CARBON DIOXIDE RESPONSE CURVES FOLLOWING MIDAZOLAM AND DIAZEPAM

S. J. POWER, M. MORGAN AND M. K. CHAKRABARTI

SUMMARY

The ventilatory response to carbon dioxide was measured in volunteers before, and at intervals after the i.v. administration of midazolam 0.075 mg kg\(^{-1}\) and diazepam 0.15 mg kg\(^{-1}\). In the doses used neither drug caused any statistically significant respiratory depression and there were no differences between the drugs.

Diazepam i.v. has been used extensively to produce sedation during surgery performed under local anaesthesia, but is not the ideal agent because of its long duration of action (Greenblatt and Shader, 1974; Hillestad et al., 1974) and its propensity to cause thrombophlebitis (Graham, Pagano and Connor, 1978). This latter problem has been overcome by using diazepam in the form of an emulsion (Olesen and Hiittel, 1980), although the prolonged duration of activity remains. Midazolam maleate is a water soluble 1-4 benzodiazepine derivative which has central nervous system depressant effects similar to those of diazepam, but is approximately twice as potent (Dundee et al., 1980). As it has a shorter duration of action (Brown et al., 1979) and causes few venous sequelae, it would appear to be a suitable agent to produce sedation during local anaesthetic procedures.

It is desirable that any drug used in this context does not produce respiratory depression. The purpose of this study was to examine the effects of diazepam and midazolam i.v. on the ventilatory response to carbon dioxide. Throughout this paper diazepam refers to its formulation in an emulsion (Diazemuls).

SUBJECTS AND METHODS

Studies were carried out on seven healthy volunteers (four male) of average age 29.3 yr (SEM 0.61 yr) and weight 68.7 kg (SEM 3.22 kg). The subjects received both drugs with at least 1 week elapsing between measurements. They were taking no additional medication. They were familiarized with the test apparatus the day before the study. Each study started at 8.30 a.m. following a normal night's sleep and an overnight fast. An i.v. cannula was sited in the dorsum of the non-dominant hand. The subjects were lying on a trolley with two pillows supporting the head for 30 min before any measurements were made, and remained in this position throughout the study. A control response to carbon dioxide was performed. The subject breathed to atmosphere through a wide-bore tap with the lips firmly applied to a mouthpiece and with the nares occluded until regular respirations were achieved. Then at end-expiration the rebreathing procedure was begun by switching the tap. Ten minutes were allowed to elapse before midazolam 0.075 mg kg\(^{-1}\) or diazepam 0.15 mg kg\(^{-1}\), chosen randomly, was given i.v. over a period of 30 s. The subject was unaware of which drug had been administered. Measurements were repeated 3, 15 and 30 min, and 1, 2, 3 and 4 h after completion of the injection. The same procedure was repeated 1 week or more later with the other drug.

The ventilatory response to carbon dioxide was measured using the method described by Read (1967). Subjects rebreathed into a 6-litre bag filled to a volume of approximately their vital capacity plus 1 litre and containing 7% carbon dioxide in oxygen. Rebreathing continued until the end-tidal carbon dioxide concentration was 9%. Ventilation was recorded by enclosing the rebreathing bag in a large bottle in the base of which was a Fleisch head pneumotachograph. The output from the latter was processed, amplified and integrated with a Gould Godart system and a continuous record of tidal volume was obtained on one channel of a heated stylus recorder incorporated in the Gould Mark III capnograph. End-tidal carbon dioxide was measured using the same capnograph and displayed on

© The Macmillan Press Ltd 1983
the other channel of the recorder. The sampled gas was returned to the rebreathing bag. There was a fuel cell oxygen analyser in the circuit for safety purposes. The calibration of the capnograph and pneumotachograph was repeatedly checked each day before, during and at the end of the experiment with a preanalysed gas mixture and a calibrated syringe pump, respectively.

The carbon dioxide response curves were calculated from the chart recorder. The line of best fit was drawn along the expiratory edge of the carbon dioxide trace and the expired minute volume calculated for every 24-s interval, the first 30 s during equilibration being omitted. This produced 7 to 10 paired carbon dioxide–minute volume values. Using the method of least squares, a regression line was computed of ventilation and PCO₂ during rebreathing. The slope of this line expressed the sensitivity to carbon dioxide and the intercept on the x-axis, that is the PCO₂ when ventilation equals zero was calculated, expressing the threshold of the respiratory centre. The means, standard deviations and standard errors were calculated for each group at each time for the slopes and the intercepts. Two-way
analysis of variance was applied to compare the mean values at each time with the control values for each drug and for comparison between the drugs.

