Anesthesiology
V 75, No 3A, Sep 1991

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Title: A COMPARISON OF THE CEREBRAL PROTECTIVE EFFECTS OF ISOFLURANE AND MILD HYPOTHERMIA IN A MODEL OF INCOMPLETE FOREBRAIN ISCHEMIA

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Introduction: It is reasonable to suspect that isoflurane might protect the brain against ischemic injury because it can produce substantial suppression of cerebral metabolic rate. However, laboratory studies to date have not uniformly demonstrated protection by isoflurane[1,2]. Mild hypothermia has also been reported to significantly attenuate ischemic injury[3]. The present study sought to provide corroboration for the protective properties attributed to isoflurane and to compare those effects with the protection provided by mild hypothermia.

Methods: Wistar-Kyoto rats were anesthetized with halothane (H) or isoflurane (I) and assigned to one of three groups: H-normothermia (H-normo), I-normothermia (I-normo) and H-hypothermia (H-hypo) (n=7/group). After surgical preparation all animals received 1.3 MAC end-tidal H or I. Pericranial temperature was maintained at 38°C in both normo groups and was decreased to 35°C in the H-hypo group. Ischemia was induced by temporary (10 min) bilateral carotid artery occlusion with simultaneous hypotension (MAP 35 mmHg). Post-ischemia, H-hypo group animals were immediately rewarmed to 38°C. Perfusion fixation was performed after a 3 day recovery. Neuronal injury in striatum (STR), cerebral cortex (CTX), hippocampus (CA1 and CA3) and reticular nucleus of thalamus (RNT) was evaluated in standard H&E stained coronal sections of rostral and caudal forebrain. The location of the sections was chosen to permit assessment of regions with ischemic insults of varying severity. Histologic damage was scored according to the following scale: 0=no damaged neurons, 1=less than 10% damaged, 2=less than 50% damaged, 3= 50% or more damaged.

Results: (see Figure) In the rostral areas, the animals in both normo groups sustained moderately severe and statistically similar damage. In the H-hypo group, ischemic injury was markedly attenuated. (Three animals were completely normal). In the caudal section, the damage was less severe than in the rostral areas. Again, damage did not differ between the H- and I-normo groups but was significantly less severe in the H-hypo group.

Conclusions: The data indicate that, in the circumstances of the present study, 1.3 MAC isoflurane was not cerebroprotective relative to an equi-MAC halothane control state but that mild hypothermia (by 3°C) markedly attenuated ischemic injury. The data suggest that the choice of volatile anesthetic may ultimately prove to be less relevant to cerebral protection than the application of mild hypothermia.

References: 1. Warner et al, *Anesthesiology* 64:19-23, 1986. 2. Milde et al, *Anesthesiology* 69:905-13, 1988. 3. Busto et al, *JCBFM* 7:729-38, 1987.

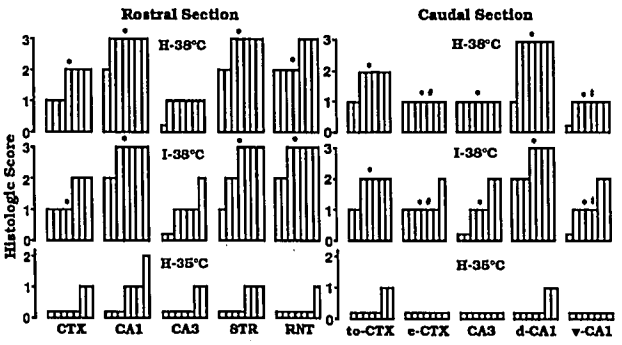

Figure: Histologic scores in five brain regions in rostral and caudal brain sections in H-normo, I-normo and H-hypo group animals.

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SEVOFLURANE REDUCES NEUROLOGIC DEFICIT FOLLOWING INCOMPLETE ISCHEMIA IN RATS

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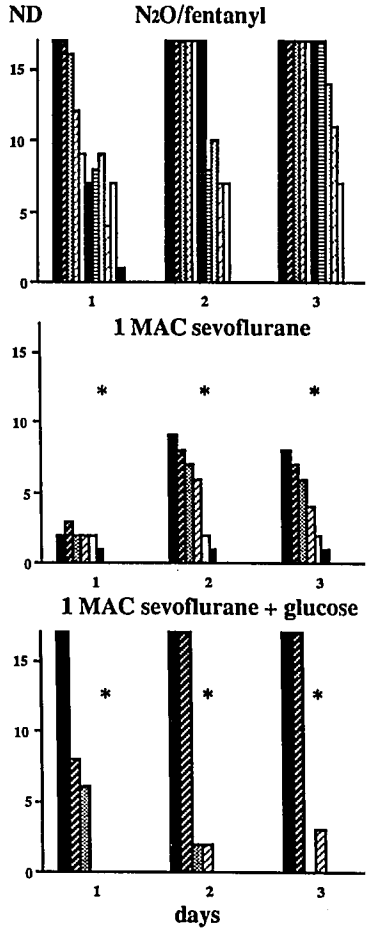
This study investigates the effects of sevoflurane on neurologic outcome following incomplete cerebral ischemia in rats.

Following institutional approval, 28 male Sprague-Dawley rats (430-490 g) were anesthetized, intubated and mechanically ventilated with isoflurane and 30 % O_2 in air. Catheters were inserted into the right femoral artery, both femoral veins and into the right jugular vein. At completion of surgery isoflurane was discontinued and the rats were allowed to equilibrate for 30 minutes according to the following protocol: Rats in group 1 (n=11) received N_2O/O_2 and fentanyl (bolus:10 µg/kg iv; infusion:25 µg/kg/h). Rats in group 2 (n=10) received 1 MAC sevoflurane in O_2 and air. Rats in group 3 (n=7) received 1 MAC sevoflurane in O_2 and air plus i.p. injection of 40 % glucose (6ml/kg). Ischemia was produced by combined unilateral carotid artery ligation and hemorrhagic hypotension to 35 mmHg for 30 minutes. Temperature, arterial blood gases and pH were maintained constant over time. Plasma glucose was assayed before, during and after ischemia. Neurologic deficit (ND) was evaluated for 3 days following ischemia using an 17 point performance scale with 0 = normal and 17 = stroke related death.



Arterial blood pressure was significantly lower before and higher after ischemia in both sevoflurane groups compared to controls. Plasma glucose was lower in sevoflurane anesthetized rats compared to N_2O/fentanyl anesthetized or glucose-loaded sevoflurane anesthetized rats. Fig. 1 shows ND for all groups over the 3 days examination period. Anesthesia with sevoflurane improved ND in both, normal and glucose-loaded rats compared to N_2O/fentanyl anesthetized controls (* = $p<0.001$).

The improved ND in glucose-loaded rats indicates that decreased plasma glucose is not the only mechanism by which sevoflurane reduces ischemic brain injury. Improvement of ND with sevoflurane anesthesia may be due to the cerebral depressant effects of sevoflurane.