EFFECTS OF ALTHESIN ON CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION IN MAN

A. SARI, T. MAEKAWA, M. TOHJO, Y. OKUDA AND H. TAKESHITA

SUMMARY
Cerebral circulation and metabolism during Althesin anaesthesia were studied in seven healthy patients. Althesin was given in a single dose of 0.1 ml/kg and thereafter infused at a constant rate of 0.3 ml/kg/h. During Althesin infusion, the cerebral blood flow (CBF), the cerebral metabolic rate for oxygen (CMRo$_2$) were 29 ± 10 ml/100 g/min and 1.7 ± 0.4 ml/100 g/min, respectively. These values were significantly different from those obtained in awake subjects in our laboratory (CBF: 46 ± 7 ml/100 g/min; CMRo$_2$: 3.1 ± 0.6 ml/100 g/min). During CBF measurement, the mean cerebral perfusion pressure, cerebral vascular resistance (CVR) and arterial carbon dioxide tension ($P_{CO_2}$) were 89 ± 16 mm Hg, 3.4 ± 1.3 mm Hg/ml/100 g/min, and 36 ± 9 mm Hg, respectively. The relationship between CBF and $P_{CO_2}$ was studied and it was found that during Althesin anaesthesia reactivity of cerebral vessels to the alteration of $P_{CO_2}$ was maintained. It is concluded that Althesin caused cerebral metabolic depression which was accompanied by a decrease in CBF and an increase in CVR.

It has been well documented that both i.v. and inhalation anaesthetic agents have divergent effects on cerebral circulation and metabolism (Michenfelder and Theye, 1972; Smith and Wollman, 1972). A review of the effects of commonly used i.v. anaesthetic agents in man revealed that thiopentone markedly decreased the cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen (CMRo$_2$) (Pierce et al., 1962). With ketamine, CBF increased without any significant changes in CMRo$_2$ (Takeshita, Okuda and Sari, 1972). Thalamonal (fentanyl and droperidol) caused no significant changes in CBF and CMRo$_2$ (Sari, Okuda and Takeshita, 1972).

The structural and pharmacological differences between Althesin and other i.v. anaesthetic drugs (Gyermek and Soyka, 1975) and a lack of knowledge of its effects on cerebral blood flow and oxygen consumption in man prompted us to perform the present study.

METHOD
Twenty healthy patients who were undergoing elective surgery, and whose prior consent for the study had been obtained, were divided into two groups: awake group (13 patients) and Althesin group (seven patients). Examinations before operation revealed no cardiological or neurological disorders in any of the patients. CBF (ml/100 g/min) was measured over 15 min by the nitrous oxide method. In the awake group, the patients breathed a mixture of 15% nitrous oxide in oxygen whereas the patients in the Althesin group breathed a mixture of 15% nitrous oxide, 30% oxygen and 55% nitrogen. The CBF measurement in the awake group was performed to obtain a standard value in awake subjects in our laboratory. In all patients, Teflon catheters were placed in the radial artery and in the superior bulb of internal jugular vein for blood sampling and pressure measurement. Simultaneous arterial and jugular blood samples were obtained at 1, 3, 5, 7, 10, 12 and 15 min following commencement of inhalation of the nitrous oxide mixture. The concentration of nitrous oxide in the blood was determined by gas chromatography (Shimazu, GC-4A-PTF, Kyoto, Japan). The coefficient of variance of the reproducibility was less than 2%. The CBF was calculated by modification of the Kety–Schmidt method which includes prolongation of nitrous oxide saturation phase and extrapolation of the arteriovenous difference of nitrous oxide concentrations to infinity. The end-tidal carbon dioxide concentration was analysed continuously with an infra-red gas analyser (Toshiba–Beckman, Tokyo, Japan). The nasopharyngeal temperature was measured with a calibrated thermistor probe. During each CBF measurement, the arterial and internal jugular venous pressure were measured at the commencement of inhalation of nitrous oxide gas mixture, 7 min later, and at the end of the inhalation. The difference

