EFFECTS OF A DIAZEPAM-FENTANYL MIXTURE ON CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION IN MAN

J. Vernhiet, A. M. Renou, J. M. Orgogozo, P. Constant and J. M. Caille

SUMMARY
The effects of a mixture of diazepam and fentanyl on cerebral blood flow (c.b.f.) and cerebral metabolism of oxygen (CMRo₂) were studied in eight normal subjects and 13 patients with organic brain disease. The coupling of flow and metabolism and the carbon dioxide responsiveness of the c.b.f. were studied also. In the normal subjects the injection of the mixture resulted in a significant decrease in c.b.f. (34%), and a similar decrease in CMRo₂ (34.5%). The vasoreactivity of the brain to carbon dioxide was maintained. C.b.f. decreased in all patients with intracranial pathology.

The use of combinations of drugs has been shown to be of advantage in anaesthesia (Laborit, 1951) and recent advances in pharmacology have led to the development of new combinations for clinical use, for example ataralgia (Hayward-Buh, 1957), neuroleptanalgesia (Mundeleer and De Castro, 1959) and more recently diazanalgesia (Henschel, 1973). In this technique a benzodiazepine (diazepam) is associated with a powerful narcotic (Fentanyl). The use of diazepam (Campan and Espagno, 1964) and diazepam plus fentanyl (Renou et al., 1975) in anaesthesia for neurosurgery has been studied previously. Cardiovascular stability and satisfactory operating conditions were reported. In addition, the advantages of decreasing pain in comatose patients by means of such combinations has been stressed recently (Lassen and Christensen, 1976).

The present study investigated the effects of the combination diazepam-fentanyl on cerebral blood flow (c.b.f.), oxygen consumption (CMRo₂) and cerebral vascular reactivity to carbon dioxide in man, in conditions similar to those in current clinical practice.

MATERIAL AND METHODS
Twenty-one patients were studied and initially each patient underwent carotid angiography for diagnostic purposes. Subsequent to clinical examination and radiological investigation eight patients were considered normal on account of their normal levels of consciousness, lack of permanent neurological symptoms, normal carotid angiograms, normal computerized tomograms (6 out of 8 patients) and normal c.b.f. values in the awake state. The remaining 13 patients form the disease group and their main features are presented in table I.

Cerebral blood flow was measured by the xenon-133 intra-arterial injection method using 16 scintillation detectors placed perpendicular to the surface of the skull (cylindrical collimators: 50 mm long; i.d. 19 mm) and connected to 16 pulse height analysers with individual sealers (C.G.R. Médecine Nucléaire). All the calculations were performed on-line by a MULTI 20 mini-computer (Intertechnique) with an instant print-out on an ASR 33 Teletype and a display of the clearance curves through a Tektronics 4010 Graphics terminal. Three methods of calculating the results were used in all patients: "stochastic" analysis, giving a mean c.b.f. value at 10 min (rcbf₁₀), compartmental analysis giving rcbf₉ (grey matter), rcbf₇ (white matter) and percentage of grey matter, and the initial slope index (rcbf₁) calculated on the first minute of the clearance curve (J. M. Orgogozo, J. M. Callié and D. Ducassou, in preparation). Mean hemispheric values were determined by automatic averaging of the 16 individual values.

For each c.b.f. determination 1.5–2.5 mCi of xenon-133 dissolved in 0.5 ml of saline was injected into the internal carotid artery via a Teflon catheter inserted into the common carotid artery. This cannula was perfused continuously with heparinized saline (13 ml h⁻¹) via an electrical infusion pump (Dascon, Holland). For the first c.b.f. measurement the patients remained awake and local anaesthetic (2% lignocaine) was infiltrated around the carotid artery. The patients breathed room air spontaneously. At the end of the first c.b.f. determination, the patients...
were premedicated with atropine 0.5 mg i.v. Anaesthesia was induced with diazepam 10 mg and a single dose of fentanyl 10 μg kg⁻¹. Pancuronium bromide 0.1 mg kg⁻¹ was administered and once the trachea had been intubated the lungs were ventilated mechanically (SF4 respirator) with 60% nitrous oxide in oxygen. A Teflon catheter was placed in the superior bulb of the internal jugular vein to permit sampling of cerebral venous blood. In order to obtain a steady state, the second c.b.f. was determined 20 min after the induction of anaesthesia.