RESULTS

All the subjects became drowsy following the administration of the test drug, but none was unrousable and all were co-operative throughout the study.

The mean values of the slopes of the carbon dioxide response curves following both drugs are shown in Table I. Following diazepam the slope decreased from 18.9 litre min\(^{-1}\) kPa\(^{-1}\) in the control period to a minimum of 13.7 litre min\(^{-1}\) kPa\(^{-1}\) which occurred 15 min after the drug. The minimum value of the slope after midazolam occurred at 3 min and was 13.0 litre min\(^{-1}\) kPa\(^{-1}\). Thereafter, the slopes returned towards the control values.

Two-way analysis of variance showed that there

<table>
<thead>
<tr>
<th></th>
<th>Diazepam</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>18.9 (3.5)</td>
<td>21.0 (2.2)</td>
</tr>
<tr>
<td>3 min</td>
<td>15.7 (2.1)</td>
<td>13.0 (2.6)</td>
</tr>
<tr>
<td>15 min</td>
<td>13.7 (2.8)</td>
<td>16.8 (2.4)</td>
</tr>
<tr>
<td>30 min</td>
<td>16.2 (3.0)</td>
<td>18.3 (3.6)</td>
</tr>
<tr>
<td>1 h</td>
<td>17.6 (3.0)</td>
<td>17.2 (2.9)</td>
</tr>
<tr>
<td>2 h</td>
<td>19.0 (2.3)</td>
<td>19.8 (2.9)</td>
</tr>
<tr>
<td>3 h</td>
<td>17.0 (2.3)</td>
<td>20.8 (2.6)</td>
</tr>
<tr>
<td>4 h</td>
<td>20.0 (2.5)</td>
<td>20.0 (2.4)</td>
</tr>
</tbody>
</table>

Fig. 2. Mean changes from control (± SEM) in the intercepts of the ventilatory response curves to carbon dioxide expressed as test intercept minus control intercept kPa shown against time elapsed following diazepam and midazolam injection.
TABLE II. Mean intercepts (kPa) (SEM) of the ventilatory response curves to carbon dioxide following diazepam 0.15 mg kg\(^{-1}\) and midazolam 0.075 mg kg\(^{-1}\).  

<table>
<thead>
<tr>
<th></th>
<th>Diazepam</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.80 (0.30)</td>
<td>5.71 (0.26)</td>
</tr>
<tr>
<td>3 min</td>
<td>5.99 (0.24)</td>
<td>4.64 (0.75)</td>
</tr>
<tr>
<td>15 min</td>
<td>5.47 (0.30)</td>
<td>5.74 (0.40)</td>
</tr>
<tr>
<td>30 min</td>
<td>6.01 (0.33)</td>
<td>5.57 (0.59)</td>
</tr>
<tr>
<td>1 h</td>
<td>5.58 (0.48)</td>
<td>6.37 (0.33)</td>
</tr>
<tr>
<td>2 h</td>
<td>6.40 (0.24)</td>
<td>6.30 (0.36)</td>
</tr>
<tr>
<td>3 h</td>
<td>6.10 (0.19)</td>
<td>6.18 (0.24)</td>
</tr>
<tr>
<td>4 h</td>
<td>6.24 (0.29)</td>
<td>5.91 (0.35)</td>
</tr>
</tbody>
</table>

were no statistically significant differences from control after either diazepam or midazolam, nor were there any differences between the two drugs at any time ($f = 2.19$). In figure 1, the mean changes in slope from control are shown expressed as the ratio of the test and control slope.

The intercepts of the x-axis were also calculated and the results shown in table II. The mean change of the intercept from control is shown in figure 2 expressed as the test intercept−control intercept kPa.

Two-way analysis of variance showed no significant change in the intercepts at any time following midazolam or diazepam, nor was there any difference between the two drugs ($f = 2.08$).

