

## EFFECTS OF I.V. MIDAZOLAM ON UPPER AIRWAY RESISTANCE

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### SUMMARY

We have measured changes in supraglottic airway resistance ( $R_{sg}$ ) produced by midazolam. Ten subjects were studied on two occasions, receiving in a random order either midazolam  $0.1 \text{ mg kg}^{-1}$  or placebo. Supraglottic pressures were measured using a balloon-tipped catheter and air flow with a pneumotachograph.  $R_{sg}$  were calculated at a flow rate of  $0.3 \text{ litre s}^{-1}$  during inspiration. No changes in  $R_{sg}$  and no apnoeic events were noted following placebo injection. Mean  $R_{sg}$  increased from  $0.23$  (SEM  $0.07$ )  $\text{kPa litre}^{-1} \text{ s}$  to  $1.29$  ( $0.38$ )  $\text{kPa litre}^{-1} \text{ s}$  5 min after injection of midazolam ( $P < 0.01$ ), and remained increased significantly for 20 min. Twenty-two apnoeic events were recorded in six subjects, including 11 obstructive events. We conclude that midazolam in sedative doses increases  $R_{sg}$  markedly and induces central apnoea during the first few minutes after i.v. administration and this is followed by obstructive apnoea.

### KEY WORDS

Airways: supraglottic resistance. Hypnotics, benzodiazepine: midazolam.

Pharyngeal muscles play a major role in the prevention and relief of upper airway obstruction. Any drug inducing impairment in the activity of these muscles may reduce airway patency and increase upper airway resistance. It has been demonstrated that benzodiazepines reduce the activity of the genioglossus muscle [1], a muscle which is mainly implicated in maintenance of airway patency [2]. Indeed, genioglossus contraction draws the body of the tongue forward, opposing its tendency to relapse into the oropharyngeal airway [2]. The tonic activity of this muscle and other pharyngeal muscles is important in counteracting a tendency to collapse generated by the thoracic respiratory muscles during inspiration. In addition, benzodiazepines induce or increase breathing disturbances (periods of hypopnoea and apnoea) during physiological sleep [3]. However, no data are available on changes in upper airway resistance or the nature (central or obstructive) of the apnoeic events after injection of benzodiazepines in sedative dosage. In order to clarify the effects of midazolam on upper airway patency, we have assessed the changes in resistance to airflow across the upper airway and the nature of the induced apnoeas after i.v. administration.

### SUBJECTS AND METHODS

We studied 10 male subjects of mean age 28 (range 26-31) yr, mean weight 68 (2.3) kg and mean height 175 (2.3) cm (mean body mass index:  $22.3$  ( $0.7$ )  $\text{kg m}^{-2}$ ). The subjects were not taking any medication and were devoid of a history of respiratory illness, sleep abnormalities or nasal complaints. All gave informed consent to the study, which was approved by the Local Clinical Investigation Committee.

On the day of the study, the subjects came to the laboratory in the morning, after a regular night of sleep. They did not take any caffeine, nicotine or food for 8 h before the study. Throughout the study, the subjects lay supine, the head maintained in a constant neutral position.

Supraglottic pressures were recorded using a balloon-tipped catheter (17 mm long  $\times$  7 mm diameter) filled with 0.1 ml of air, placed 17-18 cm from the nares and positioned visually, 2-3 cm below the base of the tongue, at the tip of the epiglottis [4] (fig. 1). This was confirmed in one volunteer using a fiberoptic bronchoscope. The balloon catheter system was connected to a pressure transducer (Validyne DP 15). It was linear up to 2 kPa when tested in an artificial system and the frequency response of the whole measurement system had no amplitude or phase shift at 2 Hz. In order to assess the nature of the apnoeic events, pleural pressures were measured using a second balloon (50 mm long  $\times$  7 mm diameter) filled with 0.5 ml of air, positioned in the middle one-third of the oesophagus and connected to one side of a differential pressure transducer (Validyne DP 15). In order to prevent gagging, insertion of the balloon catheters was facilitated by nasal anaesthesia with two sprays of 5% aqueous solution of lignocaine (each spray containing lignocaine 8-10 mg). To avoid any contribution of upper airway anaesthesia to the measurements of resistances, no recording was obtained until at least 30 min after application of topical anaesthesia. Only nasal breathing was allowed during the study and the mouth was kept closed by sealing the lips with tape. Airflow was measured with a tightly fitting face mask (positioned to avoid pressure on the nose) connected to a Fleisch No. 2 pneumotachograph. The mask was strapped in place over the face and the catheters were brought

