Title: EFFECTS OF MIDAZOLAM ON UPPER AIRWAY RESISTANCES

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Introduction. The genioglossus muscle draws the base of the tongue forward and therefore plays a major role in the maintenance of upper airway patency. Benzodiazepines reduce genioglossus activity in humans,[1] and this effect may result in increased upper airway resistances and an higher incidence of obstructive apnoea. However, no data are available so far regarding the effects of benzodiazepines on upper airway resistances and on the nature of the induced apnoeic events. The aims of the present study were to evaluate the effects of midazolam (M) on supraglottic airway resistances (SGAR) and to determine if the drug-induced apnoeas were caused by an obstructive or a central mechanism.

Material and methods. Seven healthy volunteers (mean age: 29±2 yrs) were studied twice in a randomized double blind protocol. The protocol was approved by the local Clinical Investigation Committee. The subjects did not take any caffeine, nicotine or food 8 hrs prior to the study. Throughout the study, the patient laid supine, head held in a constant neutral position, breathing through a thigh-fitting face mask attached to a n° 2 Fleish pneumotachograph which measured air-flow. Supraglottic pharyngeal pressures were recorded using a balloon-tipped catheter (17 mm long x 7 mm diam) placed 15-17 cm from the nares to the tip of the epiglottis.[2] Pleural pressures were measured with a balloon catheter system (50 mm long x 7 mm diam) positioned in the middle third of the esophagus. Both catheter systems were connected to one side of a differential pressure transducer. Supraglottic and pleural pressures were determined simultaneously at an air-flow of 0.3 l/s. SGAR were calculated as the ratio of supraglottic pressure (H_2O cm) on air-flow (0.3 l/s).[2] Total pulmonary resistances (TPR) were calculated as the ratio of pleural pressure (H_2O cm) on air flow (0.3 l/s). Apnoea was defined as an absence of respiratory flow for at least 10 s. The central nature of an apnoea was determined as the absence of pleural inspiratory pressure deflections, while peripheral obstruction was recognized when no respiratory flow was recorded despite inspiratory deflections in pleural pressure. After a 10 min adaptation period, a control measurements were performed and the subjects received an intravenous injection randomly determined, once with M (0.1 mg/kg) and once with placebo (P). Air-flow and pressures were continuously recorded throughout a 10 min study period. Resistances were calculated on 6 consecutive respiratory cycles 1 (T1), 3 (T3), 5 (T5), and 10 min (T10) following the injection. Statistical analysis were performed using analysis of variance.

Results. Data regarding SGAR and TPR are summarized in Table 1. M injection produced a dramatic increase in both SGAR and TPR from T_3 to T_{10} when compared with P. No apnoea was noted after P injection whereas after M injection, apnoeas were observed in 5/7 subjects. The nature and the number of apneic events over 3 periods of the study are depicted in Table 2.

Discussion. Our data demonstrate that M markedly increases inspiratory resistances of the total respiratory system, mainly because of the added inspiratory supraglottic resistances. This phenomenon, by producing an higher work of breathing, may be deleterious in patients with previously compromized ventilatory pump.[3] Under M, central apnoeas primarily occured at the initial period of the study and are probably related with the peak plasmatic level of the drug. By contrast, obstructive apnoeas occuring later indicate a much more prolonged depressive effect of M on pharyngeal than on inspiratory respiratory muscle activity.

Table 1

	TPR(H2O cm/l/sec)		SGAR (H2O cm/l/sec)	
	P	M	P	M
C	6.0±3	7.6±3.1	2.2±1.3	1.6±1.8
T_1	6.1±3.6	13.1±10*	2.2±1.6	3.4±2
T_3	7.7±3.6	21.3±10.2**	1.9±1.2	6.3±3**
T_5	8.6±5.9	24.1±13.1**	2.2±1	8.2±7.6**
T_{10}	8.2±6.1	20.8±7.9**	2.3±0.9	5.5±1.9**

* $p < 0.05$ vs P, ** $p < 0.01$ vs P

Table 2. Number of apnoeas in 7 subjects and time of occurence after M administration.

	0 - 3 min	3 - 5 min	5 - 10 min
Apnea			
central	6	2	1
obstructive	0	2	4

References

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2. Stauffer JL, et al. Am Rev Respir Dis 136:623-627, 1987
3. Roussos C, Macklem PT. N Engl J Med 307:786-797, 1982