ATSUO SARI, M.D.; TSUYOSHI MAEKAWA, M.D.; MASAHARU TOHJO, M.D.; YOSHIKI OKUDA, M.D.; HIROSHI TAKESHITA, M.D.; Department of Anesthesiology, Yamaguchi University Hospital, Ube, Yamaguchi, Japan.
All correspondence to H. Takeshita.
between the mean arterial pressure (MAP), measured using an electrical transducer, and the internal jugular venous pressure, measured by a water manometer with the zero point at the mastoid process, was defined as cerebral perfusion pressure (CPP). Cerebral vascular resistance (CVR) was calculated as the ratio of CBF to CPP. Arterial and internal jugular venous blood were sampled simultaneously at the time of each pressure measurement. Arterial and jugular venous Po$_2$, Pco$_2$ and pH were measured with an IL Meter (Model 313, Instrumentation Laboratories, Boston, U.S.A.). Oxygen saturation and haemoglobin concentration (Hb) were measured with an IL Co-oximeter (Model 182, Instrumentation Laboratories, Boston, U.S.A.). Oxygen content was calculated from the haemoglobin oxygen-carrying capacity and the amount of dissolved oxygen, as estimated from Po$_2$ and oxygen solubility. CMR$_0$_2 was calculated as the product of CBF and the oxygen content difference between the arterial and the internal jugular venous blood (CaO$_2$—CvO$_2$). The cerebral circulatory index (CCI) was calculated as the ratio of CBF to CMR$_0$_2. All determinations except CBF were made in triplicate, and the averages were used for statistical analysis. During the entire period of the study, about 250 ml of 0.9% saline solution was given by i.v. infusion and 50 ml of blood was removed for the analyses.

In the awake group, CBF was measured 30 min after i.m. injection of atropine 0.5 mg and thereafter anaesthesia was induced. The subjects breathed 100% oxygen for 15 min before the start of CBF measurement. In the Althesin group, anaesthesia was induced with a single dose of Althesin 0.1 ml/kg 30 min after the injection of atropine 0.5 mg i.m., and the trachea was intubated with the aid of suxamethonium 40 mg. Five minutes after the injection of suxamethonium, pancuronium bromide 4 mg was given i.v., the Althesin infusion 0.3 ml/kg/h was started and the patients were ventilated mechanically with a non-rebreathing system, for 15 min, with 30% oxygen in nitrogen to obtain a steady end-tidal carbon dioxide concentration before the start of CBF measurement. After CBF measurement, the Althesin infusion was stopped and anaesthesia was maintained with nitrous oxide and halothane for the scheduled operation. The fronto-occipital electroencephalogram (e.g.g.) was recorded continuously to estimate the depth of anaesthesia and was analysed every 10 sec with a frequency analyser throughout the study (Nihon-Koden, MAF-5, Tokyo, Japan). Representative e.g.g. traces are shown in figure 1.

Differences between the two groups were tested using the unpaired $t$ test. $P<0.05$ was considered statistically significant.

### RESULTS

The results are summarized in table I. As MAP and the internal jugular venous pressure of the Althesin group did not differ from those of the awake group, there was no significant difference of CPP between the two groups. With Althesin, CBF decreased by 37% from the value in awake subjects and this was accompanied by an increase of CVR. Individual values of PaCO$_2$ in the Althesin group varied from 24 mmHg to 51 mmHg, but the mean value was not significantly different from that in the awake group. The relationships between CBF and PaCO$_2$, and between CBF and jugular venous Po$_2$ are shown with regression lines in figures 2 and 3, respectively. Arterial and internal jugular venous blood-gas values revealed no significant differences between the two groups except for PaO$_2$ which was significantly high...
# Table I. Cerebral circulation and metabolism during Althesin anaesthesia

<table>
<thead>
<tr>
<th></th>
<th>Awake (n = 13)</th>
<th>Althesin (n = 7)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44</td>
<td>42</td>
<td>-2</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>95</td>
<td>95</td>
<td>0</td>
</tr>
<tr>
<td>Jugular venous pressure (mm Hg)</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Perfusion pressure (mm Hg)</td>
<td>90</td>
<td>89</td>
<td>-1</td>
</tr>
<tr>
<td>Cerebral blood flow (ml/100 g/min)</td>
<td>46</td>
<td>29</td>
<td>-17*</td>
</tr>
<tr>
<td>Cerebral vascular resistance (mm Hg/ml/100 g/min)</td>
<td>2.0</td>
<td>3.4</td>
<td>-1.4*</td>
</tr>
</tbody>
</table>

Arterial
- $P_{O_2}$ (mm Hg): 473 vs 175$,\ d$; $F_{IO_2} = 36.2 ±0.3$ °C in the Althesin and the awake group, respectively.

