present findings

are consistent with these reports; in doses providing spontaneous eye closure with response to verbal commands ( $0.12 \pm 0.01 \text{ mg} \cdot \text{kg}^{-1}$ ), midazolam decreased the ventilatory response to hypoxia by 41%.

Three minutes after flumazenil, both  $\dot{V}_{E90}$  and slope exceeded their premidazolam control values; this suggests that flumazenil augmented ventilation in all conditions of chemical drive, with  $PET_{CO_2} \approx 48 \text{ mmHg}$  and  $Sp_{O_2}$  in the range of 100 to 70 percent (fig. 4A). Three minutes after placebo,  $\dot{V}_{E90}$  and slope were no longer significantly less than baseline (fig. 4B); this can be attributed to the waning effect of midazolam, since the 3-min poststudy drug hypoxic response determinations began 30–35 min after the last dose of midazolam. Nonetheless, increases in slope and  $\dot{V}_{E90}$  after flumazenil were significantly greater than those following placebo, establishing a salutary effect of flumazenil under these conditions. The decrease in tidal volume following midazolam and diazepam may predispose patients to hypoxemia;<sup>10</sup> therefore, the increased tidal volume and minute ventilation following flumazenil may alleviate benzodiazepine-induced hypoxemia.

Our findings contrast with those of Mora *et al.*, who were unable to find a consistent effect of flumazenil on diazepam-induced depression of the hypoxic ventilatory response.<sup>3</sup> This discrepancy may be related to the fact that Mora *et al.* did not measure the hypoxic ventilatory response at the same  $CO_2$  tension throughout their study. Their study design suggests that postdiazepam hypoxic response measurements were performed at higher  $CO_2$  tensions than prediazepam or postflumazenil determinations; this may have caused an artificial decrease in the slope of the postflumazenil hypoxic ventilatory response curve, masking the actual effect of the drug.<sup>3</sup> Additionally, although the investigators did not comment on the effect of flumazenil on the displacement of the hypoxic ventilatory response, their figures suggest an upward shift similar to that shown in our figure 4A.<sup>4,5</sup>

By using hyperoxic gas mixtures, it is possible to eliminate hypoxic drive during measurement of hypercarbic ventilatory response. In contrast, one cannot entirely eliminate hypercarbic drive while determining hypoxic ventilatory response. However, as noted by Knill *et al.*, the fact that hypercarbia potentiates the hypoxic chemoreflex leads to a "requirement for strict isocapnic conditions in comparative studies."<sup>11</sup> In the current study, we followed the examples of Rebeck and Campbell,<sup>12</sup> as well as those of Ward and Bellville<sup>13</sup> and Knill *et al.*,<sup>11</sup> by maintaining a constant degree of

hypercarbia for each subject. This modest hypercarbia ( $PET_{CO_2} = 46\text{--}48$  mmHg) allowed subjects to maintain spontaneous ventilation, even during midazolam sedation. Thus, in contrast to the study of Mora *et al.*, drug-induced changes in hypoxic ventilatory response were not confounded by varying degrees of hypercapnic stimulation. In addition, the rapid response of peripheral chemoreceptors to changing  $O_2$  tension enabled us to obtain valid slope and displacement data using a rebreathing technique.<sup>14</sup>

The current data complement our understanding of the effect of benzodiazepines and flumazenil on hypercarbic ventilatory control. Jordan *et al.*,<sup>15</sup> Gross *et al.*,<sup>2,16</sup> Spaulding *et al.*,<sup>17</sup> and Forster *et al.*<sup>18</sup> describe consistent decreases in the ventilatory response to hypercarbia after intravenous benzodiazepines, while Cohen *et al.*<sup>19</sup> and Bailey *et al.*<sup>20</sup> suggest that this effect may be more variable. Although flumazenil appears to shift hypercarbic ventilatory response curves to the left following midazolam, it does not appear to significantly affect the slope of the  $CO_2$  response as determined by the Read rebreathing technique.<sup>2</sup> It is not coincidental that the effect of midazolam and flumazenil on  $\dot{V}_{E90}$  and TV90 is similar to the effect of these drugs on  $\dot{V}_{E46}$  and TV46 ( $\dot{V}_E$  and TV at  $PET_{CO_2} = 46$  mmHg) in our previous study.<sup>2</sup> The only difference between these two variables is that  $\dot{V}_{E46}$  and TV46 were determined during hyperoxia, while  $\dot{V}_{E90}$  and TV90 were determined at an  $Sp_{O_2}$  of 90%. In each case, these "point" measurements serve as an index of the displacement of the corresponding ventilatory response curve. However, the study design makes it impossible to apportion changes in these displacement measurements to hypoxic, as opposed to hypercarbic, ventilatory control.

Three minutes after flumazenil,  $\dot{V}_{E90}$  and TV90 significantly exceeded their respective premidazolam values. An intriguing explanation for this finding would be that our subjects were developing acute tolerance to the effects of midazolam on hypoxic response; such tolerance to the ventilatory depressant effects of midazolam has been described in both animal models<sup>21,22</sup> and human volunteers.<sup>23</sup> In this instance, flumazenil could have precipitated a subclinical withdrawal syndrome, which was manifested by an increase in the hypoxic ventilatory response to supranormal values. This hypothesis is supported by the data of Nutt *et al.*, who found that flumazenil may cause CNS agitation in

patients with underlying alterations in benzodiazepine receptor sensitivity.<sup>24</sup> Of course, it is also possible that flumazenil caused a nonspecific augmentation of ventilation; this distinction cannot be established from the current data.

The present study examined the effects of flumazenil on respiratory depression induced by midazolam alone. Frequently, however, patients also receive other respiratory depressants, such as opioids, in the course of a diagnostic or therapeutic procedure; they are, therefore, susceptible to the ventilatory depressant effects of both drugs.<sup>25</sup> The efficacy of flumazenil under these circumstances has not been fully evaluated. Using a Read rebreathing technique, Dailland *et al.* found an increase in the slope of the ventilatory response to  $CO_2$  after intravenous flumazenil in patients who had received both midazolam and fentanyl.<sup>†</sup> Weinbrum and Geller, on the other hand, showed that, while flumazenil reversed ventilatory depressant effects of midazolam, it had no effect on patients who had received both midazolam and an opioid.<sup>26</sup> In a study by Tolksdorf *et al.*, patients who received flumazenil after fentanyl/midazolam anesthesia had more frequent episodes of severe hypoxia ( $Sp_{O_2} < 90\%$ ) than patients who had not received flumazenil, despite apparent increases in the level of awareness of the flumazenil recipients.<sup>27</sup> Clearly, further study is required to define the effect of flumazenil on ventilatory control when both benzodiazepines and opioids have been given.

Drug administration in the current study was designed to simulate clinical conditions, where midazolam is administered to effect, and a single dose of flumazenil is given for reversal. Because of the waning effects of midazolam, ventilatory drive would be expected to increase to some extent following placebo as well as flumazenil. Under these conditions, the most sensitive indicator of a flumazenil-specific effect would be the *change* in ventilatory variables following administration of the study drug. In fact, we found that the most dramatic differences between flumazenil and placebo occurred immediately after study drug administration.

In conclusion, following sedation with midazolam and in the presence of a constant level of hypercarbia, flumazenil was associated with a greater increase in hypoxic ventilatory response than was a placebo. Flumazenil also restored tidal volume to premidazolam levels. These data suggest that flumazenil increases ventilation throughout a wide range of conditions of chemical drive, and, thus, may be useful in the treatment of benzodiazepine-induced ventilatory depression.

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