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The effect of oral midazolam and diazepam on respiration in normal subjects

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ABSTRACT: Benzodiazepine have been shown to suppress ventilatory responses to hyperoxic hypercapnia (HCVR) and isocapnic HVR when taken parenterally. Most patients would, however, prefer to take an oral rather than parenteral preperation but the effect of oral benzodiazepine on these ventilatory responses has not been well studied.

We therefore studied the effect of oral midazolam (7.5 mg) and diazepam (5 mg) both given orally on resting ventilation and respiratory drive, as assessed by HCVR and HVR. Flumazenil, a specific benzodiazepine antagonist, was administered intravenously to reverse the effect. A mental alertness-drowsiness index in five grades, from 1 (awake and alert) to 5 (asleep), was used to assess the sedation effect. Six normal male subjects, (aged 31±1.6 yrs) (mean±SD), participated in the study.

Mean resting ventilation, and ventilatory response to HCVR and HVR were not significantly altered by these drugs when taken orally. Flumazenil also had not significant effect on HCVR and HVR. However the mental alertness-drowsiness index rose from 1 to 2.83 with oral midazolam and reversed to 1.25 with flumazenil. Similarly, this index increased from 1 to 2.25 after oral diazepam and reversed to 1.42 after flumazenil.

In conclusion, we found that even though oral midazolam and diazepam produced a significant sedation effect, which was reversed with flumazenil, the drugs had no effect on ventilation at rest and the ventilatory responses to hypoxia and hypercapnia.

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Benzodiazepines are widely used for sedation, premedication, anxiety and insomnia. Through the years, benzodiazepines have shown themselves to be efficacious and safe. However, their action on respiration is of concern. Parenteral benzodiazepines have been shown to alter resting tidal breathing. Using non-invasive monitoring in 102 patients who underwent upper gastrointestinal endoscopy, BELL *et al.* [1] found that *i.v.* midazolam and diazepam both produced significant falls in minute ventilation ($\dot{V}E$) and oxygen saturation (Sao_2). In another study, on baseline respiratory variables in eight healthy subjects, BERGGREN *el al.* [2] showed that *i.v.* midazolam and diazepam both produced a fall in tidal volume (Vt) associated with a rise in partial pressure of carbon dioxide in arterial blood ($Paco_2$). $\dot{V}E$ was unchanged but the respiratory rate increased. FORSTER *et al* [3] also showed that *i.v.* midazolam depressed Vt, increased respiratory rate and had no effect on $\dot{V}E$. Furthermore, SUNZEL *et al* [4] found that *i.v.* midazolam and diazepam, in eight healthy volunteers, resulted in an increase in $Paco_2$ which was maximal at about 50–60 min. In addition, benzodiazepines have also been shown to affect respiratory drive. In a study by MORA *et al.* [5] 5 out of 10 otherwise healthy patients, who were given *i.v.* diazepam for sedation during minor surgery, had significant depression of the hypoxic ventilatory response (HVR) to isocapnic hypoxia. In another study [6], *i.v.* midazolam suppressed the HVR in eight healthy volunteers. FORSTER *et al* [7] used equipotent doses of parenteral midazolam and diazepam in eight healthy volunteers, and found that the ventilatory and mouth occlusion pressure responses to carbon dioxide were equally depressed by both drugs.

It is more common to use the oral rather than the parenteral route of administration for complaints such as insomnia. However, the effect on respiration *via* this route of administration is not well-documented. Therefore, we evaluated the effects of oral midazolam and diazepam on sedation, resting ventilation, HVR and ventilatory response to hyperoxic hypercapnia (HCVR). Intravenous flumazenil, a specific benzodiazepine antagonist, was administered for the reversal of these effects [8].

Diazepam is a commonly used benzodiazepine and is relatively lipid soluble and water insoluble. Midazolam, on the other hand, is water soluble. Both drugs are rapidly and completely absorbed after

oral administration, with similar distribution (midazolam 0.8–1.5 $l \cdot kg^{-1}$; diazepam 0.7–1.2 $l \cdot kg^{-1}$) and protein-binding (midazolam 94–97%; diazepam 97–99%) characteristics. Peak plasma levels after oral ingestion are achieved after similar time intervals for both drugs (midazolam 0.32–1.52 h; diazepam 0.5–1.0 h). However, midazolam is cleared more rapidly than diazepam, the drug clearance rates being 6.4–11.1 for midazolam and 0.24–0.53 $ml \cdot min^{-1} \cdot kg^{-1}$ for diazepam. Therefore, the elimination half-life is much shorter for midazolam (1.7–4.0 h) than diazepam (24–57 h) (table 1) [9–12].