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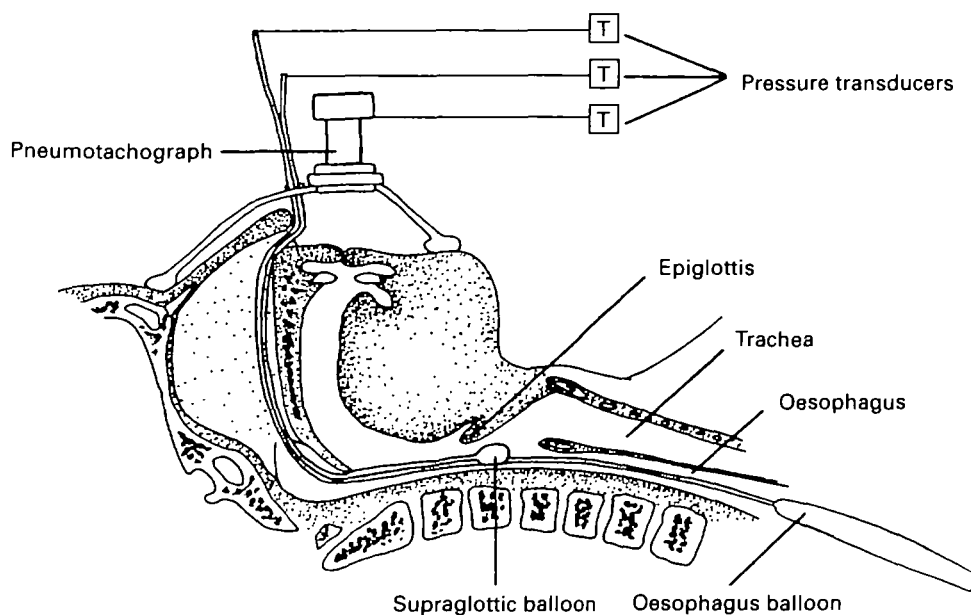


FIG. 1. Positions of the supraglottic balloon, oesophageal balloon and face mask. Each catheter was connected to a separate pressure transducer, and the face mask to a pneumotachograph.

out through an additional opening in the mask, which was sealed with putty, thus fixing the catheter position with respect to the nose and pharynx. After satisfactory placement, no further changes in catheter or mask position were permitted. The pneumotachograph was connected to a differential pressure transducer (Validyne DP 15). The flow signal was linear over the range of flows encountered during quiet breathing and was integrated to yield tidal volume ( $V_T$ ). All signals were recorded on a Gould ES 1000 polygraph. All subjects wore earphones and listened to light music; their eyes were covered with a mask to minimize external stimuli.

Supraglottic pressure was measured at an inspiratory flow rate of  $0.3 \text{ litre s}^{-1}$  during eight consecutive ventilatory cycles without swallowing or other extraneous movements. Supraglottic resistances ( $R_{sg}$ ) were calculated as the ratio of absolute supraglottic pressure change (kPa) to inspiratory airflow ( $0.3 \text{ litre s}^{-1}$ ) [4]. In our study, equipment related resistance was included in the supraglottic resistance measurement. However, the resistance of the system was low ( $0.03\text{--}0.04 \text{ kPa litre}^{-1} \text{ s}$ )—produced only by the pneumotachograph, as there was no valve or tubing.