Arterial and jugular venous $P_{O_2}$ and $P_{CO_2}$ and pH values were measured with a BMS 3 Mk 2 (Radiometer). Blood-gas and acid–base values were measured on several occasions during each c.b.f. determination to check the stability of $P_{ACO_2}$ and to monitor the changes in oxygen metabolism. The oxygen saturation was calculated from "$P_{O_2}$–oxygen saturation Nomogram" (Radiometer, Copenhagen) with corrections for temperature and pH. Oxygen content was calculated from the haemoglobin oxygen-carrying capacity and the amount of dissolved oxygen, as estimated from $P_{O_2}$ and oxygen solubility. CMRO₂ was calculated by the product of mean cbf₁₀ and the oxygen content difference between arterial and internal jugular venous blood ($C_{O_2a} - C_{O_2v}$).

The rectal temperature was measured with a calibrated thermistor probe. The comparison between the different determinations of c.b.f. was made following correction of the flow values to take account of the variations in $P_{ACO_2}$ (Olesen, Paulson and Lassen, 1971).

Differences between the two groups of flow values (before and after anaesthesia) were assessed using relevant statistical methods with a mini-computer (Digital Equipment Corporation, PD P8).

RESULTS

Normal subjects (table II)

Following the administration of diazepam and fentanyl the grey matter flow decreased by 56% (±13), the average decrease in cbf₁₀ was 34% (±9) and cbf₁₀ did not change significantly.

The mean decrease in CMRO₂ was 34.5% (±16.6). The relationship between cbf and $P_{ACO_2}$ is shown in figure 1. For awake subjects, the equation of the regression line was:

$$cbf = 25.6 P_{ACO_2} - 35$$

(Fisher test: $P<0.01$).

The exponential regression was:

$$cbf = 20 \exp (0.03 P_{ACO_2})$$

($P<0.01$).

![Figure 1](image-url)
### Table II. Effects of analgesia on cerebral metabolism and circulation in subjects with and without structural brain disease

<table>
<thead>
<tr>
<th></th>
<th>No structural brain disease (n=8)</th>
<th>Brain disease (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Awake</td>
<td>Analgesia</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>131</td>
<td>4</td>
</tr>
<tr>
<td>Arterial $P_{O_2}$ (kPa)</td>
<td>10.9</td>
<td>2.0</td>
</tr>
<tr>
<td>$P_{CO_2}$ (kPa)</td>
<td>4.8</td>
<td>0.8</td>
</tr>
<tr>
<td>pH</td>
<td>7.40</td>
<td>0.04</td>
</tr>
<tr>
<td>Jugular $P_{O_2}$ (kPa)</td>
<td>4.8</td>
<td>0.67</td>
</tr>
<tr>
<td>$P_{CO_2}$ (kPa)</td>
<td>5.6</td>
<td>0.9</td>
</tr>
<tr>
<td>pH</td>
<td>7.36</td>
<td>0.04</td>
</tr>
<tr>
<td>$(CaO_2-CvO_2)$ (vol. %)</td>
<td>6.5</td>
<td>2.2</td>
</tr>
<tr>
<td>CMRO$_2$ (ml 100 g min$^{-1}$)</td>
<td>2.85</td>
<td>0.8</td>
</tr>
<tr>
<td>cbf$_{10}$ (ml 100 g min$^{-1}$)</td>
<td>55</td>
<td>8</td>
</tr>
<tr>
<td>cbf$_w$ (ml 100 g min$^{-1}$)</td>
<td>101</td>
<td>12</td>
</tr>
</tbody>
</table>

n.s. = Not significant.

Under analgesia, the equation of the regression line was:

\[ \text{cbf}_g = 17.3 \text{ Pa}_{CO_2} - 40.4 \]

(Fisher test: \( P<0.05 \)).

The exponential regression was:

\[ \text{cbf}_g = 4.5 \exp (0.45 \text{ Pa}_{CO_2}) \]

\( P<0.05 \).

