Sedative and ventilatory effects of midazolam infusion: effect of flumazenil reversal

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The purpose of this study was to evaluate the effects of flumazenil (1 mg iv) on the ventilatory response of premedicated patients receiving a continuous infusion of midazolam for sedation. After assessing baseline ventilatory function using a modified Read rebreathing method for determining hypercapnic ventilatory drive, 16 healthy outpatients were administered fentanyl, 50 µg iv, and midazolam 2 mg iv, followed by a variable-rate midazolam infusion, 0.3–0.5 mg·min⁻¹. Upon termination of the midazolam infusion, serum midazolam concentrations were measured and ventilatory function was reassessed. Then, 10 ml of either saline or flumazenil (1 mg) were administered according to a randomized, double-blind protocol. Ventilatory function was subsequently measured at 5 min, 30 min and 60 min intervals after study drug. Compared with the baseline value, midazolam infusion reduced tidal volume and increased respiratory rate and alveolar dead space. However, midazolam did not decrease the slope of the CO₂-response curve. Flumazenil reduced the degree of midazolam-induced sedation and the decrease in tidal volume ($P < 0.05$), but not the change in resting respiratory rate. In some patients, the

ventilatory response to hypercarbia actually decreased after flumazenil administration compared with the immediate pre-reversal (sedated) values. It is concluded that midazolam infusion, 0.43 mg·min⁻¹, did not impair CO₂-responsiveness. Flumazenil's effect on central ventilatory drive was more variable than its reversal of midazolam-induced sedation.

Cette étude vise à évaluer les effets du flumazénil (1 mg iv) sur la réponse ventilatoire de patients prémédiqués qui reçoivent, pour fin de sédation, une perfusion continue de midazolam. Après avoir établi la ventilation initiale avec une méthode de réinspiration de Read modifiée, dans le but de déterminer l'effort ventilatoire hypercapnique, 16 patients ambulatoires bien portants reçoivent fentanyl 50 µg iv et midazolam 2 mg iv suivis d'une perfusion de midazolam à débit variable à la vitesse de 0,3–0,5 mg·min⁻¹. Une fois la perfusion terminée, les concentrations sériques de midazolam sont mesurées et la ventilation réévaluée. Par la suite, une solution de 10 ml contenant soit du soluté physiologique soit du flumazénil (1 mg) est administrée aléatoirement et à double aveugle. La ventilation est par la suite mesurée à des intervalles de 5 min, 30 min et 60 min. Comparativement aux valeurs de base, la perfusion de midazolam diminue le volume minute et augmente la fréquence respiratoire et l'espace mort alvéolaire. Cependant, le midazolam ne modifie pas la pente de la courbe de réponse au CO₂. Le flumazénil diminue le niveau de sédation induit par le midazolam et la baisse du volume courant ($P < 0,05$), mais non le changement de la fréquence respiratoire. Chez certains patients, la réponse ventilatoire à l'hypercarbie diminue après l'administration de flumazénil comparativement aux valeurs qui précèdent immédiatement l'antagonisme. En conclusion, une perfusion de midazolam 0,43 mg·min⁻¹ n'altère pas la réactivité au CO₂. L'effet du flumazénil sur l'effort respiratoire central est plus variable que sa capacité de renverser la sédation induite par le midazolam.

Key words

ANAESTHETIC TECHNIQUES: intravenous; infusion;
ANALGESICS: fentanyl;
ANTAGONISTS: benzodiazepines; flumazenil;
HYPNOTICS: benzodiazepines; midazolam;
MEASUREMENT TECHNIQUES: CO₂ response curve.

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Benzodiazepines and opioid analgesics are widely used for producing sedation and analgesia during monitored anaesthesia care. Large bolus doses of midazolam can

produce large decreases in both ventilatory drive and haemoglobin oxygen saturation,¹ in particular when combined with potent opioid analgesics.^{2,3} However, there are conflicting data in the literature regarding the respiratory effects of sedative doses of benzodiazepines.⁴⁻⁹ Although most patients experience varying degrees of ventilatory depression following administration of intravenous bolus doses of benzodiazepines, some patients may display enhanced respiratory drive.⁵ The effect of a continuous intravenous infusion of midazolam on the ventilatory response to hypercarbia has not been previously reported.

