Title: VENTILATORY EFFECTS OF VARIOUS DOSES OF I.V. MIDAZOLAM ASSESSED BY A NON-INVASIVE METHOD IN HEALTHY VOLUNTEERS

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Introduction. The conflicting data concerning the ventilatory effects of benzodiazepines may be due to a large variability in the conditions of investigation (i.e. patients, drug and dosage, method). In order to decrease the influence of these methodological factors we performed a randomized double-blind study evaluating the ventilatory effects of different doses of midazolam (MDZ) compared to placebo (PL) in healthy volunteers with a non-invasive technique.

Methods. 8 healthy men accustomed to investigational environement, mean age 30±4 years ($\bar{x}$±SD), mean weight 76±8kg volunteered for the study. None of them had a previous medical history or did take regular medication or alcohol. Informed consent was obtained and the Committee for Ethics and Human Research of our institution approved the study. Tidal volume (V_T) and respiratory rate were measured with a non-invasive method using 2 bellows pneumographs (Hewlett Packard (HP) model 108 pneumograph) attached circumferentially around the rib cage and the abdomen. The bellows were connected to differential pressure transducers (HP 267BC) and their signals stored on a microcomputer (Apple II plus). Any change in circumference of the rib cage and the abdomen produces a linear variation of pressure within the bellows. Calibration was done before each experiment by adjusting these signals to match the volumes mesured with a pneumotachograph (Godart type 17212) according to a computer-aided procedure described by Abraham et al. (1). The calibration was judged satisfactory when the mean differences between the volumes obtained by the non-invasive technique and those obtained with the pneumotachograph were less than ± 10% with various breathing patterns. The calibration procedure was repeated at the end of the experiment to test the fiability of our results. The percentage error remained always below ± 10 %. End-tidal carbon dioxide (F_ECO_2) was recorded from a nasal catheter using an infrared CO_2 analyzer (Godart model KK). Oxygen saturation was continously measured with a HP 47201A ear oxymeter. Each subject was studied 4 times at intervals of at least 4 days, once after an I.V. injection of PL, and 3 times after different doses of MDZ (0.05mg/kg, 0.1 mg/kg and 0.2 mg/kg) administered over a 15-second period. The experiments were performed randomly and in a double-blind fashion. The subjects were studied in a supine position, in a quiet dark room, disconnected from the pneumotachograph, comfortably installed with ear phones listening to music and with the eyes covered with a cloth, a 5% dextrose infusion beeing started. Arterial blood pressure and EKG were monitored. Statistical analysis was done using an analysis of variance (AOV), with differences between groups detected by a Scheffé test. A paired t-test was used to assess statistical differences between the control values before and after injection. The data are expressed as mean ±SEM.

Results. The results are illustrated in fig. 1 and table 1. When compared with the preinjection values, all measured variables remained stable with PL. With the 3 doses of MDZ the following changes were significant ($p < 0.05$, paired t-test): decrease in V_T, minute volume and O_2 saturation, increase in respiratory rate and F_ECO_2. When compared with PL (1-way AOV) V_T was significantly different with the 3 doses of MDZ, respiratory rate only with the 0.05 and 0.1 doses and F_ECO_2 not significantly different. Only the largest dose of MDZ produced a significant difference in O_2 saturation, which could be related to the longer mean duration of apneas seen in this group (table 1).

Discussion. This study confirms the ventilatory depressant effect of midazolam, even in non anxious healty subjects and demonstrates a poor dose-response relationship. The non-invasive method used may explain the difference in these results from other studies, where a more invasive technique to measure ventilation was used.

References.

1. Abraham WM, et al: Non invasive ventilatory monitoring by respiratory inductive plethysmography in conscious sheep. J Appl Physiol 51: 1657-1661, 1981

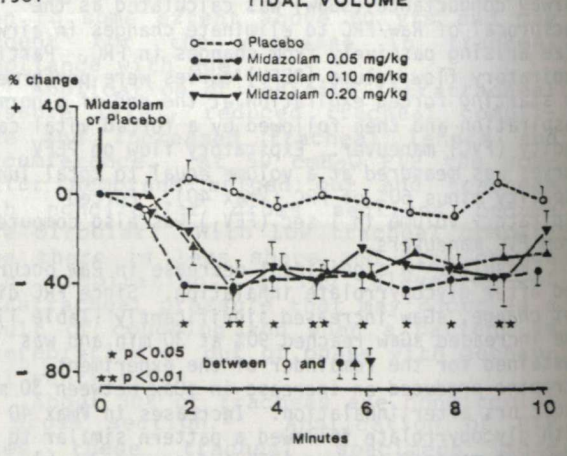

Fig. 1 Comparison of V_T changes during the first 10 minutes after an injection of placebo or 3 different doses of midazolam, illustrating the poor dose-effect relationship. (n = 8, $\bar{x}$ ± SEM, statistical significance indicated between treatment groups with an 1-way analysis of variance).

TABLE 1 COMPARISON OF INCIDENCE AND CUMULATIVE DURATION OF APNEAS AFTER THE FIRST 10 MINUTES OF AN INJECTION OF PLACEBO AND 3 DIFFERENT DOSES OF MIDAZOLAM (n=8)

APNEA (absence of breathing for >10sec)	PLACEBO	DOSES OF MIDAZOLAM		
		0.05 mg/kg	0.1 mg/kg	0.2 mg/kg
Number of subjects presenting an apnea	2 (25%)	5 (63%)	6 (75%)	6 (75%)
Total number of apneas	7	20	10	32
Cumulative duration of apneas (sec)	78	342	191	694
Mean ($\bar{x}$ ± SD) duration of apneas (sec)	11 ± 2	17 ± 6	19 ± 8	22 ± 9 *

* statistically different at $p < 0.05$ when compared to placebo

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