Table 1. – Midazolam and diazepam, some pharmacokinetic variables

Property	Midazolam	Diazepam
Absorption	Rapid and complete	Rapid and complete
Time to reach peak blood level h	0.32–1.52	0.5–1.0
Distribution $l \cdot kg^{-1}$	0.8–1.5	0.7–1.2
Protein-bound %	94–97	97–99
Metabolite	α-hydroxymidazolam	desmethyldiazepam
(activity compared to drug)	(less active)	(as active)
Elimination half-life h	1.7–4.0	24–57
Clearance $ml \cdot min^{-1} \cdot kg^{-1}$	6.4–11.1	0.24–0.53

Materials and method

Subjects

The study was carried out on six healthy male subjects, with their informed consent, at the department's respiratory function laboratory. They were fasted 6 h before each run and abstained from beverages containing alcohol and caffeine. No subjects used benzodiazepines or any other drugs on a long-term basis, except for one who was on chlorpheniramine, 2 mg *o.n.*, for vasomotor rhinitis.

Ventilatory responses to isocapnic hypoxia and hyperoxic hypercapnia

HCVR was assessed using the method described by READ [13]. The circuit was filled with calibrated gas made up of 5% CO_2 and 95% O_2. End-tidal CO_2 concentration (ET_{CO_2}) was measured by an Engstrom Eliza Carbon Dioxide Analyser. This apparatus was calibrated with the following gas mixtures: 5% CO_2 and 95% O_2; 7% CO_2 and 93% O_2 and 9% CO_2 and 91% O_2. Sampled gas was returned to the rebreathing bag. The arterial O_2 saturation (Sa_{O_2}) and pulse were measured by an Ohmeda Biox™ III Pulse Oximeter using a finger probe. Tidal volume was measured with a bag-in-a-box connected to a Bell spirometer. Ventilation, Sa_{O_2} and ET_{CO_2} were recorded on a Gould 2800S 8-channel recorder. The test was terminated when the ET_{CO_2} was 10%, or when the patient was unable to continue the test and the ET_{CO_2} was at least 9%. HVR was assessed by the method described by REBUCK and CAMPBELL [14] using a 5% CO_2 in air gas mixture. The set-up was similar to that above, except that a CO_2 scrubber circuit was attached in parallel and adjusted to keep ET_{CO_2} between 5–6%. The run was terminated when the Sa_{O_2} was 75% or less.

Midazolam

At baseline, each subject performed both the HVR and HCVR. A dose of 7.5 mg midazolam was then administered orally. HVR and HCVR were restudied 30–50 min later, and again 5 min after the administration of *i.v.* flumazenil, 0.25 mg [15].

Diazepam

The protocol was identical to that described for midazolam except that 5 mg of oral diazepam was used.

The benzodiazepines were studied at least a week, but no more than two weeks, apart and the order of study was randomized.

Alertness-drowsiness index

A mental alertness-drowsiness index (table 2), similar to that used in previous studies [5, 6, 15–17], graded the degree of sedation of the subject at baseline, after the benzodiazepine and after flumazenil. Both the subject and the observer scored independently (except for grade 5). The averaged score was used.

Statistics

The best fit slope was plotted for ventilation, partial pressure of end-tidal carbon dioxide ($P_{ET_{CO_2}}$) and Sa_{O_2} in each subject. The ventilation at Sa_{O_2} of 90% ($\dot{V}_{O_2}90$) and $P_{ET_{CO_2}}$ of 60 mmHg ($\dot{V}_{CO_2}60$) were used to compare the positions of the lines.

Table 2. – Definition of mental alertness-drowsiness index

Score	Description
1	Awake and alert
2	Awake but drowsy
3	Drowsy
4	Asleep but arousable
5	Asleep and not arousable

Points were obtained by measuring the minute ventilation over 20 s intervals and the mean Sao_2 and $ETco_2$ over the same period. Only points between 95–75% and 50–71 mmHg were used for Sao_2 and $Petco_2$ respectively.

Two-way analysis of variance (ANOVA) was used to examine the differences between the slopes. An alternative method, using the t-test with a pooled variance for slopes, was also used for analysis. Data management and statistical analysis were assisted by the programmes FOXPRO and Statistical Package for the Social Sciences SPSS (ver. 3.1).

Results

The anthropometric and lung function data of the subjects are listed in table 3. Effects of midazolam and diazepam on resting ventilation are shown in tables 4 and 5, respectively. None of the changes were statistically significant.

