DEPRESSION OF RESPIRATORY DRIVE BY DIAZEPAM AS PREMEDICATION

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SUMMARY

The respiratory effects of premedication with i.v. injection of diazepam have been assessed in 10 healthy patients awaiting minor operative procedures. Measurements were recorded before and 60 min after administration of diazepam 0.14 mg kg⁻¹. Mouth occlusion pressure (P₀.₁) was used as an index of neuromuscular inspiratory drive. Minute-ventilation (Vₑ), respiratory frequency (f) and mean inspiratory flow rate (VT/T₁) were significantly reduced after diazepam. During carbon dioxide rebreathing the slopes of Vₑ, f, VT/T₁ and P₀.₁ with PAO₂ were significantly reduced. These results confirm that i.v. diazepam produces significant respiratory depression in healthy subjects. We conclude that diazepam used under clinical conditions depresses the respiratory centre.

METHODS

Patients and methods

Ten ASA class I subjects, three women and seven men, awaiting minor elective surgical procedures, were studied. Their mean age (mean ± SD) was 33.5 ± 14.1 yr, mean weight 66.3 ± 11.2 kg. They had normal cardiovascular and respiratory systems and had received no medication on the days preceding the study. The procedure was explained and all the subjects consented freely to the study.

Patients were fitted with a rubber metabolic mouth-piece attached to a breathing system (fig. 1). Airway pressure was measured with a Statham (PM5) differential transducer. Inspiratory and
The expiratory lines were separated by a Rudolph valve. The deadspace of the mouth-piece and valve was 70 ml. The volume between the Rudolph valve and the occlusion valve system was 12.5 ml. The inspiratory line was fitted with an occlusion valve system (Delavault and Saumon, 1980), which permitted closure of the inspiratory line during the first 100 ms of inspiration, after automatic command during the respiratory cycle preceding the occlusion. The expiratory line was connected to a carbon dioxide infra-red analyser (Siemens Ultramat M-CO₂).

The inspiratory and expiratory lines were connected to a spirometer that recorded the spirogram at a speed of 40 mm s⁻¹. The cut-off frequency of the spirometer was 1.5 Hz. The spirometer was filled with a gas containing 5% carbon dioxide and 50% oxygen in nitrogen. A soda-lime cannister placed on the inspiratory line was removed at the beginning of each rebreathing test. The resistance of the inspiratory and expiratory lines, measured after removing the soda-lime cannister, was 0.4 kPa litre⁻¹ s⁻¹ at a flow rate of 5 litre s⁻¹. Calibrations of the carbon dioxide analyser with two different gases, and of the pressure transducer, were performed before each procedure.

Time of measurements

Control data were obtained after the subject had been resting in bed for at least 1 h. The rebreathing procedure (Read, 1967) lasted 4–6 min. PACO₂ at the end of rebreathing ranged from 7.3 to 9.4 kPa. After an initial equilibration period of about 40 s, a series of occlusions was performed at the rate of about one every 20 s. There were at least 10 occlusions in each rebreathing run. The rebreathing procedures were performed in the supine position. Each patient was submitted to two rebreathing tests. The first was regarded as practice, and only the second test was compared with the post-drug response. Diazepam 0.14 mg kg⁻¹ was administered i.v. over 5 min. Measurements were recorded 60 min later and the operation commenced.

Calculation and statistical analysis

Data are means ± SEM. Inspiratory, expiratory, and total breathing cycle durations (T₁, Tₑ, Tₑₑ) and tidal volume (Vₚ) were obtained from the spirogram. The other ventilatory indices were calculated from these values: mean inspiratory flow (Vₚ/T₁), respiratory duty ratio (T₁/Tₑₑ), respiratory frequency (f), and minute ventilation (Vₑ). The three breaths immediately preceding each occlusion were analysed and averaged. All values presented for resting ventilation were the mean of five occlusions, and of the corresponding preceding control breaths. The values of the different occlusion measurements were highly reproducible in all subjects.