Jugular venous
- $P_{O_2}$ (mm Hg): 40 vs 39
- $P_{CO_2}$ (mm Hg): 48 vs 46
- pH: 7.38 vs 7.42
- $(C_{AO_2} - C_{VO_2})$ (vol %): 6.9 vs 6.5
- CMRO$_2$ (ml/100 g/min): 3.1 vs 1.7
- Cerebral circulatory index: 15.1 vs 19.3

* Significantly different from awake. $F_{IO_2} = 1.0$; $F_{IO_2} = 0.3$.  

**DISCUSSION**

The present study indicates clearly that Althesin reduces CBF. It is well known that thiopentone reduced CBF to 52% of the value in awake subjects (Pierce et al., 1962), whereas ketamine increased CBF strikingly in man (Takeshita, Okuda and Sari, 1972). Thalamonal had no significant effects on CBF in man (Sari, Okuda and Takeshita, 1972). Therefore, it can be said that i.v. anaesthetic agents, with the
except of ketamine, do not cause an increase in CBF, whereas most inhalation anaesthetic agents increase CBF (Smith and Wollman, 1972). In this study, the reduction in CBF was accompanied by an unchanged CPP, resulting in an increase in CBF. In other studies, the effect of Althesin on arterial pressure was variable, with some workers reporting a decrease (Clarke et al., 1971; Savege et al., 1971), and others an increase (Campbell et al., 1971). It is noteworthy that the relatively large doses of Althesin used in this study did not cause a decrease in arterial pressure. The decrease in CBF suggests that Althesin caused cerebral vasoconstriction. In man, Turner and others (1973) observed that a single dose of Althesin (0.05 ml/kg) resulted in a decreased intraventricular pressure, measured in one lateral ventricle, and suggested that a decrease in intracranial pressure was the result of a reduction in CBF and cerebral blood volume. Our results strongly support their conclusion. Takahashi and others (1973) also reported a decrease in cerebrospinal fluid pressure associated with Althesin.

It is generally accepted that the relationship between CBF and $P_{aCO_2}$ (within the range 20–60 mm Hg) is almost linear (Reivich, 1964) and that the response of the cerebral circulation to the alteration of $P_{aCO_2}$ is maintained during general anaesthesia with either i.v. or inhalation agents, but the extent of the reactivity of the cerebral vessels during general anaesthesia is different from that during the normal awake state (Pierce et al., 1962; Wollman et al., 1964; Alexander et al., 1968). In this study, individual $P_{aCO_2}$ values varied in the range 24–51 mm Hg. This allowed us to compare the cerebrovascular response to the alteration of $P_{aCO_2}$ during Althesin with that during thiopentone (fig. 2). The regression equations for the two agents are as follows:

**Althesin:** $\text{CBF} = 0.907P_{aCO_2} - 3.19\ (r = 0.843)$

**Thiopentone:** $\text{CBF} = 0.441P_{aCO_2} + 8.64\ (r = 0.660)$

The regression equation for thiopentone was derived from individual data reported by Pierce and others (1962). There was no significant difference between the two equations ($t = 0.706; P > 0.5$). These results indicated that the response of cerebral vessels to the alteration of $P_{aCO_2}$ was maintained during both Althesin and thiopentone anaesthesia (Pierce et al., 1962). When the individual values of CBF were plotted against the corresponding values for jugular venous $P_{O_2}$, a linear correlation was found, suggesting that jugular $P_{O_2}$ is a good index of CBF. We believe that, in this study, individual variations of CMRO$_2$ were minimal, because the e.e.g. patterns were similar.