Midazolam

The mean slope of the ventilatory response to hypoxia ($\Delta\dot{V}E/Sao_2$) was -0.354 (SEM±0.028) at baseline, -0.280(±0.035) after midazolam and -0.325(±0.083) $l \cdot min^{-1}/\%Sao_2$ after flumazenil. The mean slope of the ventilatory response to CO_2 ($\Delta\dot{V}E/\Delta Petco_2$) was 2.72(±0.40) at baseline, 2.17 (±0.22) after midazolam and 2.44 (±0.38) $l \cdot min^{-1} \cdot mmHg^{-1}$ after flumazenil. None of the changes was statistically significant (fig. 1). The changes in each subject were also not statistically significant, when the responses in each subject were analysed individually.

The mean $\dot{V}o_2 90$ was 10.07(±0.46) at baseline, 10.00 (±0.64) after midazolam and 8.69(±0.58) $l \cdot min^{-1}$ after flumazenil. The mean $\dot{V}co_2 60$ was 31.08(±5.46) at baseline, 32.76(±4.06) after midazolam and 36.28(± 5.76) $l \cdot min^{-1}$ after flumazenil. These changes were not statistically significant.

The mean mental alertness-drowsiness index rose from 1(±0) to 2.83(±0.31) after midazolam (p=0.002). Flumazenil reversed it to 1.25(±0.17) (p=0.005).

Table 3. – Anthropometric and lung function data of subjects

Subject no.	Age yrs	Height m	Weight kg	FEV_1 l	FVC l
1	38	1.80	64.0	4.26	5.14
2	33	1.70	67.5	3.47	4.69
3	28	1.72	76.0	3.83	4.30
4	29	1.71	59.0	3.30	3.63
5	28	1.70	58.0	3.06	3.29
6	32	1.73	54.0	3.83	4.04
Mean	31	1.73	63.1	3.63	4.18
SEM	1.6	0.02	3.2	0.18	0.28

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

Table 4. – Effect of midazolam on resting ventilation

Subject no.	Baseline $l \cdot min^{-1}$	Midazolam $l \cdot min^{-1}$
1	9.21	8.08
2	6.03	6.83
3	10.25	8.94
4	6.60	7.31
5	7.20	8.22
6	8.13	8.91
Mean	7.90	8.06
SE	0.66	0.35

Table 5. – Effect of diazepam on resting ventilation

Subject no.	Baseline $l \cdot min^{-1}$	Diazepam $l \cdot min^{-1}$
1	9.59	10.73
2	13.58	11.97
3	7.80	7.93
4	7.07	6.79
5	7.39	8.17
6	8.19	10.62
Mean	8.94	9.37
SE	1.00	0.82

Diazepam

$\Delta\dot{V}E/\Delta Sao_2$ was -0.397(±0.134) at baseline, -0.522 (± 0.155) after diazepam and -0.477(±0.155) $l \cdot min^{-1}/\%\ Sao_2$ after flumazenil. $\Delta\dot{V}E/\Delta Petco_2$ was 2.33(±0.46) at baseline, 2.26(±0.36) after diazepam and 2.39(±0.37) $l \cdot min^{-1} \cdot mmHg^{-1}$ after flumazenil. None of the changes was statistically significant (fig. 2). The changes in each subject were also not statistically significant, when the responses in each subject were analysed individually.

The mean $\dot{V}o_2 90$ was 10.35(±1.15) at baseline, 10.97 (±1.36) after diazepam and 9.11(±0.97) $l \cdot min^{-1}$ after flumazenil. The mean $\dot{V}co_2 60$ was 33.25(±8.85) at baseline, 31.85(±7.66) after diazepam and 38.17 (± 9.83) $l \cdot min^{-1}$ after flumazenil. These changes were not statistically significant.

The mental alertness-drowsiness index rose from 1 (±0) to 2.25(±0.17) after diazepam (p=0.001). Flumazenil reversed it to 1.42(±0.20) (p=0.004).