The response to carbon dioxide of the different ventilatory indices and of the occlusion pressure was expressed as the slope of the linear regression equation (method of least squares) of the ventilatory indices and PACO₂ during rebreathing. The intercept of the carbon dioxide response line of Vₑ and P₀₁ with carbon dioxide axis were calculated. The ratio P₀₁/(Vₚ/T₁) called ‘effective’ respiratory impedance (Sorli et al., 1978), has been proposed as an index of the conversion of respiratory drive into inspiratory flow. These ratios were determined before and after diazepam.

The significance of differences between the pre-and post-drug values for each variable was established using the t test for paired samples.

RESULTS

Resting ventilation

Table I shows the values of the different ventilatory variables and of mouth occlusion pressure. Resting minute ventilation decreased significantly from 8.7 litre min⁻¹ before diazepam to 7.2 litre min⁻¹ after the drug. There was a lower respiratory frequency with no significant difference in the tidal volume. The mean

| Table 1. Mean ventilatory variables and mouth occlusion pressure during resting ventilation before and after diazepam administration. *P < 0.05; n.s. = not significant |
|---------------------------------|-----------------|-----------------|
|                                | Before diazepam (± SEM) | After diazepam (± SEM) |
| Vₑ (litre min⁻¹)               | 8.7 ± 0.6        | 7.2 ± 0.4       |
| P₀₁ (kPa)                      | 0.20 ± 0.02      | 0.16 ± 0.02     |
| f (b.p.m.)                     | 14.3 ± 0.8       | 12.6 ± 1.0      |
| Vₚ (ml)                        | 607 ± 27         | 598 ± 46        |
| T₁ (s)                         | 2.10 ± 0.15      | 2.55 ± 0.25     |
| Tₑₑ(s)                         | 2.22 ± 0.14      | 2.52 ± 0.24     |
| Vₚ/T₁ (ml s⁻¹)                 | 300 ± 21         | 242 ± 15        |
| T₁/Tₑₑ (s⁻¹)                   | 0.486 ± 0.011    | 0.502 ± 0.011   |
inspiratory flow was decreased and the inspiratory
time increased after diazepam, but these
differences were not significant.

**Rebreathing runs**

Table II shows the values of the slopes of the
different ventilatory variables and of mouth
occlusion pressure. The mean correlation
coefficient of the regression equations was +0.96
(range 0.85-0.99) for minute ventilation, and
+0.93 (range 0.89-0.98) for mouth occlusion
pressure.

| Table II. Mean slopes of the ventilatory variables and mouth occlusion pressure with \( PA_{CO_2} \), before and
after diazepam administration. \( *P<0.05 \), n.s. = not significant |
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<tr>
<td>Before diazepam</td>
<td>After diazepam</td>
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<tr>
<td>( \Delta V_e/\Delta PA_{CO_2} ) (litre min (^{-1}) kPa (^{-1}))</td>
<td>( 15.6\pm 1.2 )</td>
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<tr>
<td>( P_{0.1}/PA_{CO_2} )</td>
<td>( 0.82\pm 0.13 )</td>
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<tr>
<td>( f/PA_{CO_2} ) (b.p.m. kPa (^{-1}))</td>
<td>( 5.47\pm 0.97 )</td>
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<tr>
<td>( VT/PA_{CO_2} ) (ml kPa (^{-1}))</td>
<td>( 634.5\pm 107.2 ) n.s.</td>
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<tr>
<td>( T_{1}/PA_{CO_2} ) (s kPa (^{-1}))</td>
<td>( -0.51\pm 0.12 ) n.s.</td>
</tr>
<tr>
<td>( T_{1}/PA_{CO_2} ) (s kPa (^{-1}))</td>
<td>( -0.61\pm 0.14 ) n.s.</td>
</tr>
<tr>
<td>( (VT/T_{1})/PA_{CO_2} ) (ml s (^{-1}) kPa (^{-1}))</td>
<td>( 498\pm 31 ) *</td>
</tr>
<tr>
<td>( (T_{1}/T_{TOT})/PA_{CO_2} ) (kPa (^{-1}))</td>
<td>( 0.022\pm 0.013 ) n.s.</td>
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We observed a significant decrease in the slope
of minute ventilation after diazepam. This was
explained by a decrease in the slope of respiratory
frequency. The slope of mean inspiratory flow was
significantly decreased after diazepam. We did not
observe any difference in the slopes of inspiratory
and expiratory times, tidal volume and inspiratory
duty ratio. The slope \( P_{0.1}/PA_{CO_2} \) was decreased
significantly.