Apnoea was defined as an absence of respiratory flow for at least 10 s. The central nature of an apnoea was identified as the absence of pleural inspiratory deflections, while an obstructive apnoea was recognized when no respiratory flow was recorded despite inspiratory pleural deflections. Mixed apnoea was defined as a central respiratory pause followed by obstructed ventilatory efforts. As the number of disordered breathing events in this study was small, mixed and obstructive events were pooled and termed obstructive apnoeas.

All subjects were studied twice with an interval of at least 7 days. After a 30-min rest period, a control set of measurements was performed ( $T_c$ ), then the

subjects received either midazolam  $0.1 \text{ mg kg}^{-1} \text{ i.v.}$  or placebo i.v. over a 30-s period in random order. Eight sets of measurements were performed at 1 ( $T_1$ ), 3 ( $T_3$ ), 5 ( $T_5$ ), 7 ( $T_7$ ), 10 ( $T_{10}$ ), 13 ( $T_{13}$ ), 15 ( $T_{15}$ ) and 20 ( $T_{20}$ ) min after injection. Tidal volume ( $V_T$ ), air flow ( $\dot{V}$ ), and supraglottic pressure changes were monitored continuously.

All values are mean (SEM). The data were subjected to analysis of variance. Statistical significance was inferred at  $P < 0.05$ .

## RESULTS

After administration of placebo, there were no changes in  $R_{sg}$ ,  $V_T$  and ventilatory frequency ( $f$ ) parameters (table I). After midazolam there was a significant increase ( $P < 0.05$ ) in  $R_{sg}$ , from  $0.23 (0.07) \text{ kPa litre}^{-1} \text{ s}$  at  $T_c$  to  $0.52 (0.13) \text{ kPa litre}^{-1} \text{ s}$  at  $T_1$  (table I). A subsequent increase in  $R_{sg}$  occurred at  $T_5$ :  $1.29 (0.38) \text{ kPa litre}^{-1} \text{ s}$ , after which  $R_{sg}$  reached a plateau and remained significantly increased ( $P < 0.01$ ) compared with  $T_c$ , until the end of the study. A typical tracing before and 10 min after midazolam is shown in figure 2. A significant decrease ( $P < 0.01$ ) in  $V_T$  occurred from  $T_1$  to  $T_{20}$ .  $f$  was reduced slightly at  $T_1$  because several apnoeas occurred in the first few minutes after administration of midazolam. This was followed by a subsequent, but non-significant, increase in  $f$ . No migration of the supraglottic balloon catheter was observed during the study.

After administration of midazolam, all the subjects fell asleep, responding to physical stimuli but not to speech. Twenty-two apnoeic events were recorded in six of 10 subjects. These six did not differ from the four who did not experience apnoeic events, in age ( $28 (0.6) \text{ yr vs } 28 (0.7) \text{ yr}$ ) or body mass index ( $21.3 (0.7) \text{ kg m}^{-2} \text{ vs } 23.8 (0.3) \text{ kg m}^{-2}$ ). The nature and the time of occurrence of the apnoeas are depicted in table II. The mean duration of the apnoeas was 17.1

TABLE I. Mean (SEM) values for supraglottic resistances ( $R_{sg}$ ), tidal volume ( $V_T$ ) and ventilatory frequency ( $f$ ) at control (Tc), 1 (T1), 3 (T3), 5 (T5), 7 (T7), 10 (T10), 13 (T13), 15 (T15) and 20 (T20) min after administration of midazolam (M) and placebo (P). \*P < 0.05; \*\*P < 0.01