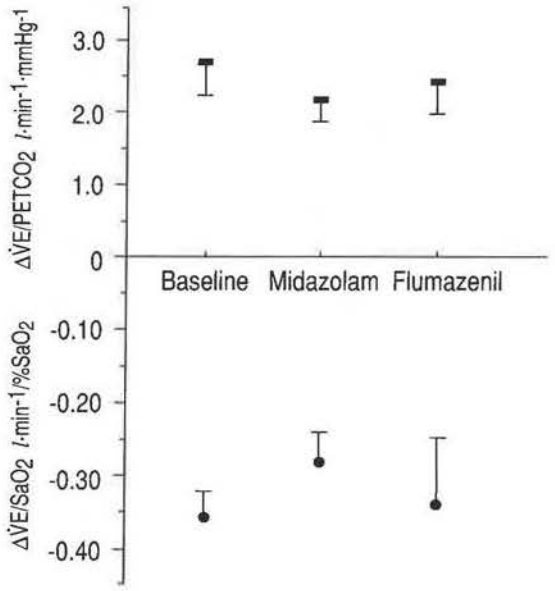

Fig. 1. – Ventilatory responses to hyperoxic hypercapnia (upper panel) and isocapnic hypoxia (lower panel) at baseline, after midazolam and after flumazenil. ■: mean ventilatory response to hyperoxic hypercapnia (±1 SEM); ●: mean ventilatory response to isocapnic hypoxia (±1 SEM); $\dot{V}E$: minute ventilation; P_{ETCO_2}: partial pressure of end-tidal carbon dioxide; Sa_{O_2}: arterial oxygen saturation.

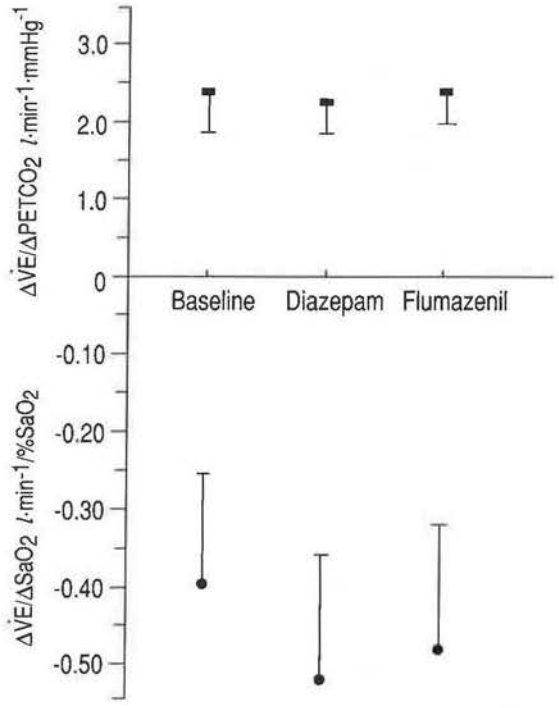

Fig. 2. – Ventilatory responses to hyperoxic hypercapnia (upper panel) and isocapnic hypoxia (lower panel) at baseline, after diazepam and after flumazenil. ■: mean ventilatory response to hyperoxic hypercapnia (±1 SEM); ●: mean ventilatory response to isocapnic hypoxia (±1 SEM). For abbreviations see legend to figure 1.

Discussion

We found that in normal subjects, oral midazolam (7.5 mg) and diazepam (5 mg) produced a significant sedative effect, which was reversed with flumazenil, but had no significant effect on ventilation at rest and the ventilatory responses to hypoxia and hypercapnia.

Since diazepam is a well-tested benzodiazepine, we decided to compare the pharmacological effects on respiration and sedation of midazolam against diazepam. FORSTER *et al.* [7] showed an equivalent depressant effect on respiration with intravenous doses of 0.15 $mg \cdot kg^{-1}$ midazolam and 0.3 $mg \cdot kg^{-1}$ diazepam. Also, DRIESSEN *et al.* [17] demonstrated an equivalent degree of sedation with either 15 mg of oral midazolam or 10 mg oral diazepam. We used 15 mg of midazolam in two subjects and found that it was technically impossible to perform tests of respiratory drive because the subjects fell asleep and kept coming off the mouth-piece. SMITH *et al.* [9] and PENTIKÄINEN *et al.* [18] also found that all of their patients became very drowsy or fell asleep after 10 and 15 mg of oral midazolam tablet, respectively. Therefore, we chose to use midazolam at 7.5 mg and diazepam at 5 mg.

In their study, SMITH *et al.* [9] showed that drowsiness appeared on average of 0.38 h (0.25–0.55 h) after oral midazolam. Their subjects became very drowsy or asleep from 0.5–0.74 h. The sleep period averaged 1.17 h (0.5–2.33 h). The peak plasma level was achieved between 0.32–1.52 h (mean 0.74 h). The time courses of plasma concentration of midazolam and the effect on reaction time and the number of errors in the tracing test were found to be identical. Peak plasma levels and maximal effects were both achieved within 30 min [17]. KOOPMANS *et al.* [19] studied the circadian effect of midazolam and found that in the evening, the time to reach highest drug concentration ranged from 0.55–0.81 h. This interval corresponded to the maximal effect on the α-rhythm on the electroencephalogram and the increase in the latency period of visual-evoked potential. Studies on diazepam [9, 10] showed that deterioration in the ability to perform simple arithmetical problems, coordination, blurring of vision and sleepiness occurred maximally between 30–60 min after an oral dose. These, too, correlated with the highest serum level. Based on the above results on the period of time to obtain maximal effects on the nervous system and peak blood levels, we therefore studied our subjects at 30–50 min after oral administration of these two benzodiazepines. Blood levels for midazolam were performed for two of our subjects. Midazolam was absent at baseline. After the administration of the drug and just before the subjects were restudied, the blood levels were 316 and 116 $ng \cdot ml^{-1}$, respectively. After the completion of the entire experiment, the levels fell to 200 and 83 $ng \cdot ml^{-1}$, respectively.

