Flumazenil abolishes midazolam-induced increase in the work of nasal breathing

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Purpose: To evaluate the effects of midazolam sedation followed by flumazenil antagonism on the work of nasal breathing in normal humans.

Methods: We measured minute ventilation through the nasal route, respiratory frequency, nasal resistance (R_n) and the work of nasal breathing under three conditions: awake, during midazolam sedation, and after flumazenil antagonism in eight healthy human subjects. A custom-made, partitioned face mask enabled nasal and oral airflow to be measured separately. To calculate R_n and the work of nasal breathing, nasal mask and oropharyngeal pressure was also measured.

Results: Total resistive work spent on the upstream segment of the nasal route per minute (W_n) ($J \cdot \text{min}^{-1}$) was greater during midazolam sedation (3.6 ± 2.9) than while awake (1.6 ± 0.9) and after flumazenil antagonism (1.7 ± 0.6), respectively (mean $\pm$ SD) ($P < 0.05$). Total resistive work spent on the upstream segment of nasal breathing (W_n/V_{nE}) ($J \cdot L^{-1}$) increased from 0.31 ± 0.14 to 0.75 ± 0.61 after midazolam administration ($P < 0.05$) and decreased to 0.31 ± 0.10 after flumazenil. Following midazolam administration, a strong correlation was observed between changes in W_n/V_{nE} and changes in R_n ($r = 0.852$, $P < 0.0001$), whereas there was no correlation between changes in W_n and changes in R_n ($r = 0.159$, $P = 0.279$).

Conclusion: The work of breathing spent on the upstream segment of the nasal route increases during midazolam sedation and returns to baseline after flumazenil antagonism.

Objectif : Évaluer les effets sédatifs du midazolam dont l'administration est suivie de celle d'un antagoniste, le flumazénil, sur le travail ventilatoire nasal chez des humains normaux.

Méthode : Nous avons mesuré la ventilation-minute par voie nasale, la fréquence respiratoire, la résistance nasale (R_n) et le travail ventilatoire nasal sous trois conditions : à l'état d'éveil, pendant une sédation avec du midazolam et après l'action antagoniste du flumazénil, chez huit sujets en santé. L'utilisation d'un masque cloisonné, fabriqué sur mesure, a permis la mesure séparée de l'écoulement d'air nasal et oral. On a aussi mesuré la pression du masque nasal et de l'oropharynx pour calculer la R_n et le travail ventilatoire nasal.

Résultats : Le travail de résistance total effectué, par minute, sur le segment en amont de la voie nasale (W_n) ($J \cdot \text{min}^{-1}$) est plus important pendant la sédation au midazolam ($3,6 \pm 2,9$) qu'à l'état d'éveil ($1,6 \pm 0,9$) et qu'après le flumazénil ($1,7 \pm 0,6$), respectivement (moyenne $\pm$ écart type) ($P < 0,05$). Le travail de résistance total en amont de la respiration nasale (W_n/V_{nE}) ($J \cdot L^{-1}$) augmente de $0,31 \pm 0,14$ à $0,75 \pm 0,61$ après l'administration de midazolam ($P < 0,05$) et diminue à $0,31 \pm 0,10$ après celle du flumazénil. Avec le midazolam, une forte corrélation est observée entre les changements de W_n/V_{nE} et ceux de la R_n ($r = 0,852$, $P < 0,0001$), tandis qu'il n'y a pas de corrélation entre les changements de W_n et ceux de la R_n ($r = 0,159$, $P = 0,279$).

Conclusion : Le travail ventilatoire effectué sur le segment en amont de la voie nasale augmente pendant la sédation au midazolam et reprend les valeurs de base sous l'action antagoniste du flumazénil.

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THE velopharynx, that portion of the nasopharynx bounded by the soft palate, is the most common site of narrowing during sedation,¹ which increases upper airway resistance.²⁻³ However, a change from nasal to oral breathing occurs if the velopharynx is occluded.⁴ Therefore, the final result of sedation on the work of breathing spent on the nasal route is difficult to predict and has not been previously reported. Furthermore, no data are available regarding the effects of flumazenil on midazolam-induced increase in the work of breathing.⁵ The present study was performed to elucidate the effects of midazolam sedation followed by flumazenil antagonism on the work of breathing through the nasal route in normal humans.

Methods

The study protocol was approved by the Ethics Committee of Tokyo Medical and Dental University. Five male and three female healthy volunteers, aged 27.5 ± 3.9 yr (mean $\pm$ SD), participated in this study. The height and weight were 168.0 ± 7.0 cm and 60.2 ± 8.3 kg, respectively. As demonstrated by low BMI (21.3 ± 1.8 kg·m⁻², mean $\pm$ SD), none was obese. After obtaining written informed consent from each subject, we conducted a history and physical examination. Exclusion criteria were clinical evidence of nasal, pulmonary, cardiac, or CNS disease, obesity, use of centrally acting medications within the previous week, a history of smoking, sleep disordered breathing, recent upper respiratory infections, drug or alcohol abuse. Subjects refrained from oral intake for eight hours, and from alcohol and caffeine for 24 hr before the study.