The intercepts of the carbon dioxide response
lines for \( \Delta V_e \) and \( P_{0.1} \) with the carbon dioxide axis were
\( 5.11\pm 0.24 \) kPa and \( 5.84\pm 0.16 \) kPa
respectively before diazepam, and \( 4.95\pm 0.28 \) kPa
and \( 5.65\pm 0.24 \) kPa after diazepam. These
differences were not significant.

The slope of “effective” respiratory impedance
\( (P_{0.1}/(VT/T_{1})) \) decreased from \( 1.40\pm 0.14 \) to
\( 1.15\pm 0.11 \) kPa m \(^{-1}\) after diazepam adminis-
tration \( (P<0.05) \).

**DISCUSSION**

These results are consistent with previous reports.
Dalen and others (1969) found a 28% decrease in
minute ventilation 10 min after diazepam
administration. Catchlove and Kafer (1971) also
found a decreased ventilatory response to carbon
dioxide after administration of diazepam. Steen
and others (1966), Utting and Pleuvry (1975) and
Gasser and Bellville (1976) did not observe a
significant change in the ventilatory response to
carbon dioxide but a significant displacement of
the slope to the right, reflecting a decrease in
minute ventilation for a given value of \( PA_{CO_2} \). In
the present study, the slope was significantly
decreased after diazepam, but without any shift to
the right.

Soroker and others (1978) could not
demonstrate ventilatory depression with
diazepam. However, they administered diazepam
i.m. and absorption via this route is irregular and
incomplete (Gamble, Mackay and Dundee, 1973;
Greenblatt, Shade and Koch-Weser, 1974). In
addition, patients studied by Soroker and others
(1978) had abnormally increased resting minute
ventilation with a mean value of \( 13.7 \) litre min \(^{-1}\).
Pearce (1974) found no change in blood-gases, but
no carbon dioxide stimulation test was performed
in this study.

Decreased occlusion pressure, at rest and during
carbon dioxide stimulation, indicates that the
decreased minute ventilation observed after
administration of diazepam is secondary to an
alteration of the inspiratory regulatory
mechanism. This depressant effect may be caused
by different factors such as modification of the
output of the respiratory centres, the conduction
of inspiratory nerves, or the contraction of
inspiratory muscles. A peripheral neuromuscular
effect can be excluded on the basis of the work of
Bradshaw and Maddison (1979) who showed that,
with doses similar to those used in our study,
Diazepam therefore appears to exert its respiratory depressant effect on the central control mechanism, as is suggested by occlusion pressure. However, there are two reservations in the interpretation of the results obtained with this method. The first concerns the shape of the pressure curve during airway occlusion. It is assumed that the shape of the pressure curve is not modified by diazepam. Derenne and others (1976) showed that, during stable anaesthesia with methoxyflurane, the shape of the pressure wave remained identical for different $P_{ACO_2}$ values. We have confirmed that the relationship of occlusion pressure at 100 ms to maximum pressure did not vary during stable halothane anaesthesia, before and after an i.v. injection of diazepam 10 mg. Moreover, interpretation of the occlusion pressure implies that there is no change in functional residual capacity (FRC). This was unaffected by diazepam (Cottrell, Wolfson and Siker, 1976), so that the respiratory depression induced by this drug can be stated to be related to an effect on the central regulatory mechanism.

