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Changes in $CMRO_2$, EEG and concentration of etomidate in serum and brain tissue during craniotomy with continuous etomidate supplemented with N_2O and fentanyl

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Fourteen patients with supratentorial cerebral tumours were anaesthetized with continuous etomidate infusion (30 or 60 μg kg^{-1} min^{-1}) supplemented with N_2O 67% and fentanyl. Peroperatively cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) were measured twice by the Kety and Schmidt method. Simultaneously with the CBF measurements, blood for serum etomidate was sampled and EEG was recorded in 2-min periods in 12 patients. In 10 patients a brain biopsy for etomidate was taken peroperatively and correlated with the other data. The results indicate a dose-dependant increase in serum etomidate and brain tissue etomidate, a decrease in $CMRO_2$ and suppression of EEG activity. In individual studies an increase in serum etomidate or a decrease in $CMRO_2$ correlated to a suppression of the EEG activity, and *vice versa*. However, the wide variations in these relationships within and between patients make any conclusion regarding $CMRO_2$ impossible from the EEG recording, infusion rate of etomidate or serum concentration of etomidate.

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Etomidate injected as a bolus induces a decrease in cerebral blood flow (CBF) (1–3), a decrease in cerebral metabolic rate of oxygen ($CMRO_2$) (3), a decrease in intracranial pressure (ICP) (4–6), and suppression of cerebral activity in EEG (7–10). In comparison with inhalation anaesthesia and thiopental, induction of anaesthesia with etomidate results in only a minimal decrease in mean arterial blood pressure (MABP), and consequently cerebral perfusion pressure (CPP) is unchanged during etomidate induction (4–6).

Continuous etomidate infusion supplemented with fentanyl and nitrous oxide has been proposed as an alternative in neuroanaesthesia, and recently CBF and $CMRO_2$ have been measured during steady-state infusion of etomidate in patients subjected to craniotomy for supratentorial tumours. The results of the study indicate a dose-related suppression of $CMRO_2$ and preserved relative CO_2 reactivity on the contralateral side of the cerebral tumour (11). In the present study, the relationship between $CMRO_2$, EEG activity on the contralateral side of the tumour, serum etomidate concentration, and the concentration of etomidate in brain tissue in the ipsilateral hemisphere has been investigated.

PATIENTS AND METHODS

Patients

Fourteen patients (mean age 62, range 41–73 years), with supratentorial cerebral tumours with shift of midline structures less than 10 mm on CT scanning, were included in the study.

Preoperatively, all patients were awake, ASA group I–II, and all patients except one were on treatment with steroid (methylprednisolon 10 mg × 4). All patients gave informed consent according to the Helsinki II declaration, and the study was approved by the scientific ethics committee of Copenhagen.

Anaesthesia

Pentobarbitone 2 mg kg^{-1} i.m. 1 h before induction of anaesthesia was used for premedication. For induction of anaesthesia, etomidate 0.28 ± 0.03 mg kg^{-1} (mean ± s.e.mean) was given intravenously during a period of 30–60 s followed by fentanyl 0.2 mg and pancuronium 0.10 mg kg^{-1}. After intubation the dose of etomidate infusion was 30 μg kg^{-1} min^{-1} and the anaesthesia was supplemented with nitrous oxide 67% and fentanyl in doses of 0.1 mg per 70 kg body weight every 30–60 min. Pancuronium was given in doses of 1–2 mg under control of neuromuscular blockade with train-of-four stimulation. In Group I (seven patients) the dose of etomidate was 30 μg kg^{-1}

min^{-1} throughout the anaesthesia. In Group 2 (seven patients) the etomidate infusion was increased to 60 μg kg^{-1} min^{-1} after the termination of the first CBF study.

CBF measurement

CBF was measured contralaterally to the cerebral tumour by a modification of the Kety and Schmidt method using intravenous ^{133}Xe and a desaturation period of 30 min. $CMRO_2$ was calculated as the product of CBF and (a-v)diffO_2 as recently described (11, 12). The first CBF was measured 72 ± 2 min after induction of anaesthesia, and the second CBF study was performed 132 ± 2 min after induction.