	$R_{sg}$ (kPa litre <sup>-1</sup> s)		$V_T$ (ml)		$f$ (b.p.m.)	
	M	P	M	P	M	P
Tc	0.23 (0.07)	0.28 (0.06)	649 (54)	616 (46)	14.1 (0.7)	12.9 (0.6)
T1	0.52 (0.13)*	0.29 (0.07)	486 (60)**	629 (46)	11.9 (1.8)	13.2 (0.8)
T3	1.25 (0.35)**	0.31 (0.08)	394 (64)**	628 (41)	13.8 (1.1)	12.6 (0.6)
T5	1.29 (0.38)**	0.31 (0.07)	453 (52)**	636 (44)	13.9 (1.1)	12.6 (0.6)
T7	1.02 (0.27)**	0.3 (0.07)	437 (42)**	650 (43)	14.5 (0.7)	12.7 (0.8)
T10	1.23 (0.37)**	0.32 (0.06)	448 (45)**	621 (50)	14.9 (0.5)	13.2 (0.7)
T13	1.08 (0.41)**	0.23 (0.09)	384 (62)**	581 (24)	15.4 (0.9)	13.2 (1.1)
T15	1.06 (0.38)**	0.37 (0.17)	475 (47)**	579 (28)	14.4 (0.6)	12.4 (0.9)
T20	0.91 (0.38)**	0.28 (0.11)	455 (59)**	625 (37)	14.2 (0.5)	13.6 (1.1)

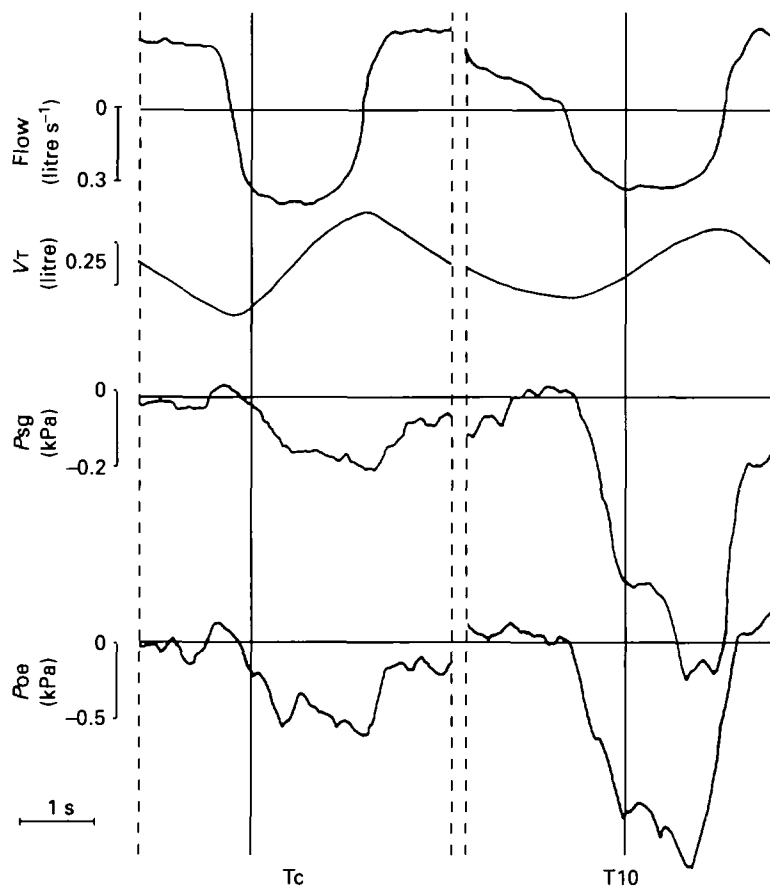


FIG. 2. Representative record of flow (downward deflection = inspiration), tidal volume ( $V_T$ ), supraglottic pressure ( $P_{sg}$ ) and oesophageal pressure ( $P_{oe}$ ) for baseline (Tc) and 10 min (T10) after administration of midazolam. Vertical lines are dropped from the point where inspiratory flow reaches 0.3 litre s<sup>-1</sup>, to show corresponding  $P_{sg}$ .