Our results show that Althesin is a potent cerebral metabolic depressant. In this respect, Althesin was again similar to thiopentone. Picketrodt and colleagues (1972) reported that, in baboons, CMRO$_2$ of grey matter measured by xenon clearance was 46.5% less than the control value during anaesthesia from Althesin 0.05 ml/kg. Our result is compatible with their findings, although the method of CBF measurement and the dose used were different. Thiopentone and propanidid also caused cerebral metabolic depression. Pierce and others (1962) reported that deep thiopentone anaesthesia (25 mg/litre blood concentration) in man decreased CMRO$_2$ by 45% from that observed in conscious, normocapnic subjects. The magnitude of the reduction in CMRO$_2$ with Althesin was similar to that observed with profound thiopentone anaesthesia. Dose-related metabolic depression has been known to occur with thiopentone and propanidid (Homburger et al., 1946; Takeshita, Miyauchi and Ishikawa, 1973). However, in man, ketamine did not cause significant changes in CMRO$_2$ (Takeshita, Okuda and Sari, 1972), although in dogs it caused an increase in CMRO$_2$ (Dawson, Michenfelder and Theye, 1971). Pethidine and fentanyl in clinical doses reduced CMRO$_2$ (Messick and Michenfelder and Theye, 1969; Michenfelder and Theye, 1971). Morphine reduced CMRO$_2$ in dogs (Takeshita, Michenfelder and Theye, 1972). Sari, Okuda and Takeshita (1972) reported that thalamonal did not cause any significant changes in CMRO$_2$ in man. Michenfelder and Theye (1972) stated that CMRO$_2$ during anaesthesia may be increased, decreased or unchanged, suggesting that CMRO$_2$ might be a secondary manifestation of altered cerebral function. Although a decrease in CMRO$_2$ may reflect a decreased neuronal activity or an increase in CMRO$_2$, an increased neuronal activity, it must be considered that the CMRO$_2$ measured during anaesthesia is the net change occurring simultaneously in both inhibitory and excitatory neuronal compartments. The reduction in CMRO$_2$ observed in this study paralleled the reduction in CBF. Thus there were no significant changes in ($C_{aO_2} - C_{vO_2}$), CCI and jugular venous $P_{O_2}$. It was apparent that CBF during Althesin anaesthesia was sufficient to meet the cerebral oxygen demand. The decrease in CMRO$_2$ was accompanied by a slowing of e.e.g. as observed during thiopentone anaesthesia (Pierce et al., 1962).
In this study, possible factors affecting CMRO₂ and CBF such as anaesthetic depth, arterial pressure, blood-gas values and body temperature were considered carefully. With Althesin infusion, e.g. showed consistent, irregular slow-wave activity which indicated a relatively deep level of anaesthesia. The MAP was well within a range of autoregulation. To test the response of the cerebral circulation to the alteration of $P_{\text{aco}_2}$ individual $P_{\text{aco}_2}$ was varied intentionally. The mean $P_{\text{o}_2}$ differed significantly in the two groups—in the awake group the subjects breathed 85% oxygen during CBF measurement. However, it has been shown that inhalation of a high concentration of oxygen does not affect CBF or CVR (Turner et al., 1957). Therefore, we believe that our findings are not affected by the difference in $P_{\text{o}_2}$ between the two groups. It is concluded that, in man, both Althesin and thiopentone (Pierce et al., 1962), unlike ketamine (Takeshita, Okuda and Sari, 1972), reduce CMRO₂ and cause a proportional decrease in CBF.

ACKNOWLEDGEMENTS

We are grateful to Mr Toshizo Ishikawa for his gas chromatographic analysis and to Miss Machiko Shinoda for secretarial help.

REFERENCES


Turner, J., Lambertson, C. J., Owen, S. G., Wendel, H., and Chiiodi, H. (1957). Effects of 0.08 and 0.8 atmospheres of inspired $P_{\text{o}_2}$ upon cerebral hemodynamics at a “constant” alveolar $P_{\text{aco}_2}$ of 43 mm Hg. *Fed. Proc.*, 16, 130.


