

Title: CEREBRAL METABOLIC EFFECTS OF ISOFLURANE AT AND ABOVE CONCENTRATIONS WHICH SUPPRESS THE EEG

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Introduction. Previous studies have suggested that anesthetics reduce cerebral metabolism (CMR_{O_2}) only to the extent that they depress neuronal function. Thiopental produces a dose-related decrease in CMR_{O_2} until the production of an isoelectric EEG. Thereafter additional barbiturates fail to alter this "basal" metabolism: that necessary for the maintenance of cellular integrity.¹ Volatile anesthetics, in clinical concentrations, also decrease CMR_{O_2} . Only halothane has been studied in concentrations sufficient to abolish neuronal electrical activity (< 4.5%). At and above this concentration it has a dose-related direct toxic effect on oxidative phosphorylation.² Isoflurane is unique among the volatile anesthetics in that it produces an isoelectric EEG at clinical concentrations (2 MAC in man). The present study investigated the effect on cerebral metabolism of isoflurane in concentrations up to and beyond those required to abolish neuronal function.

Methods. In the same dog model used for the studies of thiopental and halothane, 6 dogs were anesthetized with 1.4% isoflurane. The animals were intubated and ventilation was controlled to maintain normocarbida. Cannulae were placed into the femoral artery for pressure measurement and blood sampling and into a femoral vein for fluid and drug administration. EEG was recorded continuously. The sagittal sinus was isolated and cannulated³ and cerebral blood flow (CBF) was measured directly by an electromagnetic flowmeter. Arterial and venous blood oxygen, glucose, lactate and pyruvate contents were measured and the cerebral metabolic rates for oxygen and glucose calculated. Thirty minute steady state measurements were obtained at 1.4%, 3%, and 6% end-expired isoflurane. After the last measurements were obtained, four sequential cortical biopsy specimens were taken and analyzed for ATP, ADP, AMP, phosphocreatine, glucose, lactate, and pyruvate. Values were compared at each isoflurane concentration by analysis of variance and significant differences were tested by Student's t-test for paired data. Cerebral metabolic concentrations were compared to normal values by Student's t-test for unpaired data.

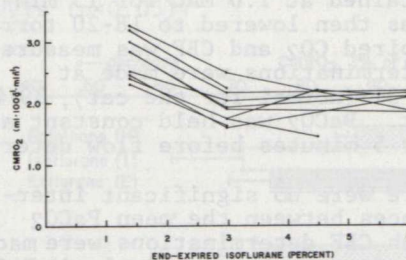
Results. Isoflurane produced a dose-related reduction in CMR_{O_2} until an abrupt change in the EEG was observed. At 3% isoflurane the EEG became isoelectric or isoelectric with superimposed spikes (10-60/min). Once this change in EEG occurred, increasing concentrations of isoflurane to as high as 6% failed to alter the CMR_{O_2} . The basal CMR_{O_2} produced was $2.02 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}$ at 3% and $2.06 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}$ at 6% isoflurane. The CMR_{glucose} similarly decreased. Adequacy of cerebral oxygen delivery was indicated by the maintenance of CBF

above $60 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ and high oxygen tensions in the sagittal sinus blood (> 57 mmHg). The cerebral tissue assays for ATP and phosphocreatine and the calculated energy charge were within normal limits although a mild dose-related cerebral lactic acidosis did occur ($2.84 \mu\text{mol/g}$ at 6%).

Discussion. Like thiopental, isoflurane produced a dose-related reduction in CMR_{O_2} only until the onset of an isoelectric EEG, indicative of cessation of neuronal function. Despite further administration of isoflurane, cerebral metabolism was maintained at a constant rate ($2.1 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$), that required for the maintenance of cellular integrity. This basal metabolic rate is similar to that obtained with thiopental ($2.2 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$). Unlike halothane, isoflurane appears to have no direct or toxic effects on oxidative phosphorylation since the cerebral energy stores remained within normal limits. Thus, at normothermia, clinically applicable concentrations of isoflurane can maximally reduce cerebral metabolism by abolishing the functional energy requirement without toxicity or marked alterations in systemic hemodynamics. Isoflurane may be unique among the volatile anesthetics in that it has a potential for cerebral protection during situations of reduced oxygen delivery.

References.

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The effect of isoflurane on the CMR_{O_2} .