CEREBRAL BLOOD FLOW AND METABOLISM DURING ETOMIDATE ANAESTHESIA IN MAN

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SUMMARY

The effects of etomidate on regional cerebral blood flow (rc.b.f.) and cerebral metabolic rate for oxygen (CMRo₂) were studied in seven patients undergoing diagnostic carotid angiography. Following determination of baseline rc.b.f. while awake, the patients were anaesthetized with a single dose of etomidate 15 mg. Thereafter, an infusion of etomidate (2 or 3 mg min⁻¹) was administered. Etomidate decreased both rc.b.f. (mean decrease 34%) and CMRo₂ (mean decrease 45%). It was concluded that etomidate is a potent cerebral metabolic depressant. Furthermore, the cerebrovascular reactivity to carbon dioxide was maintained under etomidate anaesthesia.

Etomidate, a carboxylated imidazole derivative, is an i.v. hypnotic introduced in 1971 (Janssen et al., 1971). Since early studies in man (Doenicke et al., 1973), considerable information has accumulated concerning the haemodynamic (Brugmans and Jageneau, 1974; Du Cailar et al., 1976), respiratory (Rifat, Gamulin and Gemperle, 1976; Morgan, Lumley and Whitwam, 1977) and electroencephalographic aspects (Paty et al., 1977) and the clinical characteristics (Holderroff et al., 1976; Kay, 1976) of the drug. In a previous paper (Macrez et al., 1976) the effects of etomidate on patients undergoing anaesthesia for neuroradiological investigations have been assessed. However, to our knowledge, there have been no reports on the effects of etomidate on cerebral blood flow and intracranial pressure. The aim of this paper was to evaluate the changes occurring in cerebral blood flow and metabolism during etomidate anaesthesia in man.

METHODS

The study was undertaken in seven patients (three males and four females), undergoing diagnostic carotid angiography for the assessment of focal cortical epilepsy or headache. The patients were examined either during the interictal phase or at a considerable time after the prodromal and headache phases. Their ages ranged from 24 to 43 yr (mean 34 yr). Each patient was fully alert, with no neurological deficit or impairment of conscious level. In each patient the cerebral angiogram and computerized axial tomogram were normal.


The first measurement of cerebral blood flow (c.b.f.) was carried out in the awake patient to determine the baseline flow. Each patient acted as his own control. Following the infiltration of local anaesthesia (lignocaine 1.0%, 3–5 ml) the internal carotid artery was punctured using the Seldinger technique. C.b.f. was measured always at least 20 min after angiography to avoid the effects of the contrast media on flow. During this study the patients were breathing room air spontaneously.

A second c.b.f. measurement was performed following the administration of etomidate at least 20 min after the initial study. Fifteen minutes before the induction of anaesthesia each patient received atropine 0.5 mg i.v., and a single i.v. dose of etomidate 15 mg administered over 1 min initially, followed immediately by an i.v. infusion of etomide 60 mg dissolved in 250 ml of saline given at a constant rate of 2 or 3 mg min⁻¹. When neuromuscular block had been obtained (pancuronium 6 or 8 mg) the trachea was intubated and ventilation was controlled with a non-rebreathing system (SF4 ventilator) which delivered 30% oxygen in room air. The end-tidal carbon dioxide tension was measured by an infra-red carbon dioxide analyser (Beckman). Blood-gas analysis was performed repeatedly during each measurement, using suitably calibrated electrodes (Radiometer BMS 3MK₂, Copenhagen). Venous blood was collected at the superior bulb of an internal jugular vein using a Teflon catheter (20-g Longdwell) and arterial blood samples were taken from the internal carotid artery. The oxygen saturation was calculated using “Po₂–O₂ Saturation Nomogram for whole blood” (Radiometer, Copenhagen) and oxygen content was derived from the sum of the haemoglobin
oxygen-carrying capacity and the amount of dissolved oxygen. CMRo₂ was calculated as the product of mean c.b.f.₁₀ and the corresponding arteriovenous oxygen content difference. PaO₂, mean arterial pressure and body temperature were maintained constant in each patient. However, PaCO₂ varied among the different patients and in this way the vasoreactivity to carbon dioxide could be assessed.

Regional cerebral blood flow (rc.b.f.) was measured using the xenon-133 intra-carotid injection technique (Lassen and Ingvar, 1963) using a 16-channel detector system (Orgogozo, Caille and Ducassou, 1977). Regional c.b.f. was calculated as follows: (a) two compartmental analysis, which estimates the fast flow, representing mainly grey matter flow (c.b.f.₉), and the slow flow, representing mainly white matter flow (c.b.f.ₜ) and (b) stochastic analysis, calculated from the height area equation (c.b.f.₁₀).