The relationship between cbf$_{10}$ and PVO$_2$ is shown in figure 2.

The variation in the individual values of cbf$_{10}$ in the disease group is shown in figure 3. In these patients, despite their varied neurological states, diazepam-fentanyl anaesthesia caused marked decreases in c.b.f.

![Fig. 2. Relationship between cbf$_{10}$ and PVO$_2$ in subjects without intracranial disease. (i.e. \( y = 5.26x + 2.3, r = 0.91, P<0.01 \))](image)

![Fig. 3. Change in cbf$_{10}$ (correlated with Pa$_{CO_2}$) in the disease group on transition from the waking state (●) to anaesthesia (○) is shown by the arrows. Analgesia caused a decrease of mean cbf$_{10}$ in all patients.](image)

### DISCUSSION

Previous studies of the effects of drugs on cerebral blood flow showed that, in dogs, the combination droperidol-fentanyl caused a decrease in c.b.f. (Kreuscher, 1965), but, later Barker and others (1968) found no significant changes using the same combination. Furthermore, the decrease in cerebral flow was correlated with the decrease in CMRO$_2$ in
animals (Miller and Barker, 1969; Michenfelder and Theye, 1971), whereas the variations in c.b.f. and CMRO₂ in normal man were not significant (Sari, Okuda and Takeshita, 1972). In cats fentanyl alone caused an increase in c.b.f. associated with an increase in CMRO₂ (Nilsson and Ingvar, 1966; Freeman and Ingvar, 1967). In dogs, however, fentanyl caused a decrease in c.b.f. and CMRO₂ (Michenfelder and Theye, 1971). A similar decrease had been observed following the administration of morphine in normocapnic dogs (Takeshita, Michenfelder and Theye, 1972). More recently, it was demonstrated that the anaesthetic combination nitrous oxide–morphine in normal normocapnic man did not affect significantly either c.b.f. or autoregulation (Jobes et al., 1975). In dogs diazepam alone has been shown to decrease c.b.f. and cause a parallel decrease in CMRO₂ (Maekawa, Sakabe and Takeshita, 1974), the decrease in the flow appearing as early as the second minute after administration (Sari et al., 1975). In comatose patients with diffuse cerebral lesions, the decreases in flow following the administration of diazepam were associated with similar decreases in metabolism (Cotev and Shalit, 1975).

Although 70% nitrous oxide has a modest action on c.b.f. and CMRO₂ (Smith and Wollman, 1972) it seems that there is a synergistic effect when nitrous oxide is used with another anaesthetic agent, for example an increase in c.b.f. in association with halothane (McDowall and Harper, 1965; Sakabe et al., 1976), and a decrease of c.b.f. in association with diazepam (Carlsson et al., 1976).

In this study we noted that the technique of analgesia decreased both c.b.f. and CMRO₂. The decrease in c.b.f. affected the grey compartment only—the slow component of the flow did not vary. In the group of normal patients, the changes in cbf₁₀ and CMRO₂ were similar (—34% and —34.5%) and thus resemble the effects of the barbiturates (Pierce, Lambertsen and Deutch, 1964) and Althesin (Sari et al., 1976). The relationship between cbf₁₀ and PvO₂ is linear and of the same order as that obtained under Althesin (Sari et al., 1976). Constancy of jugular venous oxygen tension is a good index of coupling between flow and metabolism. The cerebrovascular responsiveness of our normal subjects to carbon dioxide was in good agreement with Reivich (1964), and we found that only the fast flow component was sensitive to changes in PCO₂.

A comparative analysis between the individual values from Olesen, Paulson and Lassen (1971) and ours did not show any significant difference between their equation (fig. 1) giving

\[ \text{cbf}_1 \text{ exp} [0.031 (5.32 \text{ PaCO}_2)] \]

and the one derived from grey flow values in our patients (\( \text{cbf}_g = 20 \exp (0.03 \text{ PaCO}_2) \)). The comparative analysis of the \( \text{cbf}_2 - \text{PaCO}_2 \) relationships in normal subjects with and without diazepam–fentanyl did not show any statistically significant difference in the slopes of the calculated exponentials. This finding indicated a similar \( \text{cbf}_g \) reactivity per kPa to changes in \( \text{PaCO}_2 \). Thus cerebral reactivity to \( \text{PaCO}_2 \) does not seem to be altered by diazanalgesia. This validates our use of Olesen's formula for \( \text{PaCO}_2 \) correction in both the awake and the anaesthetized states.