Flumazenil, a centrally-active imidazobenzodiazepine, antagonizes the sedative, amnestic and electroencephalographic depressant effects of midazolam and diazepam.¹⁰⁻¹² Flumazenil appears to be devoid of any intrinsic sedative or respiratory depressant effects, even after large supra-therapeutic doses.¹³ However, the effect of flumazenil on respiratory drive after administration of a benzodiazepine agonist is highly controversial.^{8,14-18} In a recent publication, Flögel *et al.*¹⁸ reported that flumazenil 1 mg *iv* was sufficient "to achieve full reversal of midazolam's effects on hypnosis and ventilation." Of interest, these investigators found differences between the duration of flumazenil's reversal of midazolam-induced hypnosis and ventilatory depression.

Therefore, we designed a clinical study to: (1) assess the ventilatory effects of midazolam when administered as a continuous infusion for sedation during outpatient diagnostic procedures, and (2) determine the effects of flumazenil on the level of sedation and respiratory function following midazolam-induced sedation.

Methods

After obtaining Institutional Review Board approval, we studied 16 healthy, consenting adult outpatients scheduled to undergo diagnostic procedures (e.g., colonoscopy) requiring intravenous sedation. The patients' ages ranged from 30 to 58 yr, with a mean ($\pm$ SD) of 42.5 ± 8 yr. Patients who were obese, had a history of pulmonary disease, chronically used benzodiazepines or other centrally active drugs, or had a history of alcohol or drug abuse, were excluded. All patients were fasted for at least eight hours before entry into the study.

Experimental procedure

Before undergoing their diagnostic procedure, the patients were familiarized with the study protocol and baseline measurements of ventilatory function (respiratory rate (RR), tidal volume (V_T), minute ventilation (V_E), end-tidal carbon dioxide (PETCO₂), and the slope of the ventilatory response to carbon dioxide) were obtained using the Read rebreathing method.¹⁹ Arterial oxygen saturation (SpO₂) was measured using finger pulse oximetry.

Each patient assessed their level of sedation by placing a mark on a 100 mm visual analogue scale (0 = awake/alert to 100 = unresponsive/sleeping). Sedation was also assessed by a trained observer using a five-point scale (1 = alert, 2 = sleepy, 3 = responsive to verbal stimuli, 4 = responsive to light tactile stimulation, 5 = asleep and difficult to arouse).

Patients were transferred to the endoscopy suite and two 18 ga indwelling intravenous (*iv*) catheters were placed in contralateral upper extremities for administration of *iv* fluids (5% dextrose in lactated Ringer's solution) and the study medications, and the second catheter was used to obtain blood samples for determination of serum midazolam concentration. After placing routine monitors (ECG, blood pressure cuff and finger pulse oximeter), patients were premedicated with fentanyl, 50 μ g *iv*, and sedation was initiated with a loading dose of midazolam, 2 mg, *iv*. Sedation was subsequently maintained with a variable-rate midazolam infusion, 0.3–0.5 mg $\cdot$ min⁻¹ *iv*. Patients were breathing room air throughout the study period. The midazolam infusion rate was varied to maintain a stable level of sedation at which the patients were resting comfortably with their eyes closed, but responded to light tactile stimulation (level 3–4 on the five-point sedation scale). Upon completion of the diagnostic procedure, the degree of sedation, ventilatory drive, and respiratory variables were reassessed and the midazolam infusion was discontinued. Plasma midazolam concentration was measured, using a standard gas chromatography-mass spectrometry analytical technique,²⁰ at the end of the procedure and upon completion of the end-infusion ventilatory study. The average midazolam concentration for the two determinations was correlated with the changes in ventilatory function.

