Respiratory Depression by Midazolam and Diazepam

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The purpose of this study was to examine the respiratory depression produced by diazepam and by midazolam. Ventilatory and mouth occlusion pressure responses to CO₂ were measured in eight healthy volunteers before and after the intravenous administration of 0.3 mg/kg of diazepam and 0.15 mg/kg of midazolam. The mean ventilatory response to CO₂ (x±SEM) decreased after administration of diazepam or midazolam from 2.0 to 0.2 to 1.3 ± 0.1 l/min ·torr or from 2.1 ± 0.2 to 1.4 ± 0.1 l/min ·torr, respectively. In the same volunteers, the mouth occlusion pressure responses decreased from 0.54 ± 0.05 to 0.30 ± 0.04 cm H₂O/torr after midazolam and from 0.67 ± 0.12 to 0.28 ± 0.07 cm H₂O/torr after diazepam. When compared with the control slopes of the ventilatory and mouth occlusion pressure responses, the drug slopes were significantly different. Respiration was similarly depressed after diazepam and after midazolam. That both the ventilatory and mouth occlusion pressure responses to CO₂ are equally depressed by intravenous injections of midazolam and of diazepam at equivalent doses suggests a direct depression of the central respiratory drive by these drugs. (Key words: Carbon dioxide: ventilatory response. Hypnotics, benzodiazepines: diazepam; midazolam. Ventilation: anesthetics, effects of; carbon dioxide response.)

Benzodiazepine compounds are administered frequently by anesthesiologists for premedication, sedation, or induction of anesthesia when thiopental is contraindicated. It is generally accepted that parenteral doses of diazepam have a depressant effect on respiration1–3 which can be demonstrated by depression of the slope and/or a shift of the curve describing the relationship between end-tidal carbon dioxide (CO₂) and minute ventilation. The existence of this respiratory depression is generally admitted, although contrary observations have been reported.4,5

Midazolam, a water-soluble benzodiazepine with a short half-life,6 can be useful as an induction agent for anesthesia. The major advantages of midazolam over diazepam include a shorter duration of action6 and a better local tolerance when administered intravenously, i.e., less burning on injection7 and a lack of postoperative phlebitis.8 Midazolam has central nervous system depressant effects similar to those of diazepam, with about twice its potency.9 The purpose of this study was to evaluate the respiratory effect of midazolam and to compare it with the respiratory depression produced by diazepam.

Materials and Methods

The experiment was done in eight healthy volunteers, four males and four females. Their mean age was 30 years and mean weight, 61.5 kg. Informed consent was obtained, and the Committee for Ethics in Clinical Research of our institution approved this study.

The following variables were recorded continuously: electrocardiogram; blood pressure obtained through a radial arterial catheter; tidal volume and respiratory rate obtained by use of a Fleisch No. 2 pneumotachograph, and end-tidal carbon dioxide concentration, measured with a Godart infrared analyzer, from which end-tidal carbon dioxide tension (PetCO₂) was calculated. The gas sampled from the expiratory line was returned to the circuit.

The ventilatory response to carbon dioxide was measured with Read's rebreathing method.9 An electronic circuit interrupter inserted on the inspiratory line as shown in figure 1 permitted an airway occlusion of 0.1 second at the onset of inspiration. The mouth occlusion pressure (P₀.1) was determined through a differential pressure transducer (Hewlett-Packard, model 267 AC) at several PetCO₂ levels.10 The circuit produced a resistance of 2.0 cm H₂O/l/sec at a flow rate of 4 l/sec and had a dead space of 105 ml. The rebreathing test was performed using a bag containing a volume about equal to the subject's vital capacity plus 1 liter of a gas mixture of 7 per cent CO₂ in O₂.

Each subject was studied twice: once to examine the respiratory effects of midazolam and once to examine the respiratory effects of diazepam. The two sessions for a given subject took place at least ten days apart. The sequences of the two experiments were identical, and were as follows: after a 30-minute rest period in the supine position, the subject was connected to the mouthpiece of the circuit and a control ventilatory response to carbon dioxide was measured. During the rebreathing period the airway was occluded at end

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expiration for 0.1 s at several PETCO2 levels in order to obtain a mouth occlusion pressure response to CO2.

The subject was then allowed to rest for 20 minutes and was again connected to the mouthpiece of the circuit. The drug, either midazolam (0.15 mg/kg) or diazepam (0.3 mg/kg) was injected intravenously over a 15-second period through a short Venflon® catheter inserted on the dorsum of the hand. Four minutes after the injection of the drug, a new ventilatory and mouth occlusion pressure response to CO2 was determined.