Mean hemispheric flow, calculated as an average of the individual values, is valid if flow is homogeneous, but not if focal differences exist, because the weighting of each individual value is not known. However, despite the use of mean hemispheric flow in the subject with disease, it is interesting to note the flow values obtained under analgesia. Similar decreases in c.b.f. were observed in all patients despite the variability in the pathology. If one compares our group with those patients with head injuries studied under diazepam alone (Cotev and Shalit, 1975), the decrease in cbf₁₀ in our study was greater (32% against 24%). It is likely that the difference is caused by the addition of fentanyl, but the influence of nitrous oxide cannot be excluded.

In conclusion, in patients without intracranial disease the administration of a mixture containing diazepam and fentanyl results in similar decreases of both c.b.f. and CMRO₂. C.b.f. decreased also in all patients in the disease group.

ACKNOWLEDGEMENTS

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REFERENCES


DIAZEPAM–FENTANYL AND C.B.F.


EFFETS DE L’ASSOCIATION DIAZEPAM–FENTANYL SUR LE DEBIT SANGUIN CEREBRAL ET LA CONSOMMATION D’OXYGENE CHEZ L’HOMME

RESUME
Nous avons étudié les effets de l’association diazepam–fentanyl sur le débit sanguin cérébral (c.b.f.) et le métabolisme oxydatif du cerveau (CMRO2) chez huit sujets normaux et 13 patients porteurs de lésions cérébrales diverses. Nous avons étudié aussi le couplage débit–métabolisme, ainsi que la réactivité vasculaire cérébrale au gaz carbonique. Chez les sujets normaux l’injection du mélange entraîne une diminution significative et parallèle du c.b.f. (34%) et de la CMRO2 (34.5%). La vasoactivité cérébrale au gaz carbonique était conservée. Chez tous les sujets porteurs de lésions il existe aussi une diminution de c.b.f.

WIRKUNGEN EINER DIAZEPAM–FENTANYLMISCHUNG AUF DEN ZEREBRALEN BLUTFLUSS UND DEN SAUERSTOFFVERBRAUCH BEIM MENSCHEN

ZUSAMMENFASSUNG
Die Wirkungen eines Gemisches aus Diazepam und Fentanyl auf den zerebralen Blutfuss (c.b.f.) und auf den zerebralen Sauerstoffmetabolismus (CMRO2) wurden bei acht gesunden und bei 13 Patienten mit organischen Gehirnerkrankungen untersucht. Der Zusammenhang zwischen Blutfuss und Metabolismus sowie die Kohlendioxydreaktion des c.b.f. wurden ebenfalls studiert Bei den normalen Patienten führte die Injektion des Gemisches zu einem wesentlichen Sinken des c.b.f. (34%) und auch des CMRO2 (34.5%). Die Vasoreaktivität des Gehirns auf Kohlendioxyd blieb erhalten. Der c.b.f. sank bei allen Patienten mit interkranialen Krankheitserscheinungen.

LOS EFEKTOS QUE EJERCE UNA MEZCLA DE DIAZEPAM–FENTANYL SOBRE LA CIRCULACION DE SANGRE CEREBRAL Y EL CONSUMO DE OXIGENO EN EL HOMBRE

SUMARIO
Se estudiaron los efectos que ejerce una mezcla de diazepam y fentanil sobre la circulación de la sangre cerebral (c.b.f.) y el metabolismo cerebral de oxígeno (CMRO2) en ocho pacientes normales y 13 pacientes con una enfermedad cerebral orgánica. Además se estudió la combinación de circulación y metabolismo y la reacción del c.b.f. al dióxido de carbono. En los sujetos normales una inyección de la mezcla causó una significativa disminución en el c.b.f. (34%) y una disminución semejante de CMRO2 (34.5%). La vasoreactividad del cerebro ante el dióxido de carbono fue mantenida. La c.b.f. disminuyó en todos los pacientes con patología intracranial.