In addition to a central effect, diazepam appears to affect respiratory mechanics since the decrease in occlusion pressure is more marked than the change of ventilation during carbon dioxide stimulation. We observed a mean decrease of 40% in $P_{O_2}/P_{ACO_2}$ and 18% in $V_E/P_{ACO_2}$. Diazepam increases airway resistance (Cottrell, Wolfson and Siker, 1976) and total dynamic compliance (Gyermek, 1975). The speed of shortening of inspiratory muscles is inversely proportional to the product of airway resistance by the total compliance (Derenne, Macklem and Roussos, 1978). Consequently, the speed of shortening of inspiratory muscle could be reduced by diazepam, and because of the force-speed properties of these muscles, the pressure developed may increase for a given neural drive. An argument in favour of this hypothesis is provided by the observation of the decrease in "effective" respiratory impedance, found in the present study. However, as for any extrapolation, this index should be interpreted with caution.

It is concluded that diazepam, used under clinical conditions, causes respiratory depression secondary to a depressant effect on the respiratory centres. Peripherally, diazepam may exert a facilitating effect, but further studies would be required to authenticate such an effect.

REFERENCES

DEPRESSION DU MECANISME RESPIRATOIRE PAR LE DIAZEPAM ADMINISTRE COMME MEDICATION PREOPERATOIRE

RESUME
Les effets respiratoires d’une médication préanesthésique avec injection intraveineuse de diazépam ont été évalués sur 10 patients en bonne santé attendant de subir des interventions chirurgicales mineures. Les mesures ont été enregistrées avant et 60 min après l’administration de 0,14 mg kg⁻¹ de diazépam. On s’est servi de la pression d’occlusion de la bouche (P₀,i) comme indice du mécanisme neuromusculaire inspiratoire. L’aération (Vₑ), la fréquence respiratoire (f) et le taux moyen du débit inspiratoire (Vᵢ/Tᵢ) ont été considérablement réduits après l’administration de diazépam. Pendant la re-respiration de gaz carbonique les courbes de Vₑ, f, Vᵢ/Tᵢ et de P₀,i avec Pₐ CO₂, ont été considérablement réduites. Ces résultats confirment que le diazépam administré par voie intraveineuse produit une dépression respiratoire significative sur les sujets en bonne santé. Nous en concluons que le diazépam utilisé dans des conditions cliniques déprime le centre respiratoire.

RESPIRATORISCHE UNTERDRUCKUNG DURCH DIAZEPAM-VORBEHANDLUNG

ZUSAMMENFASSUNG

DEPRESION DE LA ENERGIA MOTRIZ RESPIRATORIA MEDIANTE DIAZEPAN ADMINISTRADO COMO PREMEDICACION

SUMARIO
Se han evaluado los efectos respiratorios de la premedicación administrada con diazepan via inyección intravenosa en 10 pacientes sanos en espera de procedimientos operativos de menor importancia. Se registraron las mediciones antes de la administración de 0,14 mg kg⁻¹ de diazepan y a los 60 minutos de ésta se hizo uso de la presión bocal de occlusión (P₀,i) como índice de la energía motriz inspiratoria de carácter neuromuscular. Después del diazepan el régimen de flujo medio de inspiración (Vᵢ/Tᵢ), la ventilación instantánea (Vₑ) y la frecuencia respiratoria (f) quedaron significativamente reducidos. Al volver a respirar dióxido de carbono y durante dicha respiración, las pendientes de Vₑ, f, (Vᵢ/Tᵢ) y de P₀,i con Pₐ CO₂, quedaron significativamente reducidas. Estos resultados confirmaron que el diazepan intravenoso produce una depresión respiratoria significativa en sujetos sanos. Concluimos que el diazepan usado bajo condiciones clínicas deprime el centro nervioso.