After completing the above assessments, 10 ml of either flumazenil, 1.0 mg (flumazenil group, *n* = 9) or normal saline (control group, *n* = 7) were administered *iv* in a randomized, double-blind fashion. The level of sedation, slope of the CO₂-response curve, respiratory variables and SpO₂ values were reassessed at 5-min, 30-min, and 60-min intervals after administration of the study medication.

Respiratory equipment

The instrumentation used for this study has been previously described²¹ and consisted of a Medical Graphics System 2001 Lab (Medical Graphics Corporation 350 Oak Grove Parkway, St. Paul MN 55110) modified for a Read rebreathing system with minimal dead space (110 ml). The breathing circuit was filled with 7% CO₂ and the balance consisted of oxygen. The total system resistance was 0.5 cm H₂O at a flow of 1 L $\cdot$ sec⁻¹. The ambient conditions were stable and instrument calibra-

tion corrections were applied to correct for any changes in temperature or humidity prior to each test. The end-tidal gases were measured with rapid response O₂ and CO₂ analyzers requiring 150 ml gas samples per minute. The analyzer's response time at the sensor was less than 100 msec. Each analyzer was calibrated with certified gas to be accurate to 0.03%. Flow was measured with a heated linear pneumotachograph (Hans Rudolph Model 3813, Hans Rudolph, Inc., Kansas City, MO), with a linear flow range from 0 to 800 L · min⁻¹.

Using on-line breath-by-breath waveform analysis, the instrument permitted close observation of V_E, PETCO₂, end-tidal O₂, V_T, and RR. Respiratory variables for any given breath could be examined on the CRT screen using the replay mode software.

Measurement of ventilatory drive

During all ventilatory drive studies, subjects were seated in an upright position with the torso at approximately 100° to the legs. The mouthpiece was positioned in the patient's mouth and the nose was sealed with a nose clip. The testing conditions were standardized with respect to room lighting and background noise. After determining that the patient was comfortable with stable V_E and PETCO₂ values and that no leaks were present in the breathing circuit, the data collection process was started. Under normal conditions, four to five minutes of breathing room air were sufficient to reach stable values of V_E and PETCO₂. Carbon dioxide rebreathing was started by turning the three-way valve to the "rebreathing" position. The test was terminated after approximately four minutes when a PETCO₂ of 60 mmHg was reached.

Calculation of respiratory variables

The CO₂ response studies were immediately replayed on the CRT screen using an X-Y graph. Approximately 40 to 70 data points were obtained during each study for the regression analysis. Swallows or coughs were rejected by the computer which recognized incomplete breathing cycles. The ventilatory slope was calculated using a regression analysis over the linear portion of the ventilation vs PETCO₂ curve. We assessed the displacement of the CO₂ response curve by determining the magnitude of the shift in the CO₂ response "threshold" value, defined as the PETCO₂ at which V_E changes linearly with further increases in carbon dioxide.²¹ In order to assess drug effects on V_T and RR, the "resting" variables were measured at the same V_E for all subjects and at a V_E of 20 L · min⁻¹ during the rebreathing period (approximately mid-phase of the CO₂ response determinations).

Changes in the physiological (respiratory) dead space were quantified using the Bohr-Engoff equation where

PaCO₂ was estimated from PETCO₂ using the method of Jones and Campbell:²²

$$\text{Estimated PaCO}_2 (\text{EPaCO}_2) = 5.5 + 0.9 \text{ PETCO}_2 - 0.0021 \text{ VT}$$

$$\text{VD} = \frac{\text{EPaCO}_2 - \text{PETCO}_2}{\text{EPaCO}_2} (\text{VT-valve dead space}).$$

Data were subjected to univariate and multivariate analysis of variance (ANOVA), with intra- and intergroup changes over time assessed using repeated measures of ANOVA. Inspection of differences between mean values was performed using the protected least significant difference test. Finally, nominal data were analyzed using the Kruskal Wallis and sign tests. A *P*-value < 0.05 was considered statistically significant.

