USE OF A CONTINUOUS INFUSION OF ALTHESIN IN NEUROANAESTHESIA

Changes in Cerebral Blood Flow, Cerebral Metabolism, the EEG and Plasma Alphaxalone Concentration

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Several i.v. anaesthetic agents are known to depress the cerebral metabolic rate for oxygen (CMRO₂) and cerebral blood flow (CBF). Barbiturates, for example, cause a suppression of synaptic transmission and corresponding decreases in blood flow and metabolism. The suppression is dose-dependent until the point of appearance of an isoelectric EEG—corresponding to cessation of synaptic transmission (Michenfelder, 1974; Nilsson and Siesjö, 1975; Astrup, Møller Sørensen and Rahbek Sørensen, 1981). Likewise, Althesin can depress CMRO₂ and CBF in man following either bolus injection or during continuous infusion (Sari et al., 1976; Rasmussen, Rosendal and Overgaard, 1978). The purpose of this study was to depress CMRO₂ significantly, and to investigate possible correlations between CMRO₂, EEG and plasma alphaxalone concentrations.

PATIENTS AND METHODS

Patients

Ten patients (five males; mean age 59 yr, range 37–75 yr; mean weight 74 kg, range 50–94 kg) with cerebral tumours were investigated. They all gave informed consent and the study was approved by the local scientific ethics committee. Selection of patients was undertaken to include those with a midline shift of less than 10 mm, as judged from either CT scanning or arteriography. All tumours were located supratentorially. Before the induction of anaesthesia, all patients were awake, ASA group I–II and were receiving treatment with steroids.

Anaesthesia

One hour before the induction of anaesthesia the patients were premedicated with pentobarbitone 2 mg kg⁻¹ i.m., and mepyramine 50 mg i.m. and cimetidine 400 mg by mouth. After preoxygenation, anaesthesia was induced with an infusion of Althesin at a rate of 1.0 ml kg⁻¹ h⁻¹ and fentanyl 0.2 mg i.v. Pancuronium 0.10–0.15 mg kg⁻¹ was given to produce neuromuscular blockade, manual hyperventilation was applied and tracheal intubation performed. From the point of intubation until the end of the first CBF measurement, the anaesthesia was maintained with a continuous infusion of Althesin 0.2 ml kg⁻¹ h⁻¹, 66% nitrous oxide in oxy-
gen and fentanyl in doses of 0.1 mg (total 7.8 ± 2.8 μg kg⁻¹ (mean ± SD)). In five patients the rate of infusion of Althesin was 0.2 ml kg⁻¹ h⁻¹ throughout the study, and CBF was measured on two occasions. In four patients the Althesin infusion rate was increased to 0.5 ml kg⁻¹ h⁻¹ 30 min before the second CBF determination. In one patient (No. 10, table I) the infusion of Althesin was unintentionally disrupted 30 min before the second CBF measurement. Ventilation was controlled throughout (Servo 900 B) and end-expiratory carbon dioxide concentration monitored.

Measurements of CBF, CMRO₂ and EEG

The internal jugular vein contralateral to the tumour was cannulated percutaneously using the anterior approach, and a catheter placed at the base of the skull. The position of the catheter was confirmed radiologically. Xenon-133 2 mCi in saline was infused i.v. over a period of 20 min to obtain saturation. Blood samples (2 ml precisely) were drawn using disposable syringes from arterial and jugular venous blood at exact time intervals of 18, 19 and 20 min during saturation and at 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 20, 25 and 30 min during desaturation. Radioactivity in the samples was counted, and the arterial and venous desaturation curves drawn (fig. 1). The amount of xenon-133 released by the brain during the 30-min desaturation period was estimated by planimetry as the area between the arterial and venous desaturation curves. CBF was calculated using the "Height-over-Area" formula (CBF₃₀) and cerebral metabolic rate of oxygen (CMRO₂) from the product of CBF and the arterio-venous oxygen difference (Kety and Schmidt, 1948; Lassen and Klee, 1965; Astrup et al., 1984). The partition coefficient for brain tissue was corrected for haemoglobin concentration (Veall and Mallet, 1965). The first CBF measurement was performed about 1 h after the induction of anaesthesia, and the second approximately 1 h later. At least 30 min was allowed to elapse after the increase in the Althesin infusion rate before xenon-133 desaturation and hence the CBF and CMRO₂ measurements.