The results of the determinations of respiratory responses to CO2 were expressed as the slope of the linear correlation between minute ventilation (V̇e, in l/min) or occlusion pressure (P₀, in cm H2O) against PETCO2 (torr) during rebreathing. The ventilatory responses were also expressed by PETCO2, computed for V̇e of 10, 20, 30, and 40 l/min (PETCO2 10, PETCO2 20, PETCO2 30, PETCO2 40) in order to detect a possible shift to the right of the hypercapnic ventilatory response curve due to midazolam or diazepam. The PETCO2 at 10, 20, 30, 40 l/min V̇e, determined by straight-line interpolation from the individual curves of the ventilatory responses to carbon dioxide, were averaged for the eight subjects. Student's t test for paired data was used for statistical comparison between the control slope and the slope after injection of the drug for the same subject, and between the mean control and post-drug values of PETCO2 at 10, 20, 30, and 40 l/min V̇e.

**Results**

Mouth occlusion pressure was not obtained for Subjects 1 and 2, for technical reasons. The individual values of control and post-drug slopes of the ventilatory responses (ΔV̇e/ΔPETCO2) and mouth occlusion pressure responses to CO2 (ΔP₀/ΔPETCO2) are listed in table 1. After the administration of midazolam, the ventilatory response to CO2 decreased from a mean of 2.1 ± 0.2 to 1.4 ± 0.1 l·min⁻¹·torr and mouth occlusion pressure, measured in six volunteers, was reduced also, from a mean of 0.54 ± 0.05 to 0.30 ± 0.04 cm H2O/torr. With one exception (Subject 4) the slopes of ΔV̇e/ΔPETCO2 decreased for all volunteers. Similar decreases of ΔV̇e/ΔPETCO2 and of ΔP₀/ΔPETCO2 were observed after the injection of diazepam; the mean slope for ventilatory response decreased from 2.0 ± 0.2 to 1.3 ± 0.1 l·min⁻¹·torr and the mean slope for mouth occlusion pressure decreased from 0.67 ± 0.12 to 0.28 ± 0.07 cm H2O/torr. The differences between the control slopes and the drug slopes for the ventilatory and the mouth occlusion responses are statistically significant. However, there was no statistically significant difference between the two slopes ob-

**Table 1. Individual Values of the Ventilatory and Mouth Occlusion Pressure Responses to CO2 (Mean ± SEM)**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>After Midazolam</th>
<th>Control</th>
<th>After Diazepam</th>
<th>Control</th>
<th>After Midazolam</th>
<th>Control</th>
<th>After Diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.39</td>
<td>1.28</td>
<td>2.25</td>
<td>1.72</td>
<td>—</td>
<td>—</td>
<td>0.52</td>
<td>0.06</td>
</tr>
<tr>
<td>2</td>
<td>3.23</td>
<td>1.50</td>
<td>1.67</td>
<td>1.52</td>
<td>—</td>
<td>—</td>
<td>0.25</td>
<td>0.84</td>
</tr>
<tr>
<td>3</td>
<td>2.63</td>
<td>1.90</td>
<td>2.60</td>
<td>1.70</td>
<td>0.75</td>
<td>0.25</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>4</td>
<td>1.80</td>
<td>1.94</td>
<td>1.87</td>
<td>1.64</td>
<td>0.54</td>
<td>0.40</td>
<td>0.40</td>
<td>0.27</td>
</tr>
<tr>
<td>5</td>
<td>1.92</td>
<td>1.30</td>
<td>2.95</td>
<td>0.74</td>
<td>0.36</td>
<td>0.18</td>
<td>0.59</td>
<td>0.18</td>
</tr>
<tr>
<td>6</td>
<td>1.13</td>
<td>1.04</td>
<td>1.13</td>
<td>0.75</td>
<td>0.56</td>
<td>0.29</td>
<td>0.29</td>
<td>0.21</td>
</tr>
<tr>
<td>7</td>
<td>1.53</td>
<td>0.98</td>
<td>1.49</td>
<td>0.96</td>
<td>0.59</td>
<td>0.42</td>
<td>1.12</td>
<td>0.59</td>
</tr>
<tr>
<td>8</td>
<td>1.86</td>
<td>1.20</td>
<td>1.67</td>
<td>1.27</td>
<td>0.44</td>
<td>0.23</td>
<td>0.96</td>
<td>0.18</td>
</tr>
</tbody>
</table>