Results

The 16 study patients received a total midazolam dose of 27.6 ± 13.1 mg *iv* (mean ± SD), infused over 63 ± 23 min (Table I). The mean (±SD) plasma midazolam concentration at the time the end-infusion (sedated) respiratory testing was performed was 364 ± 310 ng · ml⁻¹. As expected, end-infusion sedation assessment scores (determined by a trained observer) and visual analogue scale scores (assessed by the patient), were higher than the preoperative baseline values. In all patients, baseline and end-infusion respiratory measurements were within the normal range for healthy subjects (Table II).

With the exception of one subject who was prone during the procedure, all patients were positioned in the lateral decubitus position. The prone patient transiently desaturated from an SpO₂ value of 98% to 89%, and one patient who was in the lateral decubitus position experienced a decrease in SpO₂ from 98% to 92%. There was an increase in the respiratory rate and the resting PETCO₂, and a decrease in V_T at the end of the midazolam infusion (*P* > 0.01). The slope of the curve relating ventilatory response to PETCO₂ was not different from the baseline value at the end-infusion measurement. However, there was an increase in the CO₂ response curve threshold value from 48 ± 3 (baseline) to 51 ± 2 mmHg following midazolam sedation.

In comparing the V_T values when the subjects were breathing at rest (resting V_E pre-rebreathing) and at a V_E of 20 L · min⁻¹ (VT20), we found decreases from pre-sedation (baseline) values at the end-infusion testing interval. The decreases in V_T values were accompanied by concomitant increases in the RR. Respiratory dead space (VD/V_T) also increased with midazolam sedation. There was no correlation between plasma midazolam concentration and the changes from baseline to post-sedated (end-infusion) values for either PETCO₂ values or the

TABLE I Patient demographic data, duration of sedation, drug doses, and plasma midazolam levels*

	All patients	Saline group	Flumazenil group
Number (n)	16	7	9
Sex (M/F)	10/6	4/3	6/3
Age (yr)	42.5 ± 8	43 ± 5	42 ± 15
Weight (kg)	70 ± 11.5	71 ± 15	69 ± 9
ASA physical status I/II	14/2	7/0	7/2
Midazolam dosage (mg)	27.6 ± 13.1	27 ± 9	28 ± 16
Duration of sedation (min)	63.5 ± 22.7	69 ± 32	59 ± 14
Midazolam infusion rate (mg · min ⁻¹)	0.4 ± 0.16	0.4 ± 0.1	0.4 ± 0.2
Midazolam concentration (ng · ml ⁻¹)	364 ± 310	372 ± 371	358 ± 277

*Data expressed as mean values ± SD.

TABLE II Preoperative (baseline) and end-infusion sedation and respiratory variables (mean ± SD)

	Baseline	End-infusion
Sedation score (1-5)	1.0	3.6 ± 0.6*
VAS sedation scale (mm)	14 ± 14	96 ± 8*
Resting end-tidal CO ₂ (mmHg)	38.5 ± 2.7	41.6 ± 1.9†
Resting VE (L · min ⁻¹)	9.5 ± 1.6	9.6 ± 1.5
CO ₂ response (VE/PETCO ₂)	2.7 ± 1.3	3.0 ± 1.3
CO ₂ threshold (mmHg)	48 ± 3	51 ± 2†
VT at resting VE (ml)	751 ± 153	502 ± 86†
RR at resting VE (bpm)	13 ± 4	20 ± 5†
Resting VD/VT ratio	0.38 ± 0.07	0.48 ± 0.09†
VT at VE = 20 L · min ⁻¹ (ml)	1333 ± 340	996 ± 207†
RR at VE = 20 L · min ⁻¹ (bpm)	16 ± 4	21 ± 5*
Resting arterial O ₂ saturation (%)	97 ± 2	96 ± 2

*P < 0.05 from baseline values.

†P < 0.01 from baseline values.

slopes of the ventilatory response curves (data not reported).