Each subject had one nasal passage anesthetized with 0.05 ml lidocaine 8% spray. No nasal decongestants were used. Oropharyngeal pressure (Pop) was measured using a balloon catheter (Millar, o.d. 1.7 mm) introduced through the anesthetized nostril. The tip of the catheter was located just caudal to the inferior margin of the soft palate and rostral to the tongue in the oropharynx. The position was verified by direct visual examination of the posterior oropharynx. No migration of the oropharyngeal balloon catheter was observed throughout the study.

An airtight custom-made, partitioned face mask (Senkousha, Japan) was fitted while the subject rested in the supine position. A hard rubber septum separated the mask into nasal and oral chambers, each with its own port (i.d. 9 mm, length 40 mm) and a side-arm outlet (i.d. 3.5 mm). The rubber septum was positioned above the upper lip. Each mask chamber was tested separately for air leaks by pressurizing to 10 cmH₂O and ensuring that the pressure was constant

for 10 sec. The dead space for nasal and mouth chambers was 90 and 120 ml, respectively. Nasal airflow, nasal mask pressure (Pnm), and Pop were monitored with a C-P pulmonary monitor (model C-P 100, BICORE monitoring system, USA) connected to the breathing circuit. Oral airflow was measured using a Fleisch No. 2 pneumotachograph.

After inserting a 22-Gauge catheter in the left cephalic vein, we started an intravenous infusion of acetated Ringer's solution at 100 ml·hr⁻¹. Oxygen saturation, ECG, and noninvasive blood pressure measurements were recorded. After determining baseline respiratory measurements, we began midazolam administration: 0.01 mg·kg⁻¹ by rapid (< 1 sec) intravenous injection, administered every minute, until subjects reached a consciousness level where they exhibited spontaneous eye closure and responded only to prodding or shaking. This approach to assessing consciousness level has been previously described.^{3,6,7} We made respiratory measurements three minutes after the last dose of midazolam. We then gave 0.5 mg flumazenil *iv* over five minutes, and made respiratory measurements three minutes after flumazenil administration.

Nasal resistance (R_n) was calculated by dividing the transnasal pressure (Pnm-Pop) by inspiratory flow when Pop was least during inspiration. At this time, upper airway dimensions are minimal.⁸ Resistive work was measured for six consecutive breaths at each period studied. Total resistive work spent on the upstream segment of the nasal route per minute (W_n) was obtained by multiplying work per breath by the corresponding respiratory frequency. Total resistive work spent on the upstream segment per litre of ventilation through the nasal route (W_n/V_{nE}) was obtained by dividing W_n by minute ventilation through the nasal route. The latter was obtained by multiplying the V_T and respiratory frequency (f) measured on the same breaths used to compute the work of breathing. For statistical analysis, Scheffe's multiple comparison test after analysis of variance was used to determine if differences existed among the five parameters: V_{nE} , f , R_n , W_n , and W_n/V_{nE} under the three conditions. A significance level of 0.05 was used.

Results

In all the subjects sedated with midazolam, inspiratory airflow limitation was sometimes observed. After midazolam administration, four subjects continued breathing though the nasal route and the other four exhibited oronasal breathing. As shown in the Table, R_n was greater during midazolam sedation than while awake and after flumazenil antagonism ($P < 0.05$). Furthermore, W_n and W_n/V_{nE} were greater during

TABLE Changes in respiratory measurements during wakefulness, midazolam-induced sedation, and after antagonism with flumazenil. Mean $\pm$ SD values for minute ventilation through the nasal route (V_{nE}), nasal resistance (R_n), total resistive work spent on the upstream segment of the nasal route per minute (W_n), and total resistive work spent on the upstream segment per litre of ventilation through the nasal route (W_n/V_{nE}). Median for respiratory frequency (f). (A) Before midazolam administration. (B) After midazolam administration. (C) After flumazenil administration. * $P < 0.05$ compared with A, C. See text for details.

	V_{nE} ($L \cdot \min^{-1}$)	f ($\text{breaths} \cdot \min^{-1}$)	R_n ($\text{cmH}_2\text{O} \cdot L^{-1} \cdot s$)	W_n ($J \cdot \min^{-1}$)	W_n/V_{nE} ($J \cdot L^{-1}$)
A	5.3 $\pm$ 2.0	13	2.8 $\pm$ 4.0	1.6 $\pm$ 0.9	0.31 $\pm$ 0.14
B	5.0 $\pm$ 2.4	17	33.6 $\pm$ 47.9*	3.6 $\pm$ 2.9*	0.75 $\pm$ 0.61*
C	5.4 $\pm$ 1.2	15	2.7 $\pm$ 2.5	1.7 $\pm$ 0.6	0.31 $\pm$ 0.10

($n = 8$)

midazolam sedation than while awake and after flumazenil antagonism, respectively ($P < 0.05$). After midazolam administration, a strong correlation was observed between changes in W_n/V_{nE} and changes in R_n ($r = 0.852$, $P < 0.0001$). However, there was no correlation between changes in W_n and changes in R_n ($r = 0.159$, $P = 0.279$).