Recording of EEG

After induction of anaesthesia, eight EEG electrodes were positioned intracutaneously over the frontal, temporal, parietal and occipital regions contralaterally to the side of craniotomy. A 2-min EEG recording was obtained during each CBF measurement just at the start of the ^{133}Xe desaturation period, while surgery was discontinued to avoid electrical disturbances in the recordings. The EEG recordings were compared with the preoperative EEG and analysed according to the graduation of level of activity described by Prior et al. (13). In this scale, level I indicates continuous background activity of fairly constant voltage and with any combination of frequencies but without periods of either partial or total suppression. Level 2: Periods of less than 1 s duration of total or subtotal suppression separated by bursts of activity usually of 100–300 μV. Level 3: Periods of 1–3 s duration of total (occasionally subtotal) type separated by bursts of activity of 100–300 μV. Level 4: Periods of at least 3 s duration of total suppression separated by bursts of activity usually of 50–100 μV. Level 5: Periods of at least 3 s duration of total suppression separated by very brief bursts of low voltage (less than 50 μV) activity. Level 6: No evidence of any cerebral electrical activity even with high gain.

This scale, although initially designed for animal experiments with extradural ball electrodes, has recently been applied in human studies during continuous althesin infusion (14). EEG was recorded in all patients in Group 1 and in five of seven patients in Group 2. In one patient no EEG recording was available and in one patient the EEG tracings were unusable because of electrical disturbance.

The concentration of etomidate in serum

Simultaneously with each CBF measurement (5 min before and after desaturation of ^{133}Xe), 2 ml arterial blood samples were obtained and the serum was stored at −20°C. The etomidate concentration in serum was determined as etomidate sulphate by gas chromatography with the aid of a nitrogen detector. The concentrations are linear between 0.05 and 2.0 μg ml^{-1} serum. There is a 90% recovery and the detection limit is 0.03 μg ml^{-1} (15).

The concentration of etomidate in brain tissue

During the second CBF measurement, brain biopsies (about 0.5 g) were taken from intact brain tissue. The intact brain biopsy was stored at −20°C. The biopsy samples were weighed, transferred to 10 ml glass centrifuge tubes containing 1 ml of a 0.05 M phosphate buffer (pH 7.7) and homogenized by means of an ultra-turrax. After rinsing with 2 ml of the buffer solution, the combined aqueous layers were extracted twice with 4 ml of a haptene-isoamyl alcohol (98.5/1.5 V/V) mixture. The organic layers were back-extracted with 3 ml of 0.1 M sulphuric acid and, after alkalinization of the latter phase with 0.15 ml of concentrated ammonia, the compounds were re-extracted twice into 2.5 ml aliquots of the organic solvent. The extraction recovery was 90%. Samples were quantified using standards prepared in blank dog brain.

Statistical analyses

Mean values and s.e.mean were calculated. Linear regressions of correlation coefficient were calculated. The Wilcoxon test was applied for paired data and the Mann Whitney test for unpaired data.

RESULTS

The concentration of etomidate in serum and brain tissue. In Group 1 (infusion rate of etomidate 30 μg kg^{-1} min^{-1} throughout the study) the concentration of serum etomidate averaged 1.25 ± 0.31 μg ml^{-1} during the first CBF study and 1.59 ± 0.10 μg ml^{-1} during the second CBF run ($P<0.05$). Simultaneously $CMRO_2$ changed from 2.30 ± 0.43 to 2.21 ± 0.38 ml O_2 100 g^{-1} min^{-1} ($P>0.05$). In Group 2 (infusion rate of etomidate 30 μg kg^{-1} min^{-1} during the first CBF run and 60 μg kg^{-1} min^{-1} during the second CBF measurement) an increase in serum etomidate from 1.18 ± 0.16 to 3.18 ± 0.80 μg ml^{-1} ($P<0.05$) was correlated to a decrease in $CMRO_2$ from 2.52 ± 0.56 to 1.76 ± 0.40 ml O_2 100 g^{-1} min^{-1} ($P<0.05$).

A significant correlation between the concentration of etomidate in serum and brain tissue was found ($y = 0.76 + 1.31$, $r = 0.8277$, $P<0.01$). The concentration of etomidate in brain tissue was 2.0 ± 0.4 μg g^{-1} in Group 1 and 4.3 ± 0.8 μg g^{-1} in Group 2 ($P<0.05$).