In the second phase of the study, the patients were randomly assigned to either a control (saline) or flumazenil treatment group. There were no differences noted with respect to demographic data (Table I). The slopes of the pre-treatment (end-infusion) ventilatory response curves and respiratory variables (VT, RR, VD/VT, PETCO₂) did not differ between the two groups. Following the administration of the study drug (saline or flumazenil), the flumazenil-treated patients had lower sedation scores as measured by both the visual analogue scale and the observer's sedation assessment score (Figure 1). In comparing the ventilatory drive measurements performed before and after saline administration with baseline values, we found no changes in the calculated CO₂ response curves at any of the time intervals studied (Figure 2). The respiratory response to hypercarbia after flu-

FIGURE 1 (A) Sedation visual analogue scale (VAS) scores before (sedated) and after study drug administration, (B) Observer sedation assessment scores before and after study drug administration. ■ = saline, □ = flumazenil 1 mg, *P < 0.05 versus saline, +P < 0.01 versus baseline.

FIGURE 2 The slope of the CO₂ response curve (VE/PETCO₂) preoperatively (baseline), end-infusion (time 0) and at 5-min, 30-min, and 60-min intervals after either saline (■) or flumazenil 1 mg (□).

mazenil administration was decreased compared with the end-infusion measurements; however, the post-flumazenil values were not different from the pre-sedation "baseline" values (P = 0.06). In the saline group, the CO₂ threshold values were elevated above the baseline value at all sub-

FIGURE 3 The CO₂ threshold values (at which VE increases linearly with end-tidal CO₂) preoperatively (baseline), at the end of the midazolam infusion (time 0) and at 5-min, 30-min, and 60-min intervals after either saline (■) or flumazenil 1 mg (□), * $P < 0.01$ versus baseline.

sequent time intervals ($P < 0.01$). Flumazenil produced no changes in CO₂ threshold values compared with the end-infusion measurements (Figure 3).

Changes in RR and VT measured at rest and at VE = 20 L · min⁻¹ while the subject was awake (baseline), sedated, and at 5-min, 30-min, and 60-min intervals after the administration of either saline or flumazenil are summarized in Table III. Following midazolam sedation, RR increased and VT decreased at resting VE and when VE equaled 20 L · min⁻¹ in both the saline and flumazenil treatment groups. In both groups, RR, resting VT and VT20 values returned toward baseline values at the subsequent testing intervals. More importantly, no differences were found between the flumazenil and saline treatment groups with respect to resting VT and VT20 values at 30 min and 60 min after study drug administration. Finally, the study drugs had no effects on alveolar ventilation as assessed by VD/VT ratios (Figure 4).

Discussion

While large bolus doses of midazolam (0.15 mg · kg⁻¹ iv) have been associated with clinically important respiratory depression,¹ smaller doses (0.04–0.08 mg · kg⁻¹ iv) have minimal effect on respiratory drive.²⁴ Despite increases in both subjective and objective sedation scores (Table II), our data suggest that the use of a variable-rate midazolam infusion, at a mean rate of 0.43 mg · min⁻¹, did not decrease central ventilatory drive in response to a hypercapnic challenge. These data are consistent with the recent findings of Mak *et al.*¹⁷ following oral midazolam. Although it was not evaluated in our study, depression of hypoxic drive may be a more important clinical problem with large doses of midazolam.^{7,8}

As reported previously following intermittent bolus doses of midazolam,⁶ we found that midazolam infusion produced a decrease in VT, as well as a concomitant increase in both RR and respiratory dead space. Not surprisingly, an increase in resting PETCO₂ was noted at the end of the midazolam infusion. Although the RR remained above the baseline values after flumazenil 1 mg iv, the VT increased towards the baseline values during the rebreathing period. However, the resting VT values remained below baseline values following flumazenil administration. Barakat *et al.*^{*} also reported that flumazenil was only partially effective in antagonizing midazolam-induced changes in ventilatory variables, and Flögel *et al.*¹⁸ found that the reduction in the ventilation intercept at a PETCO₂ of 58 mmHg was not consistently reversed by flumazenil.

