EFFECTS OF FLUMAZENIL ON CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION AFTER MIDAZOLAM ANAESTHESIA FOR CRANIOTOMY


SUMMARY

Cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMRO₂) were measured by a modification of the Kety–Schmidt technique using i.v. xenon-133 in 20 patients undergoing craniotomy for supratentorial cerebral tumours. Anaesthesia was induced and maintained with midazolam, fentanyl and nitrous oxide. Pancuronium was given for neuromuscular block. The lungs were ventilated to normocapnia. The first flow measurements were performed approximately 1 h after induction of anaesthesia. At the end of operation the patients were allocated to two groups. Ten patients were given flumazenil 0.01 mg kg⁻¹ and 5 min later the second flow measurement was performed. In the other 10 patients the second flow measurement was performed before the administration of flumazenil. Plasma concentrations of midazolam were measured at the time of each measurement of CBF. There was no difference between the groups in plasma concentration of midazolam, CBF or CMRO₂. Flumazenil had no effect on CBF and CMRO₂.

KEY WORDS


Flumazenil is an imidazobenzodiazepine which inhibits the central effects of the benzodiazepine by competitive interaction at specific receptors [1]. The cerebrovascular effects of flumazenil may be clinically relevant as flumazenil may be useful to antagonize benzodiazepines at the end of neurosurgical operations.

The purpose of the present study was to determine if flumazenil had any effect on cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMRO₂) when administered after midazolam.

PATIENTS AND METHODS

Patients

Patients with supratentorial cerebral tumours and midline shift < 10 mm estimated by CT scanning gave informed consent to the study, which was approved by the local Ethics Committee. Patients were excluded if they had evidence of heart disease, hypertension or chronic pulmonary disease. Before operation, all patients were awake, orientated and without major neurological deficit. All patients were being treated with dexamethasone 6 mg four times daily.

The patients were premedicated with diazepam 10–20 mg orally 2 h before operation. After preoxygenation, anaesthesia was induced with midazolam 0.3 mg kg⁻¹ and fentanyl 4 μg kg⁻¹. Pancuronium 0.15 mg kg⁻¹ was given and the lungs ventilated manually until paralysis was complete. Approximately 1 min before tracheal intubation, lignocaine 1.5 mg kg⁻¹ was given i.v.

After tracheal intubation, anaesthesia was maintained with midazolam 0.65 mg kg⁻¹ h⁻¹ for 15 min, followed by 0.125 mg kg⁻¹ h⁻¹. This infusion regimen was expected to result in a steady-state concentration of about 300 ng ml⁻¹ from 45 min onwards [2]. The first CBF measurement

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was performed at a median time of 80 min (range 52–135 min) after induction, and before incision. Subsequently, the patients were given a bolus of midazolam 0.3 mg kg\(^{-1}\) and the infusion rate increased to 0.25 mg kg\(^{-1}\) h\(^{-1}\). The lungs were ventilated with 66% nitrous oxide in oxygen, followed by administration of fentanyl 4 \(\mu\)g kg\(^{-1}\) h\(^{-1}\) and pancuronium 1–2 mg—sufficient to provide neuromuscular block estimated by train-of-four stimulation. Ventilation was controlled to achieve a \(P_{\text{CO}}\) of 4 kPa, as determined by arterial blood-gas analysis (ABL-3, Radiometer, Copenhagen, Denmark). Rectal temperature was measured repeatedly and mean arterial pressure (MAP) measured continuously via a radial artery cannula which was used also for blood sampling.

After the first CBF measurement, mannitol 0.5 g kg\(^{-1}\) was administered i.v. over 5 min.

The patients were allocated randomly to two groups: in group 1 (\(n = 10\)), at the end of the craniotomy, flumazenil 0.01 mg kg\(^{-1}\) was administered and 5 min later the CBF measurement was repeated; in group 2 (\(n = 10\)), at the end of the craniotomy the CBF measurement was performed and flumazenil 0.01 mg kg\(^{-1}\) administered.