**DISCUSSION**

Diazepam and midazolam produced a transient depression in the slope of the carbon dioxide response curves, but two-way analysis of variance showed that in neither case were the changes significant. However, when paired $t$ tests were applied there was no significant change following diazepam, but after midazolam there was some depression of the slope of the carbon dioxide response curves at 3 min and 15 min which approached clinical significance at the 3% and 4% levels respectively. There was no significant difference between the two drugs at any time. Forster and colleagues (1980), in a study on volunteers, reported respiratory depression (as judged by a decrease in the slope of the carbon dioxide response curve) following midazolam 0.15 mg kg\(^{-1}\) i.v., but no change in the intercept. A similar degree of respiratory depression was seen following diazepam 0.3 mg kg\(^{-1}\). However, the doses of the drugs used were twice that of the present study and measurements were made on only one occasion 4 min after either drug.

The respiratory depressant effects of diazepam have been investigated using this technique by other workers, but the results have been confusing, partially because of different dosage regimens, routes of administration and duration of the studies. Thus, Catchlove and Kafer (1971) observed a depression of the slopes of the carbon dioxide response curves in six of 13 volunteers given diazepam 0.14 mg kg\(^{-1}\) and five of the subjects had significant depression of $V_{E2}$, that is, the minute ventilation at a $PCO_2$ of 57 mm Hg, which is a measure of the threshold of the response. Three of their subjects had no depression of the carbon dioxide response curves. Jordan, Lehanne and Jones (1980) demonstrated significant respiratory depression following diazepam 15 mg i.v., but other workers have not shown such an effect (Brown and Dundee, 1968; Cohen, Finn and Steen, 1969).

These contradictory results following diazepam could be a reflection of the extremely high degree of protein binding of the drug, so that only small variations in plasma protein concentration would markedly affect the amount of free drug available. Also, in the present study, diazepam was used in the form of an emulsion as this results in improved venous tolerance. Comparatively few pharmacokinetic data are available about diazepam in this formulation, but animal studies (Jeppsson, 1976) and subsequent clinical work (Thorn-Alquist, 1977) indicated that plasma concentrations of the drug are similar to those following the use of the preparation Valium.

The results of this study indicate that, in the doses used, neither diazepam nor midazolam causes significant respiratory depression and thus in this context either would be a suitable sedative for surgery under regional anaesthesia.

**ACKNOWLEDGEMENTS**

We are grateful to Roche Pharmaceuticals for the supply of midazolam, to the members of the Anaesthetic Department who volunteered to take part in the study and to Shirley Richens for secretarial assistance.

**REFERENCES**


---

**CARVES DE RESPUESTA DEL DIOXIDO DE CARBONO A RAIZ DE LA ADMINISTRACION DE MIDAZOLAM Y DE DIAZEPAM**

**SUMARIO**

Se midió la respuesta respiratoria al dióxido de carbono en voluntarios, antes de la administración intravenosa de 0,075 mg kg⁻¹ de midazolam y de 0,15 mg kg⁻¹ de diazepam, y a intervalos después de dicha administración. Las dosis de las drogas utilizadas no ocasionaron depresión respiratoria de significación estadística y las dos drogas no presentaron diferencia alguna.

---

**CO2 RESPONSE CURVES**

COURBES DE REPONSE AU DIOXYDE DE CARBONE APRES MIDAZOLAM ET DIAZEPAM

**RESUME**

Nous avons mesuré la réponse ventilatoire au dioxyde de carbone chez des volontaires avant et à intervalles réguliers après l'administration intraveineuse de midazolam 0,075 mg kg⁻¹ et de diazepam 0,15 mg kg⁻¹. Aux posologies utilisées, aucun des agents n'a provoqué de dépression respiratoire significative et il n'est pas apparu de différences entre les deux produits.

---

**CO2-ANTWORT-KURVEN NACH MIDAZOLAM UND DIAZEPAM**

**ZUSAMMENFASSUNG**

Bei Probanden wurde die ventilatorische Antwort auf CO₂ vor und in bestimmten Zeitintervallen nach intravenöser Gabe von Midazolam 0,075 mg kg⁻¹ und Diazepam 0,15 mg kg⁻¹ gemessen. Keines der Präparate verursachte in den verabreichten Dosen statistisch signifikante Atemdepression, und es ergab sich kein Unterschied zwischen den beiden Präparaten.