Discussion

The W_n and W_n/V_{nE} were greater during midazolam sedation than while awake and after flumazenil antagonism, respectively ($P < 0.05$). The present study is the first to demonstrate that the work of breathing spent on the upstream segment of the nasal route increases during midazolam sedation, and is reversed by flumazenil antagonism. The changes in R_n are consistent with our previous study.³ Since the tip of the oropharyngeal catheter was located just below the inferior margin of the soft palate, anatomical structures associated with R_n , W_n and W_n/V_{nE} included the nasal passage rostral to the inferior margin of the soft palate.

During midazolam sedation, inspiratory airflow limitation sometimes occurs.⁷ This leads to remarkably non-linear pressure-airflow relationships within the upper airway.⁹ Consequently, measurement of W_n and W_n/V_{nE} as well as R_n may be crucial to reveal the midazolam-induced upper airway behaviour.

A strong correlation between changes in W_n/V_{nE} and changes in R_n following midazolam administration is not surprising because these quantities depend upon the same variables for their derivation. However, there was no correlation between changes in W_n and changes in R_n . During midazolam sedation, four subjects exhibited oronasal breathing. The shift from nasal to oral breathing should allow nasal airflow to decrease. Following midazolam administration, a

decrease in nasal airflow could contribute to the lack of correlation between changes in W_n and changes in R_n while V_{nE} exhibited no change (Table).

Patients with obstructive sleep apnea have obstruction at various sites of the upper airway during sleep.^{10,11} Even normal subjects may have narrowing at different sites during sedation.¹² If the oropharynx and/or hypopharynx are narrowed during midazolam sedation, the resistive work spent on the downstream segment should increase, thereby resulting in a decrease in W_n and W_n/V_{nE} . Therefore, narrowing at different sites of the upper airway during midazolam sedation may contribute to the discrepancy between changes in W_n and changes in R_n . However, further studies are needed to demonstrate this hypothetical phenomenon.

In the previous studies conducted by Montravers *et al.*,^{2,5} the subject was allowed to breathe exclusively through the nasal route by sealing the lips with tape. In the present study, the subject was allowed to breathe without limitation of the breathing route. However, our partitioned face mask, which enables nasal and oral airflow to be measured separately, exerts a considerable pressure on the orofacial region.^{3,4,7} We cannot exclude the possibility that our results may be affected under these highly artificial circumstances. A limitation of the present study is the small number of subjects showing each type of response to midazolam sedation followed by flumazenil antagonism. Confirmation of these observations in a large number of subjects is necessary.

We conclude that the work of breathing spent on the upstream segment of the nasal route increases during midazolam sedation and returns to baseline after flumazenil antagonism.

References

- 1 Mathru M, Esch O, Lang J, *et al.* Magnetic resonance imaging of the upper airway. Effects of propofol anesthesia and nasal continuous positive airway pressure in humans. *Anesthesiology* 1996; 84: 273–9.
- 2 Montravers P, Dureuil B, Desmonts JM. Effects of i.v. midazolam on upper airway resistance. *Br J Anaesth* 1992; 68: 27–31.
- 3 Oshima T, Masaki Y, Toyooka H. Flumazenil antagonizes midazolam-induced airway narrowing during nasal breathing in humans. *Br J Anaesth* 1999; 82: 698–702.
- 4 Nishino T, Sugiyama A, Tanaka A, Ishikawa T. Effects of nasal anaesthesia on shift of breathing route in adults. *Lancet* 1992; 339: 1497–500.
- 5 Montravers P, Dureuil B, Molliex S, Demonts JM. Effects of intravenous midazolam on the work of breathing. *Anesth Analg* 1994; 79: 558–62.

- 6 Gross JB, Weller RS, Conard PF. Flumazenil antagonism of midazolam-induced ventilatory depression. *Anesthesiology* 1991; 75: 179–85.
- 7 Kawauchi Y, Oshima T, Suzuki S, Saitoh Y, Toyooka H. Advancement of the mandible facilitates nasal breathing in human subjects sedated with intravenous midazolam. *Can J Anesth* 2000; 47: 215–9.
- 8 Henke KG, Dempsey JA, Kowitz JM, Skatrud JB. Effects of sleep-induced increases in upper airway resistance on ventilation. *J Appl Physiol* 1990; 69: 617–24.
- 9 Hudgel DW, Hendricks C, Hamilton HB. Characteristics of the upper airway pressure-flow relationship during sleep. *J Appl Physiol* 1988; 64: 1930–5.
- 10 Morrison DL, Launois SH, Isono S, Feroah TR, Whitelaw WA, Remmers JE. Pharyngeal narrowing and closing pressures in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993; 148: 606–11.
- 11 Hudgel DW. Variable site of airway narrowing among obstructive sleep apnea patients. *J Appl Physiol* 1986; 61: 1403–9.
- 12 Hudgel DW, Hendricks C. Palate and hypopharynx-sites of inspiratory narrowing of the upper airway during sleep. *Am Rev Respir Dis* 1988; 138: 1542–7.