The midazolam plasma concentrations measured at the end of the infusion were higher than the levels previously reported to produce hypnosis (or unconsciousness).²³ Although these patients were very somnolent at the end-infusion assessment interval, they were easily arousable and were able to cooperate for the respiratory measurements performed prior to and five minutes after administration of the study drugs. These data suggest that tolerance to both the sedative and respiratory depressant effects of midazolam may have developed during the infusion period. Of interest, Berggren *et al.*⁶ also reported that despite increased plasma concentrations of midazolam, subsequent bolus doses of midazolam (0.05 mg · kg⁻¹) did not cause further changes in ventilatory variables. Analogous to the findings of Berggren *et al.*,⁶ we found no correlation between the plasma midazolam concentrations and changes in the resting PETCO₂ values or slopes of the CO₂-response curves (data not reported). Similarly, Sunzel *et al.*²⁴ found no correlation between the plasma concentration of midazolam and changes in any of the respiratory variables.

Given the inherent complexity of the mechanisms involved in the control of breathing and the small group sizes, it is not surprising that we were unable to find a correlation between plasma midazolam concentrations and respiratory variables. A further confounding factor may have been the small dose of fentanyl (50 µg iv) administered prior to induction of midazolam sedation. While a sedative dose of midazolam (0.05 mg · kg⁻¹ iv) produced no respiratory effects when administered to healthy volunteers,² the combination of midazolam and fentanyl increased the incidence of both hypoxemia and

*Barakat T, Lechat JP, Laurent P, Fletcher D, Clergue F, Viars P. Ventilatory effects of flumazenil on midazolam-induced sedation. *Anesthesiology* 1988; 69: A817.

TABLE III Respiratory variables at rest (pre-rebreathing) and at a $\dot{V}_E$ equal to $20 \text{ L} \cdot \text{min}^{-1}$ in the saline and flumazenil treatment groups. Data are presented as mean values $\pm$ SD

A. Changes in respiratory rate (bpm) at rest and at $\dot{V}_E = 20 \text{ L} \cdot \text{min}^{-1}$

	Resting RR		RR at $\dot{V}_E = 20 \text{ L} \cdot \text{min}^{-1}$	
	Saline	Flumazenil	Saline	Flumazenil
Baseline (preoperative)	13 ± 4	13 ± 4	16 ± 6	16 ± 2
Sedated (end-infusion)	$20 \pm 4^*$	$19 \pm 4^*$	$20 \pm 4^*$	$22 \pm 5^*$
5 min post-reversal	$16 \pm 4^{*\dagger}$	$16 \pm 5^*$	$19 \pm 5^*$	$17 \pm 5^\dagger$
30 min post-reversal	$16 \pm 5^{*\dagger}$	$17 \pm 6^*$	$17 \pm 7^\dagger$	$19 \pm 6^*$
60 min post-reversal	$16 \pm 5^{*\dagger}$	$17 \pm 5^*$	$17 \pm 5^\dagger$	$19 \pm 5^*$

B. Changes in tidal volume (ml) measured at rest and at $\dot{V}_E = 20 \text{ L} \cdot \text{min}^{-1}$

	Resting V_T		V_{T20}	
	Saline	Flumazenil	Saline	Flumazenil
Baseline (preoperative)	794 ± 194	714 ± 104	1444 ± 461	1237 ± 161
Sedated (end-infusion)	$516 \pm 77^*$	$489 \pm 97^*$	$1026 \pm 173^*$	$970 \pm 244^*$
5 min post-reversal	$611 \pm 159^*$	$600 \pm 102^{*\dagger}$	$1106 \pm 245^*$	$1234 \pm 288^\dagger$
30 min post-reversal	$694 \pm 172^\dagger$	$562 \pm 99^{*\dagger}$	$1315 \pm 388^\dagger$	$1128 \pm 235^\dagger$
60 min post-reversal	$701 \pm 187^\dagger$	$555 \pm 49^{*\dagger}$	$1278 \pm 333^\dagger$	$1116 \pm 218^\dagger$

* $P < 0.05$ versus baseline value.