EFFETS DE L’ALTHESINE SUR LE DEBIT SANGUIN CEREBRAL ET CONSOMMATION D’OXYGENE CHEZ L’HOMME

RESUME

On a étudié sur sept sujets en bonne santé la circulation et le métabolisme cérébraux pendant une anesthésie par l’Althesine. L’Althesine a été administrée en une dose unique de 0,1 ml/kg et infusée par la suite au taux constant de 0,3 ml/kg/h. Pendant l’infusion d’Althesine le débit sanguin cérébral (CBF) et le taux métabolique cérébral
pour l’oxygène (CMRO₂) ont été respectivement de 29 ± 10 ml/100 g/min et de 1,7 ± 0,4 ml/100 g/min. Ces valeurs ont différé d’une manière significative de celles obtenues dans nos laboratoires sur des sujets éveillés (CBF : 46 ± 7 ml/100 g/min ; CMRO₂ : 3,1 ± 0,6 ml/100 g/min). Pendant la mesure du CBF, la pression moyenne de la perfusion cérébrale, la résistance vasculaire cérébrale (CVR) et la tension du gaz carbonique artériel (Paco₂) ont été respectivement de 89 ± 16 mm Hg, 3,4 ± 1,3 mm Hg/ml/100 g/min et de 36 ± 9 mm Hg. On a étudié la relation qui existe entre le CBF et la Paco₂, et on a trouvé que pendant l’anesthésie par l’Althesine le pouvoir de réaction des vaisseaux cérébraux à l’alélation de la Paco₂ était maintenu. On en a conclu que l’Althesine provoqua une dépression métabolique cérébrale accompagnée d’une diminution du CBF et d’une augmentation du CVR.

AUSWIRKUNGEN VON ALTHESIN AUF DEN ZEREBRALBLUTFLUSS UND DEN SAUERSTOFFVERBRAUCH BEIM MENSCHEN

ZUSAMMENFASSUNG

Zerebralzirkulation und Metabolismus während einer Althesin-Anästhesie wurden bei sieben gesunden Patienten untersucht. Das Althesin wurde in einer einzigen Dosis von 0,1 ml/kg verabreicht, und danach auf dem Infusionswege in konstantem Tempo von 0,3 ml/kg/h zugeführt. Während der Althesin-Infusion betrug der Zerebralblutfuss (CBF) und die zerebrale metabolische Sauerstoffrate (CMRO₂) jeweils 29 ± 10 ml/100 g/min, bzw. 1,7 ± 0,4 ml/100 g/min. Diese Werte waren stark unterschiedlich zu denen, die bei wachen Versuchspersonen in unserem Laboratorium erzielt wurden (CBF : 46 ± 7 ml/100 g/min ; CMRO₂ : 3,1 ± 0,6 ml/100 g/min). Während der CBF-Messung betrug der mittlere zerebrale Druck 89 ± 16 mm Hg, der zerebrale Gefäßwiderstand (CVR) 3,4 ± 1,3 mm Hg/ml/100 g/min, und die arterielle Kohlendioxydsspannung 36 ± 9 mm Hg. Das Verhältnis zwischen CBF und der arteriellen Kohlendioxyds/spannung (Paco₂) wurde studiert, wobei sich herausstellte, dass während der Althesin-Anästhesie die Reaktivität der zerebralen Gefäße auf die Veränderung von Paco₂ bewahrt wurde. Zusammenfassend wird festgestellt, dass durch Althesin eine zerebrale metabolische Depression verursacht wurde, begleitet von einer Verringerung von CBF und einem Anstieg von CVR.

EFECTOS DEL ALTESIN SOBRE EL FLUJO SANGUÍNEO CEREBRAL Y CONSUMO DE OXÍGENO EN EL HOMBRE

SUMARIO

Se estudiaron en siete pacientes sanos la circulación cerebral y metabolismo durante anestesia con Althesin. Se administró el fármaco en dosis única de 0,1 ml/kg y posteriormente por infusión a un índice constante de 0,3 ml/kg/h. Durante la infusión del Althesin, el flujo sanguíneo cerebral (FSC), y la intensidad del metabolismo cerebral (IMC) para oxígeno (IMCO₂) fueron, respectivamente, 29 ± 10 ml/100 g/min y 1,7 ± 0,4 ml/100 g/min. Estos valores fueron significativamente distintos de los obtenidos en sujetos en vigilía en nuestro laboratorio (FSC : 46 ± 7 ml/100 g/min ; IMCO₂ : 3,1 ± 0,6 ml/100 g/min). Durante la medición del FSC, las cifras de la presión media cerebral de perfusión, resistencia vascular cerebral (RVC) y de tensión arterial del anhidrido carbónico (Paco₂) fueron 89 ± 16 mm Hg, 3,4 ± 1,3 mm Hg/ml/100 g/min, y 36 ± 9 mm Hg, respectivamente. Se estudió la relación entre FSC y Paco₂, y se halló que durante la anestesia con Althesin se mantuvo la reactividad de los vasos cerebrales a la alteración de la Paco₂. Se sacó en conclusión que Althesin causaba depresión del metabolismo cerebral que iba acompañada de un descenso en el FSC y un aumento de la RVC.