The data were analysed using Student's t test for paired data using a PDF 8 computer; P<0.05 was considered statistically significant.

RESULTS

During the administration of etomidate c.b.f.₉ and c.b.f.₁₀ decreased significantly (by 36% and 34.3% respectively) from the baseline values obtained in the awake state (fig. 1, table I). There was no significant change in c.b.f.ₜ. In addition, it was observed that the decreases in c.b.f. were identical from region to region. All flow values were corrected to a standard Pco₂ of 5.32 kPa employing a correction of 4% flow changes for each 0.133 kPa of Pco₂ (Olesen, Paulson and Lassen, 1971).

TABLE I. Effects (mean ± SD) of etomidate on mean arterial pressure, cerebral blood flow and cerebral metabolic rate for oxygen. Values for arterial and cerebral venous blood-gas tensions are included also

<table>
<thead>
<tr>
<th></th>
<th>Awake control</th>
<th>Etomidate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>130.00 ± 15</td>
<td>134.00 ± 19.00</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>C.b.f.₉ (ml min⁻¹ per 100 g)</td>
<td>94.50 ± 15</td>
<td>65.00 ± 15.10</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>C.b.f.ₜ (ml min⁻¹ per 100 g)</td>
<td>19.40 ± 4.86</td>
<td>20.70 ± 5.40</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>C.b.f.₁₀ (ml min⁻¹ per 100 g)</td>
<td>56.80 ± 10.4</td>
<td>37.30 ± 8.50</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Carotid artery</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PaO₂ (kPa)</td>
<td>9.60 ± 1.25</td>
<td>12.99 ± 3.59</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>PaCO₂ (kPa)</td>
<td>4.76 ± 0.61</td>
<td>5.21 ± 0.52</td>
<td>&gt;0.4</td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.40 ± 0.02</td>
<td>7.38 ± 0.04</td>
<td>&gt;0.2</td>
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<tr>
<td>Internal jugular vein</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PVO₂ (kPa)</td>
<td>5.05 ± 0.69</td>
<td>5.91 ± 0.84</td>
<td>&gt;0.07</td>
</tr>
<tr>
<td>PVCO₂ (kPa)</td>
<td>5.94 ± 0.89</td>
<td>6.11 ± 0.98</td>
<td>&gt;0.8</td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.35 ± 0.02</td>
<td>7.34 ± 0.05</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>(Cao₂ - Cvo₂) (vol %)</td>
<td>5.47 ± 2.27</td>
<td>4.54 ± 1.55</td>
<td>&gt;0.07</td>
</tr>
<tr>
<td>CMRO₂ (ml min⁻¹ per 100 g)</td>
<td>3.11 ± 0.70</td>
<td>1.70 ± 0.70</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

* Significantly different from control.
Following the administration of etomidate, CMRO\textsubscript{2} decreased significantly also (mean decrease 45\%) (fig. 2). Although CMRO\textsubscript{2} changed in the same direction as the c.b.f. in six patients the depression in CMRO\textsubscript{2} was greater than the decrease in c.b.f. in four patients (fig. 3). The linear ($r = 0.87$) relationship between c.b.f.\textsubscript{10} and jugular venous $P_\text{O}_2$ during etomidate anaesthesia is presented in figure 4. There was also a linear relationship ($r = 0.77$) between c.b.f.\textsubscript{g} and $P_{\text{aCO}_2}$ during etomidate anaesthesia (fig. 5).

**DISCUSSION**

The results of the present study have shown that there is a global and homogeneous decrease in c.b.f. during the administration of etomidate. Similar decreases have been reported following the administration of most i.v. anaesthetic drugs, for example thiopentone (Pierce et al., 1962), Innovar (Michenfelder and Theye, 1971), diazepam (Cotev and Shalit, 1975) and Althesin (Renou et al., 1976; Sari et al., 1976). On the other hand, ketamine (Simard, 1975) and most inhalation anaesthetic agents such as cyclopropane (Alexander et al., 1968) and halothane (Smith and Wollman, 1972) increase c.b.f. The most interesting finding of the present study was the relationship between the decrease of c.b.f. and the decrease of CMRO\textsubscript{2}. Etomidate is a potent cerebral metabolic depressant, similar in this respect to most i.v. anaesthetic drugs. The mechanism whereby etomidate decreases c.b.f. probably relates to the reduction in the cerebral metabolic rate of oxygen. This metabolic depression could induce a decrease in carbon dioxide production and a subsequent decrease in the tissue carbon dioxide tension. As a result there would be a direct vasoconstricting action on the cerebral vessels and a decrease in c.b.f.