After the induction of anaesthesia, eight EEG electrodes were positioned over the frontal, temporal and occipital regions on the side contralateral to the craniotomy. A 2-min EEG recording was obtained during each xenon-133 desaturation period, while surgery was discontinued to avoid electrical interference with the recording. The EEG recordings were compared with the preoperative EEG and analysed as described by Prior, Maynard and Brierley (1978), using a six-point scale. Level one corresponded to continuous background activity of fairly constant voltage with any combinations of frequency, but without periods of either partial or total suppression. Level two: periods of less than 1 s total or subtotal suppression, separated by bursts of activity usually of 100–300 μV. Level three: periods of 1–3 s duration of total, occasional subtotal suppression, separated by bursts of activity of 100–300 μV. Level four: periods of at least 3 s total suppression separated by bursts of activity usually of 50–100 μV. Level five: periods of at least 3 s total suppression separated by very brief bursts of low voltage less than 50 μV. Level six: no evidence of any cerebral electrical activity even with high gain. This scale, although initially designed for animal experiments with extradurally-placed electrodes, has subsequently been applied in man during the infusion of Althesin (Henderson, McGeorge and Teasdale, 1982).

Assay for alphaxalone in plasma

These analyses were performed at Glaxo Group, Research Limited, Greenford, Middlesex. Plasma alphaxalone was analysed in peripheral arterial blood sampled during each CBF measurement at the time of the EEG recording; plasma was stored at −25°C until assayed.

Plasma, to which internal standard (2β-n-butoxy, 3α-hydroxy-5α-pregnane-11, 20-dione 1 μg) had been added, was buffered to pH 11.4 and extracted.
with ether. The extract was evaporated to dryness and then derivatized with heptafluorobutyrylimidazole in toluene (10 min 55 °C).

Excess reagent was removed by washing with buffer (pH 7.4). The derivative was diluted with toluene before gas–liquid chromatography (GLC) on 2% Dexsil 300 at 245 °C. Detection was by ECD, and quantitation was by the peak–height ratio method. Assay sensitivity was 20 ng ml⁻¹ provided a rigorous conditioning procedure was applied to the GLC column before use. This involved injections of 2, 4-pentanedione and Silyl-8 onto the column at 250 °C and subsequent overnight heating at 290 °C.

Arterial pressure was monitored and the mean pressure (MAP) recorded continuously, as was rectal temperature. Arterial blood-gas analyses were performed twice during each CBF measurement (ABL 1: Radiometer). The oxygen saturations of arterial and jugular venous blood were measured in duplicate (OSM2: Radiometer).

Statistical analyses
The results are indicated as mean ± standard deviation (SD). $P < 0.05$ indicates level of significance. The Mann–Whitney test was used for unpaired data; Student's $t$ test for paired data. Linear regression and correlation coefficients were used for correlations between two variables.

RESULTS
During the first CBF study at an Althesin infusion rate of 0.02 ml kg⁻¹ h⁻¹ ($n = 10$), CBF was 24.4 ± 5.4 ml min⁻¹/100 g and CMRO₂ 1.87 ± 0.44 ml min⁻¹/100 g at $P_{\text{aco}}$ 4.1 ± 0.7 kPa and body temperature 35.7 ± 0.4 °C.

In five studies at an unchanged infusion rate of 0.2 ml kg⁻¹ h⁻¹, the changes in CBF and CMRO₂ were from 21.8 ± 5.0 to 20.0 ± 6.4 ml min⁻¹/100 g and from 1.84 ± 0.20 to 1.88 ± 0.80 ml min⁻¹/100 g, respectively (table I).

