Title : VENTILATORY EFFECTS OF FLUMAZENIL ON MIDAZOLAM-INDUCED SEDATION

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INTRODUCTION. Midazolam (MDZ), a water-soluble benzodiazepine (BZD), is commonly used for sedation or induction of anesthesia. It has been shown to produce a smooth induction with anterograde amnesia, while its disadvantage is a prolonged recovery. Flumazenil is a specific antagonist of BZD-induced effects. Midazolam with flumazenil reversal was recently reported to be a safe and promising technique for short outpatient anesthetic procedures (1).

It is generally accepted that BZD have a depressant effect on ventilation. Flumazenil was recently reported to produce a 31 % decrease in the ventilatory response to CO2 (2). However, the ventilatory effects of flumazenil on midazolam-induced sedation have not clearly been established. The present study was therefore conducted to assess the ventilatory effects of flumazenil on midazolam-induced sedation.

METHODS. Seven healthy volunteers consented to participate in this institutionally approved study. Mean age was 30 years (range : 26-37 yrs). Mean weight was 64.2 kg (range : 46-73 kg). Changes in rib cage (RC) and abdominal (AB) dimensions were measured by respiratory inductance plethysmography (RIP). The RIP bands were positioned at the mamillary and umbilical levels. Volume-motion coefficients (VMC) for RC and AB, obtained after calibration with direct spirometry, permitted calculations of : tidal volume (VT), thoracic contribution to VT (VRC/VT), respiratory rate (RR), and minute-ventilation ($\dot{V}E$). These variables were obtained during quiet breathing (5 min). Calibration of the RIP was repeated before each set of measurements.

Ventilatory measurements were also performed by direct spirometry during room air breathing and during a CO2 stimulation test (method of Read). Linear regression equations were calculated for $\dot{V}E$ versus end-tidal PCO2 (PETCO2). Results are expressed by the slope ($\dot{V}E$/PCO2) and the position of the slope at 60 mmHg ($\dot{V}E$ 60).

Swings in gastric (Pgas) and oesophageal (Poes) pressures were measured with two balloon catheters connected to Validyne (MP 45) transducers. Pgas/Poes was used as an index of diaphragmatic contribution to tidal breathing.

The subjects were studied in the supine position, in a quiet room. They were continuously monitored by ECG and pulse oximetry. Baseline measurements were obtained, including two rebreathing tests. Midazolam was then infused at a rate of 0.6 mg/min until a profound sedation was obtained. When the subjects were not responsive to verbal command, the infusion rate was set to 0.2 mg/min, and ventilatory measurements were repeated. MDZ was discontinued 40 min after the start of the infusion, and 1 mg flumazenil was administered over 5 min. Ventilatory measurements were repeated 5 and 90 min later. Values are given as mean ± SEM. Statistical significance was tested using analysis of variance and a modified t-test.

RESULTS. The administered dose of midazolam was 16.1 ± 2.8 mg (range : 7-30 mg). The results of the ventilatory variables are summarized in the table. VT and RR remained unchanged throughout the study.

This study demonstrates that MDZ-induced ventilatory depression is only partially antagonized by 1 mg flumazenil. Immediately after flumazenil, PETCO2 and VRC/VT returned to baseline values. However, $\dot{V}E$ 60 remained significantly decreased, and was not significantly different from post-MDZ values.

The second interesting finding of this study is that 90 min after 1 mg flumazenil, the MDZ-induced ventilatory depression persisted, as evidenced by the secondary rise of PETCO2 and the persistent decrease in $\dot{V}E$ 60.

DISCUSSION. This study suggests that 1 mg flumazenil induces only a partial and transitory antagonism of MDZ-induced ventilatory depression. This effect is probably related to the shorter elimination half-life of flumazenil than that of MDZ. Thus, if flumazenil is used to reverse the sedative effect of MDZ, a careful monitoring of ventilation is still mandatory because of the long-lasting ventilatory depression of MDZ.

Table : Ventilatory variables before (C), after MDZ (MDZ), after flumazenil (MDZ-FMZ), and 90 min after flumazenil (MDZ-FMZ + 90 min).

	C	MDZ	MDZ-FMZ	MDZ-FMZ + 90 min
$\dot{V}E$ l/min	4.9±0.5	5.4±0.6 ***	6.4±0.7 &&	5.7±0.3 ***£
PETCO2 mmHg	39.2±1.1	42.4±0.9 **	40.1±1.0	41.6±1.0
$\dot{V}E$/PCO2 l/min/mmHg	2.4±0.4	1.2±0.1 **	1.9±0.3 *	1.9±0.3 *
$\dot{V}E$60 l/min	47.8±7.5	24.7±3.2 **	34.5±2.9	34.3±5.0
VRC/VT %	40.2±7.5	64.7±4.3	46.6±5.4	53.1±5.7
Pgas/Poes	0.62±0.08	0.40±0.02	0.52±0.11	0.33±0.04

Comparison : * vs C ; & vs MDZ ; £ vs MDZ-FMZ
*,&,£ : p<0.05 ; **,&& : p<0.01 ; *** : p<0.001

REFERENCES
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