TABLE II. Number and nature of apnoeic events occurring at different periods after administration of midazolam

Period of the study	Central apnoea	Obstructive apnoea
Tc-T3	6	1
T3-T5	—	4
T5-T10	1	4
T10-T15	2	—
T15-T20	2	2

(3.2)s for central events and 17.9 (10.1)s during obstructive events. No apnoea was noted following administration of placebo.

DISCUSSION

The main observations of this study were that a sedative dose of midazolam produced a marked increase in upper airways resistance and that the midazolam-induced apnoeas were initially central

during the first few minutes after administration of drug and later obstructive.

A balloon-tipped catheter was chosen for measuring upper airway resistance rather than an open catheter, as the small detection area of an open system is frequently damped or occluded by saliva [4]. In our study,  $R_{sg}$  values at  $T_c$  were smaller than those reported by White and co-workers [4] using the same balloon catheter system inserted through the mouth. However, they studied older subjects. Using an open catheter inserted through the nose, Hudgel and colleagues [5] found a mean airway resistance of  $0.37 \text{ kPa litre}^{-1} \text{ s}$ .

In our study, resistances were measured during inspiration because airway collapse is known to occur in this phase of the ventilatory cycle in patients with obstructive sleep apnoea. All resistance measurements were made at an inspiratory flow rate of  $0.3 \text{ litre s}^{-1}$ , a rate which all subjects produced during spontaneous tidal breathing. This is also within the range of flow rates used previously in similar investigations [4, 6].

Local anaesthesia of the nares was used in order to reduce pain during insertion of the balloon catheter. However, it has been shown that nasopharyngeal anaesthesia may produce airway collapse and apnoea in rabbits [7]. Studies in humans demonstrated that pharyngeal anaesthesia caused an increase in upper airway obstruction during sleep [8, 9]. The implication is that airway patency is maintained partly in response to local "stretch receptors" and that topical anaesthesia may block these receptors to produce pharyngeal collapse. However, larger doses of local anaesthetics were used in these studies [8, 9] than in the present one. McNicholas and co-workers [8] produced oropharyngeal anaesthesia by spraying lignocaine 200 mg and requiring the subject to gargle with 10 ml of a 0.25% solution of bupivacaine for 1 min. During our study, only small quantities of lignocaine were likely to have reached the pharynx, and light pharyngeal anaesthesia, at least during wakefulness, has been shown to have no effect on pharyngeal patency in normal adults [4]. We decided not to begin measurements until 30 min after topical anaesthesia, as the duration of action of topical lignocaine is usually about 30 min [9, 10]. It is unlikely, therefore, that lignocaine anaesthesia accounted significantly for the increased  $R_{sg}$  and apnoea observed after midazolam.

Other factors may also have affected  $R_{sg}$ . The position of the head and neck is a critical determinant of pharyngeal patency, with neck flexion producing a considerable increase in resistance [11]. This effect was probably minimal in our study, as relative head and neck positions were maintained constant. Changes in partial pressure of carbon dioxide ( $P_{a_{CO_2}}$ ) after administration of midazolam also may have altered upper airway resistance. However, it has been demonstrated that an increase in  $P_{a_{CO_2}}$  produces a decrease rather than an increase in pharyngeal resistance [11]. Thus we believe that the observed increase in upper airway resistance after injection of midazolam was not artefactual, but resulted from diminished pharyngeal muscle tone [9, 12]. This accords with previous data demonstrating a decrease

in hypopharyngeal diameter in patients under general anaesthesia when the head remained in the neutral position [13].

The mechanism responsible for the increase in upper airway resistance after midazolam may be related to loss of consciousness, as observed during physiological sleep [5, 14], to a specific depressant effect on upper airway muscle activation, or both. In the present study, upper airway resistances were not measured during physiological sleep, and therefore it is not possible to evaluate the exact contribution of each mechanism. However, a shift from wakefulness to sleep in normal subjects is associated with a two- to three-fold increase in supraglottic resistance [5, 14] compared with a four- to six-fold increase observed in our study.