The relationship between the concentration of etomidate in serum and $CMRO_2$. In all studies except one an increase

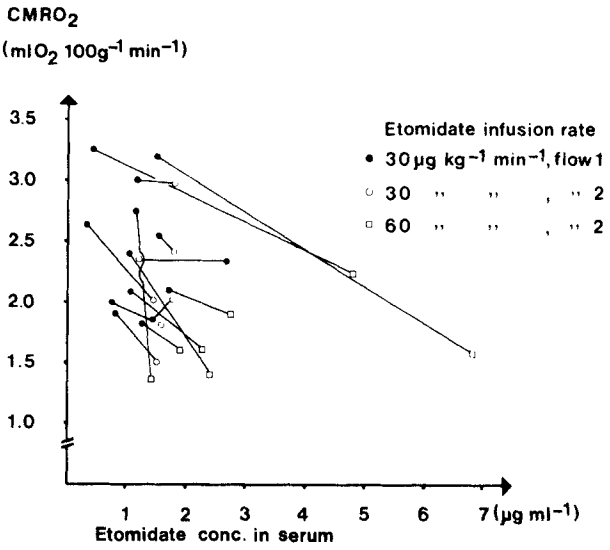

Fig. 1. The relationship betwen the concentration of etomidate in serum (μg ml^{-1}) and $CMRO_2$ (ml O_2 100 g^{-1} min^{-1}) measured on the contralateral hemisphere during craniotomy for supratentorial cerebral tumours. The anaesthesia was supplemented with N_2O, 67%, and fentanyl. The infusion rates of etomidate are indicated; flow 1 was measured 72 ± 2 *min after induction*; flow 2 132 ± 2 min after induction (mean ± s.e.mean).

in serum etomidate was associated with a decrease in $CMRO_2$. The lowest values of $CMRO_2$ and the highest values of serum etomidate were observed during infusion of 60 μg kg^{-1} min^{-1} etomidate. $CMRO_2$ above 2.3 ml O_2 100 g^{-1} min^{-1} was only observed during infusion of etomidate 30 μg kg^{-1} min^{-1}. The relationship between serum etomidate and $CMRO_2$ is shown in Figure 1 and, as indicated, a high variation in changes in serum etomidate and $CMRO_2$ was observed both inter- and intraindividually.

The relationship between concentration of etomidate in serum and the level of EEG activity is shown in Figure 2. An increase in the concentration of etomidate was associated with a suppression of EEG in 9 of 12 studies; in two studies the EEG recordings were unchanged while a small increase in the concentration of etomidate was observed. In one study an increase in serum etomidate was associated with an increase in EEG activity. In total, an increase in the concentration of etomidate was related to a suppression of EEG activity, but high inter- and intraindividual variations were observed. With the infusion rate of 60 μg kg^{-1} min^{-1} of etomidate, suppression of EEG to level 5 and 6 was observed in all studies. In contrast light to moderate EEG suppression (level 1 to 4) was only observed during the infusion rate of etomidate at 30 μg kg^{-1} min^{-1}. In all patients with serum etomidate below 1 μg ml^{-1}, the EEG recording showed continuous activity (level 1).

The relationship between $CMRO_2$ and the level of EEG activity. A fall in $CMRO_2$ was associated with suppression in EEG activity in eight studies. In two studies a decrease in $CMRO_2$ was observed with unchanged EEG activity and in two studies $CMRO_2$ was unchanged while a suppression of EEG activity was found. $CMRO_2$ above 2.3 ml O_2 100 g^{-1} min^{-1} was only observed during an infusion rate of 30 μg kg^{-1} min^{-1} etomidate, while $CMRO_2$ values below 1.75 ml O_2 were observed only with an infusion rate of 60 μg kg^{-1} min^{-1}. However, great inter- and intraindividual variations in the relationship were observed (Fig. 3).

The correlations between the concentration of etomidate in brain tissue and $CMRO_2$ and EEG activity on the contralateral side were without any statistical significance ($P > 0.05$).