In addition, we have studied jugular venous oxygen because it relates directly to the coupling between flow and metabolism. The linear correlation obtained during etomidate anaesthesia showed that jugular
$P_{O_2}$ remains a good index of c.b.f. in the normal subject.

In awake patients, apprehension with subjective signs of anxiety had mild effects on ventilation. This may explain why mean $P_{A CO_2}$ was low (9.58 kPa). The lowest arterial $P_{O_2}$ recorded during the study was 8.58 kPa. Lamberts (1961), Reivich (1964) and many authors have found that arterial oxygen tensions greater than 6.65 kPa had no effect on cerebral blood flow. During the administration of etomidate our patients were breathing room air with added oxygen to avoid the effects of nitrous oxide on c.b.f. We know that non-depolarizing neuromuscular blocking agents produce no change in c.b.f. or metabolism in normal man at the doses studied.

On the other hand, individual $P_{A CO_2}$ values varied from 4.66 to 6.52 kPa. When the individual values of c.b.f. were plotted against the corresponding values of $P_{A CO_2}$ the regression line suggested that the carbon dioxide responsiveness of the cerebral vessels to carbon dioxide was maintained. Unfortunately we have not studied the effects of etomidate on intracranial pressure and therefore must await studies on this aspect before using etomidate as an induction agent in neurosurgery or in neuroradiology, particularly if intracranial hypertension is suspected.

REFERENCES


DEBIT Sanguin et métabolisme CéRBrAl pendant une anesthésie a l’etomidate chez l’homme

RESUME

On a étudié, sur sept malades subissant une angiographie de la carotide, si l’etomidate a un effet sur le débit sanguin et le métabolisme cérébral. Les résultats ont été comparés à ceux obtenus avec d’autres anesthésiques (fentanyl, droperidol et Innovar). Les malades analysés ont été sous anesthésie d’etomidate de
15 mg. On leur a administré par la suite une infusion d'étomidate (2 ou 3 mg min⁻¹). L'étomidate a fait baisser le r.c.b.f., (diminution moyenne 34%) et le CMRO₂ (diminution moyenne 45%). Il en a été conclu que l'étomidate est un modérateur puissant du métabolisme cérébral. La réactivité cérébrovasculaire à l'acide carbonique a en outre été maintenue sous l'anesthésie à l'étomidate.

ZEREBRALER BLUTKREISLAUF UND STOFFWECHSEL IM MENSCHEN WÄHREND EINER ETOMIDATNARKOSE

ZUSAMMENFASSUNG
Die Wirkungen von Etomidat auf den ortlich begrenzten zerebralen Blutkreislauf (r.c.b.f.) und der zerebrale Sauerstoffmetabolismus (CMRO₂) wurden in sieben Patienten, die sich einer diagnostischen Angiographie der Halseschlagader unterzogen, untersucht. Nach der Feststellung der Grundwerte des r.c.b.f.'s im Wachzustand wurden die Patienten mit einer einmaligen Dosis von 15 mg Etomidat anästhesiert. Danach wurde eine Infusion von 2 oder 3 mg/min Etomidat verabreicht. Etomidat verringerte den r.c.b.f. 10 (Durchschnittsverringerung 34%) und CMRO₂ (Durchschnittsverringerung 45%). Daraus wurde geschlossen, dass Etomidat ein starkes zerebral-metabolisches Hemmungsmittel ist. Ausserdem war die zerebrovaskuläre Reaktion auf Karbondioxid unter der Etomidatnarkose beibehalten worden.

CIRCULACION SANGUÍNEA CEREBRAL Y METABOLISMO DURANTE ANESTESIA DE ETOMIDATA EN EL HOMBRE

SUMARIO
Se estudiaron los efectos que ejerce la etomidata sobre la circulación sanguínea cerebral regional (r.c.b.f.) y la rapidez metabólica cerebral del oxígeno (CMRO₂) en siete pacientes sometidos a angiografía carotidea diagnóstica. Tras determinarse la r.c.b.f. básica estando despiertos, los pacientes fueron anestesiados con una sola dosis de etomida 15 mg. En adelante se administró una infusión de etomida (2 o 3 mg/min). La etomida disminuyó tanto la r.c.b.f. (disminución media 34%) como el CMRO₂ (disminución media 45%). Se concluyó que la etomida es un potente sedante metabólico cerebral. Además se mantuvo la reactividad cerebrovascular al dioxido de carbono bajo anestesia de etomida.