(n)  (8) (8) (8) (8) (6) (6) (7) (7)

Mean 2.06 1.39 1.95 1.26 0.54 0.30 0.67 0.28

± SEM 0.23 0.13 0.21 0.14 0.05 0.04 0.12 0.07

P  <0.02 <0.02 <0.01 <0.01

**FIG. 1.** Diagram of the breathing circuit. V = pneumotachograph; ⊗ = inspiratory circuit interrupter. The gas sampled from the expiratory line was returned to the circuit.
Table 2. Control and Drug Values of \( \text{PET}_{\text{CO}} \) at 10, 20, 30, and 40 Liters per Minute Expired Volume (Mean ± SEM)

<table>
<thead>
<tr>
<th>Minute ventilation (l/min)</th>
<th>( \text{PET}_{\text{CO}} ) (torr)</th>
<th>Significance</th>
<th>( \text{PET}_{\text{CO}} ) (torr)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>After Midazolam Injection</td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>10</td>
<td>41 ± 1.3</td>
<td>39.5 ± 1.6</td>
<td>NS</td>
<td>39.8 ± 0.9</td>
</tr>
<tr>
<td>20</td>
<td>46.4 ± 1.1</td>
<td>47.1 ± 1.7</td>
<td>NS</td>
<td>45.4 ± 0.5</td>
</tr>
<tr>
<td>30</td>
<td>51.7 ± 1.3</td>
<td>54.7 ± 2.1</td>
<td>( P &lt; 0.05 )</td>
<td>50.1 ± 0.7</td>
</tr>
<tr>
<td>40</td>
<td>57.6 ± 2.1</td>
<td>62.3 ± 2.5</td>
<td>( P &lt; 0.02 )</td>
<td>56.5 ± 1.2</td>
</tr>
</tbody>
</table>

Tained after administration of the two drugs. Values of \( \text{PET}_{\text{CO}} \) 10, 20, 30, and 40 l/min \( V_e \) are shown in table 2. Since the differences between the control and drug values for \( \text{PET}_{\text{CO}} \) were significantly different only for \( V_e \)'s of 30 and 40 l/min, we conclude that no shift to the right in the hypercapnic ventilatory response curve occurred, only a decrease of its slope. During the 72 hours following the experiments, we noticed the development of clinical signs of phlebitis at the injection sites in all volunteers who received diazepam, whereas none of them experienced phlebitis after receiving midazolam.

**Discussion**

The results of the present study demonstrate that intravenous administrations of 0.15 mg/kg of midazolam and of 0.3 mg/kg of diazepam produce comparable and significant respiratory depression in healthy volunteers. The slopes of the ventilatory response curves to \( \text{CO}_2 \) after injection of these two benzodiazepine compounds were flatter than the control slopes, but they were not shifted to the right as is observed with respiratory depression induced by narcotics.

We estimated respiratory depression by use of two methods: determination of the ventilatory response to \( \text{CO}_2 \), which not only reflects the output of the respiratory centers but can also be affected by lung and chest-wall mechanics even when the chemoreceptors are functioning normally, and determination of the mouth occlusion pressure response to \( \text{CO}_2 \), which seems to be an adequate index of chemosensitivity and is not affected by the resistance and compliance of the respiratory system.

The decreases of both the ventilatory response and the mouth occlusion pressure response to \( \text{CO}_2 \) by midazolam and diazepam indicate that these two drugs directly depress the central respiratory drive. Benzodiazepines also have some muscular relaxation properties, and the possibility that the two drugs studied did produce some depression of respiratory muscle strength cannot be excluded. However, if midazolam or diazepam had produced only respiratory muscle depression without central respiratory inhibition, a decreased ventilatory response to \( \text{CO}_2 \) and a normal mouth occlusion pressure response to \( \text{CO}_2 \) similar to the changes observed after methoxyflurane would have been found where changes in lung elastance were responsible for decreased ventilatory responses to \( \text{CO}_2 \).

We conclude that midazolam and diazepam injected intravenously in equi-potent doses depress respiration significantly and similarly. The results of the present study indicate that these effects are due to a direct depression of the central respiratory drive; however, a simultaneous depression of respiratory muscle efficiency cannot be excluded. Although when compared with diazepam, midazolam does not produce less respiratory depression, it does offer advantageous clinical features such as a shorter duration of action and, especially, much better venous tolerance.

**References**


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