DISCUSSION

The CBF measurement presented in this study is based on a steady-state period of 30 min during the ^{133}Xe desaturation period. This presumption was not always fullfilled completely during the first CBF run, which coincided with the period of incision when the sympathetic discharge secondary to pain and stimulation induced a transitory increase in blood pressure. In animal experiments in anaesthetized dogs it has been shown that nociceptive stimulation induced by the operation might increase $CMRO_2$ and induce activation in EEG (16). In order to reduce these inter-

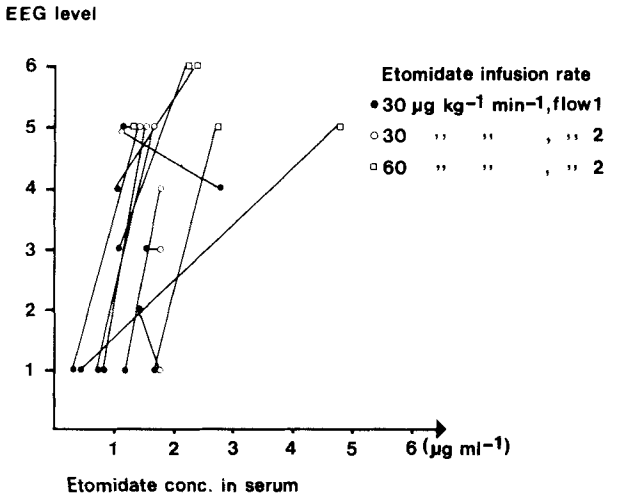

Fig. 2. The relationship between the concentration of etomidate in serum (μg ml^{-1}) and the level of activity of EEG according to Prior et al. (13). EEG was traced contralaterally to the tumours. Level 1 indicates continuous background activity; level 2 to 5 increasing suppression of activity with bursts; and level 6 isoelectric recording. The infusion rates of etomidate during anaesthesia are indicated; anaesthesia was supplemented with N_2O, 67%, and fentanyl. Flow 1 was measured 72 ± 2 min after induction; flow 2 132 ± 2 min after induction (mean ± s.e.mean).

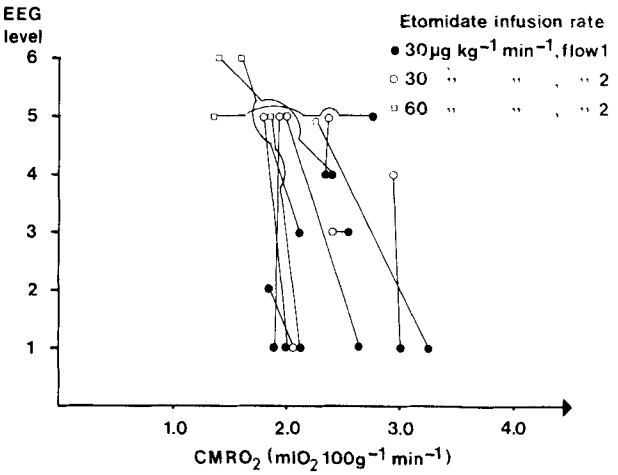

Fig. 3. The relationship between $CMRO_2$ (ml O_2 100 g^{-1} min^{-1}) and the level of activity of EEG using the graduation of level proposed by Prior et al. (13). Level 1 indicates continuous background activity; level 2 to 5 increasing suppression of activity with bursts; and level 6 isoelectric recording. Both $CMRO_2$ and EEG were measured contralaterally to the tumour. The infusion rates of etomidate during anaesthesia are indicated; anaesthesia was supplemented with N_2O, 67%, and fentanyl. Flow 1 was measured 72 ± 2 min after induction; flow 2 132 ± 2 min after induction (mean ± s.e.mean).

ferences, the first 15 min of the ^{133}Xe desaturation period did not coincide with the period of incision.

During the second CBF run surgical evacuation of the tumour was performed. In this period blood pressure was stabilized as blood loss was continuously replaced, but the surgical manipulation on the contralateral hemisphere might theoretically influence CBF and $CMRO_2$ in the contralateral hemisphere by inducing a luxury perfusion (17) which would increase the degree of contamination of blood in the contralateral hemisphere, decrease the (a-v)diffO_2 and lead to an underestimation of $CMRO_2$. However, in general the jugular venous saturation was lowest during the second CBF study. We therefore assume that contamination from the contralateral hemisphere provoked by a state of luxury perfusion did not interfere with the perfusion on the contralateral hemisphere and did not induce methodological errors in the estimation of CBF and $CMRO_2$.

