

Title: CEREBRAL PROTECTION BY ISOFLURANE DURING HYPOXEMIA OR ISCHEMIA

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**Introduction.** Anesthetics may protect the brain in situations of impaired oxygen delivery to the extent that they can decrease cerebral metabolism ( $CMRO_2$ ). Thiopental, by abolishing neuronal electrical activity as evidenced by an isoelectric EEG, can reduce  $CMRO_2$  to 44% of normal and can provide some limited protection in situations of incomplete global ischemia.<sup>1,2</sup> Isoflurane is unique among the volatile anesthetics in that it can produce an isoelectric EEG at clinically applicable concentrations. Like thiopental, isoflurane produces a dose-related reduction in  $CMRO_2$  until the abolition of neuronal function.<sup>3</sup> The purpose of this study was to investigate possible cerebral protection afforded by isoflurane in two models in which barbiturates have been shown to provide limited protection.<sup>1,2</sup>

**Methods.** In the hypoxia study mice were exposed to room air or 1%, 1.4%, 2%, or 3% isoflurane in room air for 30 min prior to exposure to 5% oxygen in nitrogen. Survival time, the time from the initiation of the hypoxic gas flows to the cessation of respiration, was recorded for each animal. Differences in mean survival time between the control and isoflurane groups were analyzed by analysis of variance and a weighted Student's t-test for unpaired data.

The possible protective effects of isoflurane in incomplete global ischemia as produced by acute hemorrhagic hypotension was studied in 12 dogs. The animals were intubated and ventilated. Arterial cannulae were placed for pressure measurements, blood sampling and hemorrhage. EEG was recorded continuously. A craniotomy was performed to expose the cerebral hemispheres for cortical biopsies. The untreated group of six dogs was maintained on 70%  $N_2O$  in  $O_2$  while the other group was exposed to 3% isoflurane in 30%  $O_2$  and  $N_2$ . After a 20 min control period, the animals were bled to a MAP of 30 mmHg. Serial cerebral cortical biopsies were taken at 0.5, 1.5, 3, 5, 7, and 9 min after the onset of hypotension. Each specimen was analyzed for ATP, ADP, AMP, phosphocreatine, lactate, and pyruvate. Differences in cerebral metabolites between the 2 groups were analyzed by Student's t-test for unpaired data.

**Results.** In the hypoxic mouse study mean survival time of the control group was  $5.0 \pm 0.2$  min. Mean survival times of the groups exposed to 1.0% and 1.4% isoflurane were  $9.6 \pm 0.5$  and  $7.2 \pm 0.3$  min respectively, both significantly prolonged over the control group. The survival time of the group exposed to 2.0% isoflurane was similar to control, while the group exposed to 3.0% isoflurane had a significantly shortened survival time ( $3.0 \pm 0.25$  min).

In the canine ischemia study, the EEG remained

active in the untreated dogs. In the dogs exposed to 3% isoflurane the EEG pattern was one of electrical silence with rare spikes or bursts of high-amplitude slow waves superimposed. During the period of hypotension, cerebral ATP and PCr and the energy charge were maintained at a significantly higher level in the isoflurane group. Lactate accumulation increased 10 fold in the untreated group but was half that in the isoflurane group (Table 1).

**Discussion.** In the hypoxic mouse model low concentrations of isoflurane did prolong survival time significantly. Both cerebral metabolic depression and suppression of hypoxic convulsions could have contributed to this. The higher concentration of isoflurane may have decreased survival time through hypoventilation or hypotension. In the canine ischemia study 3% isoflurane abolished the energy requirement for neuronal activity so that energy was necessary only for maintenance of cellular integrity. Presumably this effect improved the brain's tolerance for decreased oxygen delivery during the period of hypotension, indicated by better maintenance of cerebral energy stores and less lactate accumulation. We conclude that clinical concentrations of isoflurane via the anesthetic effect on neuronal activity and consequent reduction in cerebral metabolism can, like barbiturates, provide some cerebral protection against hypoxemia or ischemia in situations of decreased oxygen delivery which are insufficient to abolish neuronal function.

# References

- Secher O, Wilhjelm B: The protective action of anesthetics against hypoxia. Can Anaes Soc J, 15: 423, 1968.
- Michenfelder JD, Theye RA: Cerebral protection by thiopental during hypoxia. Anesthesiology, 39: 510, 1973.
- Newberg LA, Milde JH, Michenfelder JD: The cerebral metabolic effects of isoflurane at and above concentrations which suppress neuronal electrical activity. (Unpublished data).

Cerebral tissue energy stores during the 9 min period of hemorrhagic hypotension

	ATP ( $\mu$ mol/g)		PCr ( $\mu$ mol/g)		EC		Lactate ( $\mu$ mol/g)	
	untreated	isoflurane	untreated	isoflurane	untreated	isoflurane	untreated	isoflurane
Normal *	$2.14 \pm 0.10$		$3.04 \pm 0.17$		$0.92 \pm 0.01$		$1.04 \pm 0.14$	
Time (minutes)								
0.5	2.03	2.10	2.51	3.13	0.89	0.92*	2.59	1.39*
1.5	1.87	2.01	1.78	2.74*	0.85	0.91*	4.31	1.75*
3.0	1.84	1.95	1.99	2.68	0.85	0.90*	6.12	2.65*
5.0	1.55	1.94	1.50	2.57*	0.77	0.87	6.89	3.27*
7.0	1.23	1.80*	1.04	2.36*	0.66	0.85*	10.79	5.22*
9.0	1.21	1.46	1.16	1.53	0.67	0.82*	11.07	5.14*

\* from a previous study<sup>13</sup>

Values are the mean for six dogs

\* Significantly different from the untreated groups ( $P < 0.05$ )