**Measurement of CBF and CMRO\(_{2}\)**

After induction of anaesthesia, a catheter was introduced percutaneously into the internal jugular vein with the tip of the catheter at the base of the skull. Xenon-133 (3 mCi dissolved in saline 30 ml) was injected i.v. over a period of 20 min. During a 30-min desaturation period, 2-ml blood samples were withdrawn from the arterial and the internal jugular vein catheters at exact time intervals. Radioactivity was counted in a well counter (Berthold LB MAG 510). CBF was calculated according to the i.v. modification [3] of the height-over-area formula of the classical Kety–Schmidt method [4].

The arterio-venous oxygen difference (\(C_{\text{aO}}-C_{\text{vO}}\)) was calculated as the difference in oxygen content between arterial and jugular venous blood calculated from the oxygen saturation, \(P_{\text{O}}\), and haemoglobin concentration of the samples. (\(C_{\text{aO}}-C_{\text{vO}}\)) was measured in duplicate at each CBF measurement. CMRO\(_{2}\) was calculated as the product of (\(C_{\text{aO}}-C_{\text{vO}}\)) and CBF.

**Statistical analysis**

Data were analysed by Wilcoxon test for paired data and Mann–Whitney test for unpaired data. \(P < 0.05\) was considered significant.

**RESULTS**

The median age of the patients (14 male, six female) was 48 yr (range 21–71 yr). There were no significant differences between the groups in sex, age, weight, histologic diagnosis of tumour or tumour size. The first CBF measurement was performed at a median time of 80 min (range 52–135 min) after induction, and before incision; the second was performed at the end of the craniotomy at a mean 185 min (range 120–270 min) after the first flow measurement.

There were no differences between the groups in plasma concentration of midazolam or \(P_{\text{aCO}}\). MAP was constant during flow measurements. At
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the first flow measurement, there was no difference, but at the second measurement MAP increased in the group which received flumazenil. There were no differences in CMRO₂ or CBF within or between the groups (table I).

DISCUSSION

We have shown that flumazenil did not have any effect on CBF or CMRO₂ when administered after midazolam anaesthesia in neurosurgical patients.

In an animal study [5], flumazenil was found to have no effect on cerebral metabolic rate, but there was a decrease in MAP, and an increase in CBF and intracranial pressure (ICP). In another study [6], flumazenil was evaluated in 18 patients following craniotomy for tumour or aneurysm surgery. Flumazenil induced rapid recovery after prolonged administration of midazolam, enabling the surgeon to perform an accurate neurological assessment. In patients with severe head injury and unstable ICP sedated with midazolam, an increase in ICP has been reported after administration of flumazenil [7]. A study in human volunteers demonstrated absence of effects of flumazenil on CBF when injected alone, and the efficacy of flumazenil in antagonizing the depressant effects of midazolam on cerebral haemodynamics [8].

CBF and CMRO₂ were measured peroperatively during craniotomy for supratentorial cerebral tumours. Regional flow differences have been observed in patients with cerebral tumours, close to the tumour region [9] and in regions remote from the tumour [10].

In the present study, flow measurements were performed in patients with small cerebral tumours without greater midline shift; thus the CBF and CMRO₂ values obtained may be affected mostly by the large preponderance of normal brain tissue.

Cerebral blood flow was measured using an i.v. modification of the inhalation method described by Kety and Schmidt [4]. This technique has been validated for CBF measurements in awake patients with supratentorial cerebral tumours [3]. The values found corresponded with values found in normal man, which argues against a major influence of tumour on global CBF. Furthermore, this technique has produced reliable results in repeated CBF studies [11].

As mannitol causes an increase in CBF 10-20 min after a bolus dose [12], and a variable increase in CMRO₂ [12, 13], it was decided to treat all patients in this study with mannitol. Thus the influence of mannitol on cerebral circulation and metabolism should be comparable in both groups.

The midazolam-fentanyl anaesthesia was tolerated well in all patients, and provided good surgical conditions. Flumazenil provoked rapid and complete recovery after midazolam anaesthesia. None of the patients required artificial ventilation after operation and they were all awake and co-operative. A few of the patients required further doses of flumazenil because the degree of sedation increased after a period of 30-120 min.

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REFERENCES