During the second CBF measurement (infusion rate 0.5 ml kg⁻¹ h⁻¹ (patients Nos 6–9, table I)) CBF decreased from 25.0 ± 5.7 to 20.1 ± 8.6 ml min⁻¹/100 g and CMRO₂ from 1.85 ± 0.71 to 1.50 ± 0.30 ml min⁻¹/100 g. The decrease in CMRO₂ was greater than 15% in three patients while a small increase was found in one patient.

### Table I

<table>
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<th>Patient No.</th>
<th>Althesin infusion rate (ml kg⁻¹ h⁻¹)</th>
<th>Central temp. (°C)</th>
<th>Arterial pressure (MAP) (kPa)</th>
<th>$P_{\text{aco}}$ (kPa)</th>
<th>EEG level</th>
<th>Plasma alphaxalone concn (ug ml⁻¹)</th>
<th>CBF (ml min⁻¹/100 g)</th>
<th>CMRO₂ (ml min⁻¹/100 g)</th>
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patient, an interruption to the Althesin infusion was associated with an increase in CMRO2 (patient No. 10, table I).

The changes in the EEG, and the correlations between CMRO2 and EEG values are shown in figure 2. As indicated, CMRO2 never decreased below 1.6 ml min⁻¹/100 g at EEG level 1, and CMRO2 did not surpass 2.1 ml if EEG traces were level 3 or more. In three patients a decrease in CMRO2 was associated with suppression of EEG activity. In six patients a decrease in CMRO2 was observed while the EEG level was unchanged, and in one patient suppression of EEG activity was found with an unchanged CMRO2.

The correlations between corresponding values of plasma alphaxalone and CMRO2 are shown in figure 3. In six patients, an increase in plasma alphaxalone was associated with a decrease in CMRO2; in three patients with an increase in CMRO2; in one patient, unchanged plasma alphaxalone concentration was observed at two different values of CMRO2. As in figure 2, great inter- and intraindividual differences in the relationship was found. In total (n = 20) the correlation between plasma alphaxalone concentration and CMRO2 was insignificant.

The relationship between changes in plasma alphaxalone concentration and EEG level is shown in figure 4. Again, great inter- and intraindividual differences were observed. In only three patients was an increase in plasma alphaxalone concentration associated with a suppression of EEG activity; in six patients unchanged EEG activity was observed at different alphaxalone concentrations and in one patient a suppression of EEG activity was associated with unchanged plasma alphaxalone concentration.

DISCUSSION

The method used in this study to measure CBF and CMRO2 is a modification of the inhalation method described by Kety and Schmidt (1948). We
recent study of CBF and CMRO₂ in awake unpre-
mass circulations and metabolism to a minor degree. In a
study was low and would only influence the cerebral
intracranial pressure in the contralateral hemisphere
was assumed to be minimal. Therefore, we assumed that
the influence of the contralateral hemisphere was
assumed to be minimal. Therefore, we assumed that
intracranial pressure in the contralateral hemisphere
was low and would only influence the cerebral
circulation and metabolism to a minor degree. In a
recent study of CBF and CMRO₂ in awake unpre-
massed patients with supratentorial tumours, we
the i.v. modification of Kety and Schmidt as
described in the present study, and obtained CBF values
of 47 ml min⁻¹/100 g and CMRO₂ of 3.3 ml min⁻¹/
100 g (Astrup et al., 1984). These values correspond
to the values found in normal man (Lassen, 1959),
and argue against a major influence of the tumour on
the contralateral hemisphere. Nevertheless,
methodological errors may occur. These errors include contamination with extracranial blood and
blood from the contralateral hemisphere (Lassen,
1959; Lassen and Lane, 1961). Furthermore, contami-
nation by central venous blood also occurs
(Murray, Hoschl and Choy, 1978). The last men-
tioned error is a function of the difference in pres-
sure between central venous blood and the pressure
in the jugular bulb, and might be eliminated by
keeping the inspiratory pressure as low as possible.
In the present study we used a respirator frequency
of about 20 b.p.m., and the inspiratory phase of the
respiratory cycle was constant at 30%.