Several sedatives and central nervous system depressants induce or increase breathing disturbances (hypopnoea and apnoea) during sleep [3]. In our study, all subjects fell asleep after midazolam and 22 apnoeic events occurred in six of 10 subjects within 20 min. It is noteworthy that both central and obstructive apnoeas were recorded during this period. However, most of the central apnoeas occurred within a few minutes of administration of midazolam, and this is probably related to the peak plasma concentration of the agent. In contrast, most of obstructive and mixed apnoeas were observed later, when upper airway resistances were markedly increased. Indeed, this respiratory pattern is expected to favour upper airway closure [12]. As our study only documents the effects of a single dose of midazolam under highly artificial circumstances in volunteers, extrapolation to the clinical setting is questionable. However, these findings may be relevant with respect to the occurrence of respiratory depression after administration of midazolam for sedation during endoscopy [15].

#### REFERENCES

1. Leiter JC, Knuth SL, Krol RC, Bartlett DJR. The effects of diazepam on the genioglossal muscle activity in normal human subjects. *American Review of Respiratory Disease* 1985; 132: 216-219.
2. Van Lunteren E, Strohl KP. The muscles of the upper airways. *Clinics in Chest Medicine* 1986; 7: 171-188.
3. Dolly FR, Block AJ. Effect of flurazepam on sleep-disordered breathing and nocturnal oxygen desaturation in asymptomatic subjects. *American Journal of Medicine* 1982; 73: 239-243.
4. White DP, Lombard RM, Cadioux RJ, Zwillich CW. Pharyngeal resistance in normal humans: influence of gender, age and obesity. *Journal of Applied Physiology* 1985; 58: 365-371.
5. Hudgel DW, Martin RJ, Johnson B, Hill P. Mechanics of the respiratory system and breathing pattern during sleep in normal humans. *Journal of Applied Physiology* 1984; 56: 133-137.
6. Anch AM, Remmers JE, Bunce H. Supraglottic airway resistance in normal subjects and in patients with obstructive sleep apnea. *Journal of Applied Physiology* 1982; 53: 1158-1163.
7. Abu-Osba YK, Mathew OP, Thach BT. An animal model for respiratory sensory deprivation producing obstructive apnea with postmortem findings of sudden infant death syndrome. *Pediatrics* 1981; 68: 796-801.
8. McNicholas WT, Coffey M, McDonnell T, O'Regan R, Fitzgerald M. Upper airway obstruction during sleep in normal subjects after selective topical oropharyngeal anes-

- thetia. *American Review of Respiratory Disease* 1987; 135: 1316–1319.
9. Deweese EL, Sullivan TY. Effects of upper airway anesthesia on pharyngeal patency during sleep. *Journal of Applied Physiology* 1988; 64: 1346–1353.
  10. Gal TJ. Airway responses in normal subjects following topical anesthesia with ultrasonic aerosols of 4% lidocaine. *Anesthesia and Analgesia* 1980 59: 123–129.
  11. Spann RW, Hyatt RE. Factors affecting upper airway resistance in conscious man. *Journal of Applied Physiology* 1971; 31: 708–712.
  12. Remmers JE, De Groot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *Journal of Applied Physiology* 1978; 44: 931–938.
  13. Morikawa S, Safar P, De Carlo J. Influence of the head–jaw position upon upper airway patency. *Anesthesiology* 1961; 22: 265–270.
  14. Lopes JM, Tabachnick E, Muller NL, Bryan AC. Total airway resistance and respiratory muscle activity during sleep. *Journal of Applied Physiology* 1983; 54: 773–777.
  15. Editorial. Midazolam: is antagonism justified? *Lancet* 1988; 2: 140–142.