$^\dagger P < 0.05$ versus sedated value.

FIGURE 4 The V_D/V_T ratios during the preoperative (baseline) and at the end of the midazolam infusion (time 0) and at 5-min, 30-min, and 60-min intervals after either saline (■) or flumazenil 1 mg (□), * $P < 0.01$ versus baseline.

apnoea. Yet, the combination of midazolam and fentanyl did not further increase the depression of the ventilatory response to CO_2 produced by fentanyl alone. Of interest, Tolsdorf *et al.*²⁵ reported that considerably more epi-

sodes of hypoxaemia were observed when general anaesthesia with midazolam was reversed with flumazenil. These data suggested that flumazenil reversal of benzodiazepine-induced sedation might "unmask" underlying opioid-induced respiratory depression. Weinbrum and Geller²⁶ also reported that flumazenil was unable to reverse ventilatory depression in patients who had received both midazolam and an opioid analgesic. Thus, the depression in ventilatory drive noted in some of our patients following flumazenil reversal may have represented the residual effect of the fentanyl premedication.

Consistent with other reports in the literature,^{10-12,17,18} we found that flumazenil, 1 mg *iv*, was highly effective in reversing residual midazolam-induced sedation without reversing all the ventilatory effects of midazolam. The explanation for the apparent dissociation between the sedative and respiratory effects after midazolam infusion and flumazenil reversal may be related to the complex interrelationships between neurotransmitters and receptors within the central nervous system (CNS). Since drug effects on both benzodiazepine and GABA receptors appear to influence central respiratory drive,²⁷ the dissociation between the sedative and respiratory effects of midazolam

and flumazenil may be related to differing drug effects on these two receptor populations. In contrast to an intermittent bolus dosing technique, the use of a continuous midazolam infusion would be associated with a slower rate of increase in the plasma (and effect site) concentration of midazolam, as well as lower peak tissue levels. The presence of high plasma midazolam concentrations during the infusion period (>300) ng · ml⁻¹) can also induce changes in CNS benzodiazepine receptor density and affinity.²⁸ These receptors changes may influence the physiological responses to a centrally active sedative medication, and thereby contribute to the development of tolerance to midazolam's sedative and respiratory depressant effects.

When administered to elderly patients receiving midazolam (0.1 ± 0.03 mg · kg⁻¹, iv) for sedation during upper gastrointestinal endoscopic procedures, flumazenil reversed the residual sedative but not the ventilatory depressant effects of midazolam.²⁹ In contrast, we found that flumazenil was effective in reversing some components of midazolam-induced ventilatory depression (e.g., the decrease in VT). Analogous to the finding of Gross *et al.*,¹⁴ flumazenil did not reverse the depressant effects of midazolam on the CO₂ response curve. However, Blouin *et al.* reported that following sedation with midazolam in the presence of a constant level of hypercarbia, reversal with flumazenil was associated with an increase in hypoxic ventilatory responsiveness.¹⁵ While flumazenil appears to have a transient beneficial effect in reversing benzodiazepine-induced respiratory depression, these changes may not be attributable solely to specific antagonistic effects of flumazenil at the respiratory centre.¹⁶ The mechanisms responsible for the respiratory changes following flumazenil administration^{14,15,18} may be influenced by other physiological factors which are known to increase central respiratory drive, in particular enhanced wakefulness.³⁰

In conclusion, use of a midazolam infusion (0.3 – 0.5 mg · min⁻¹) to achieve "deep" sedation during diagnostic procedures was not associated with clinically important ventilatory depression. The plasma midazolam concentrations at the end of the infusion period were similar to those previously reported to be associated with unconsciousness, suggesting that patients may develop tolerance to the sedative and respiratory depressant effects of midazolam during a one hour infusion. Finally, it would appear that flumazenil is more effective in reversing benzodiazepine-induced sedation than respiratory depression.

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