This study presumes that steady-state conditions
pertain during the 30-min desaturation period. This
assumption was fulfilled as far as P_{\text{aco2}} was con-
cerned, but the mean arterial pressure did increase
during the operative procedure, especially on inci-
sion of the skin. Thus, the nociceptive stimulation
induced by the operation might influence the
measurements. According to Kuramoto and others
(1979), nerve stimulation will increase EEG activity
and CMRO₂ in anaesthetized dogs. However, in all
of the patients the first CBF measurement was com-
menced before the dura was opened, while the
second measurement was performed during the
operative evacuation of the tumour. Red cerebral
veins have often been seen during craniotomy in
patients with cerebral tumours (Feindal and Perot,
1965). This hyperoxygenation of the venous blood
can arise suddenly, and is often provoked by the
operative procedure. If a hemispheric luxury syn-
drome does occur (Lassen, 1966) on the tumour site,
the high venous oxygen saturation will result in an
underestimation of CMRO₂ as a result of contamina-
tion of the contralateral hemisphere. In the present
study this might explain the low values of CMRO₂
(< 1.4 ml min⁻¹/100 g) found in three studies of CBF.

The present study indicates that Althesin
decreases CBF and CMRO₂. This is in accordance
with studies in baboons (Pickerodt et al., 1972) and
humans (Renou et al., 1976; Sari et al., 1976; Ras-
mussen, Rosendal and Overgaard, 1978). Sari and
colleagues (1976) found CBF values of 29 ml min⁻¹/
100 g at P_{\text{aco2}} 4.8 kPa during continuous Althesin
infusion at a rate of 0.3 ml kg⁻¹ h⁻¹. According to
Sari and colleagues (1976), cerebral carbon dioxide
reactivity is maintained during Althesin anaesthesia,
and this might be the explanation for the lower val-
ues of CBF in the present study, as P_{\text{aco2}} was kept
lower. Like Sari and colleagues (1976), we found
considerable interindividual variation in CBF and
CMRO₂. The reason could be methodological errors
and difficulties in maintaining steady-state condi-
tions during the measurements. This, together with
the restricted number of investigations and a great
individual difference in sensitivity to Althesin might
explain the lack of correlation between CMRO₂,
EEG and plasma alphaxalone concentration.

After increasing the infusion rate from 0.2 to
0.5 ml kg⁻¹ h⁻¹, we found an increase in plasma
alphaxalone concentration in four studies and sup-
pression of EEG activity in only two of four patients.
The results confirm the studies by Henderson,
McGeorge and Teasdale (1982) who found a correla-
tion between rate of infusion of Althesin and sup-
pression of EEG, and the studies by Frank and col-
leagues (1982) who found a significant correlation
between plasma alphaxalone concentration and
cerebral function monitor trace. In addition, our
results are a confirmation of the study performed by
Sear and Prys-Roberts (1979), who found an almost
linear correlation between the rate of infusion of
Althesin and plasma alphaxalone concentration.
The paradoxical association of increased plasma
alphaxalone concentration and increased CMRO₂
found in three patients may be caused by
methodological errors in the estimation of CMRO₂,
or absence of steady-state conditions as a result of
the operative procedure.

Neuroanaesthesia using a continuous infusion of
Althesin produces a dose-dependent decrease in
CBF and CMRO₂ with a 50% decrease in CMRO₂ at doses of 0.5 ml kg⁻¹ h⁻¹. Simultaneously, a pronounced suppression of EEG occurs. However, great interindividual variations are present, and it is not possible to predict the actual value of cerebral oxygen uptake from EEG recordings or plasma alphaxalone concentrations.

REFERENCES