Etomidate is a hypnotic agent which induces a decrease in $CMRO_2$ (3) and suppression of EEG activity (7–10). In animal experiments of global ischemia and hypoxia a cerebral protective effect of etomidate has been found (18–20). These facts, together with the fast metabolization in the liver of etomidate by ester hydrolyses to inactive caboxylic acid (21, 22), and the observation that recovery of consciousness is rapid due to metabolism and redistribution of the drug (23), make continuous etomidate infusion supplemented with nitrous oxide and fentanyl a suitable alternative in neuroanaesthesia.

An intravenous bolus injection of etomidate is accompanied by suppression of the EEG activity and the concentrations of etomidate in serum are dose correlated to changes in EEG (7–10). The changes in EEG during induction of anaesthesia with etomidate have been described in detail (8) and involve: 1) an initial increase of alpha-amplitude with a mixture of sharp theta burst, 2) the appearance of mixed delta-theta waves, 3) predominant delta waves more or less continuously, and 4) a periodic burst suppression pattern. The two first patterns described were associated with serum etomidate concentrations below 0.50 $\mu g\ ml^{-1}$.

In the present investigation an association of the two first EEG patterns mentioned with concentration of etomidate in serum below 0.50 $\mu g\ ml^{-1}$ was only confirmed in two studies. The average concentration of etomidate in serum was higher (1.22 $\mu g\ ml^{-1}$ and 3.18 $\mu g\ ml^{-1}$ during infusion rate of 30 and 60 μg etomidate $kg^{-1}\ min^{-1}$), and consequently a pronounced suppression in EEG activity with isoelectric EEG was observed in 8% of the studies, pronounced suppression in EEG activity with burst activity in 63% of the studies, while continuous background activity was observed in only 29%. Therefore the graduation of EEG activity applied in this study seems to be usable, and our results generally show that an increase in serum etomidate concentration is associated with suppression of the EEG activity. However, high intra- and interindividual variations were observed, making any conclusion concerning the degree of suppression in the EEG activity or degree of $CMRO_2$ depression from the changes in the concentration of serum etomidate impossible, and *vice versa*. The same conclusion applies to the relationship between $CMRO_2$ and degree of EEG suppression.

In the present study a significant correlation between the concentration of serum etomidate and the concentration of etomidate in brain tissue was found. However, the correlations between the concentration of brain tissue etomidate on one hand and $CMRO_2$ and degree of EEG suppression on the other hand were without any significance. These discrepancies are not surprising as brain tissue etomidate was measured on the ipsilateral side of the tumour, and $CMRO_2$ and the EEG recording on the contralateral side. Furthermore, for technical reasons brain biopsy did not coincide exactly with the start-point of the desaturation of ^{133}Xe and the EEG recording temporally, and the few paired data make the test of correlation inadequate. Finally, the interindividual variations observed in the relationship between serum etomidate and EEG and $CMRO_2$ might result in insignificance in correlation.

CONCLUSION AND CLINICAL IMPLICATIONS

In the present study continuous etomidate infusion induced a dose-dependant increase in the concentration of serum etomidate, a decrease in $CMRO_2$ and suppression of the EEG activity. In individual studies a decrease in $CMRO_2$ will correlate to suppression in the EEG activity, and *vice versa*. However, the wide variation in these relationship within and between patients makes any conclusions regarding $CMRO_2$ impossible from the EEG recording, infusion rate of etomidate or serum concentration of etomidate. The same conclusion has been drawn in studies with continuous althesin infusion (14). Thus a change in the EEG activity, either as a suppression or an activation, will generally be associated with a decrease or an increase in $CMRO_2$, and *vice versa*, but the EEG recording will give only a rough estimate of the actual value of $CMRO_2$, and even during pronounced suppression in EEG activity with a total suppression separated by bursts, a wide range of $CMRO_2$ values is indicated.

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