We found that, at the doses studied, oral midazolam and diazepam both induced sedation in our subjects, without suppressing their respiratory drive. Flumazenil

reversed the sedation. It may be argued that the failure of our study to detect a depressant effect on the HVR is due to intrasubject variability; the coefficient of variation (COV) of repeated studies being about 20–30%. Indeed, in our laboratory, the HVR was repeated three times within the same day in each of the six subjects, the COV was 26.8%. Therefore, it may be possible that a subtle depression of the HVR may not have been detected in our study.

Whilst HVR and HCVR are useful in studying potent respiratory depressant drugs, such as opiates, resting ventilation may be more useful as a parameter to evaluate the effects on respiration of a less potent drug, such as benzodiazepines [20]. For example, a drug may have no effect on the slopes of the HVR or HCVR, but may move the resting ventilation to a different point along the slopes. Resting ventilation did not change significantly after midazolam and diazepam in our subjects (tables 4 and 5). SOROKER *et al.* [21], FORSTER *et al.* [7] and BERGGREN *et al.* [2] also did not detect any change in resting ventilation after *i.m.* diazepam, *i.v.* midazolam, and when both benzodiazepines were administered *i.v.*, respectively. Although BEAUPRE [22] reported that 10 mg of oral diazepam suppressed respiratory drive in their subjects, (patients with pulmonary disease), data on sedation were not given.

There are conflicting results from studies on the relationship between respiratory depression and sedative effects [6, 24] of parenteral benzodiazepines. TOLKSDORF *et al.* [23] studied the effects on sedation (assessed by a scoring system and response to acoustic stimulation) and respiratory depression (assessed by Sao_2) of parenteral midazolam, fentanyl and vecuronim in 40 healthy patients who underwent arthroscopy. After the procedure, flumazenil was administered to randomly selected patients. They found that patients whose sedative effects were reversed by flumazenil had more frequent and longer hypoxic spells than those who were not given flumazenil. This suggests that flumazenil reversed only the effect on sedation and not the respiratory depressant effect. SUNZEL *et al.* [4] reported that there was no relationship between the plasma concentrations (Cp) of midazolam or diazepam with the respiratory variables: respiratory rate, tidal volume, mean inspiratory flow, respiratory timing and relative end-respiratory level, although the arterial partial pressure of CO_2 ($Paco_2$) and Cp for midazolam and diazepam were adequately described by the sigmoid model. But the Cp producing half the maximal effect (EC_{50}) was lower for the effect on $Paco_2$ than sedation for midazolam [4].

Benzodiazepines are believed to act on the central nervous system (CNS) *via* gamma-amino butyric acid (GABA) and benzodiazepine receptors [11, 25] and serotonergic pathways. The explanation for the dissociation of the effect of benzodiazepines on sedation and respiration may lie in the complex interrelationship of the neurotransmitter and its receptors in the CNS. There are different concentrations of GABA, being highest in the cerebral cortex compared to the medulla and benzodiazepine receptors in the CNS [11, 25, 26], and different types of GABA, A and B, receptors which may have stimulatory or inhibitory effects [27]. Furthermore, the dose, rate of rise of Cps and peak Cps, and hence the time available for protein binding, may also be important determinants of which areas of the brain and type of GABA receptors are more affected. The slower rate of rise in Cp and lower peak level following the oral route of administration (as compared to the parenteral route) may also explain why the oral dose induced sedation and not respiratory suppression in our subjects. This is consistent with the finding of SUNZEL *et al.* [4] of a lack of correlation between Cp and respiratory effects. In addition, benzodiazepine receptors have a unique form of regulation and changes in receptor density or affinity within minutes in response to physiological, pharmacological and behavioural alterations [26].

Conclusion

We found that oral midazolam (7.5 mg) and diazepam (5 mg) produced a sedative effect without significant respiratory depression or alteration to resting ventilation in normal subjects. This may be due, at least in part, to the complex interaction of the neurotransmitter and its receptors, which mediate the action of benzodiazepines, and to the oral route of administration.

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