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The Effects of Sevoflurane on Cerebral Blood Flow, Cerebral Metabolic Rate for Oxygen, Intracranial Pressure, and the Electroencephalogram are Similar to Those of Isoflurane in the Rabbit

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The effects of 0.5 and 1.0 MAC end-tidal concentrations of sevoflurane on intracranial pressure, cerebral metabolic rate for oxygen, cerebral blood flow, and the electroencephalogram were compared to those of equi-MAC concentrations of isoflurane in rabbits anesthetized with morphine-nitrous oxide. At 1.0 MAC end-tidal level, both sevoflurane and isoflurane caused a significant reduction in cerebral metabolic rate for oxygen of about 50%. Neither anesthetic caused a significant change in global cerebral blood flow or cortical cerebral blood flow during either 0.5 or 1.0 MAC administration. However, both sevoflurane and isoflurane caused small but significant increases in intracranial pressure during 0.5 MAC and 1.0 MAC administration. The electroencephalogram of animals anesthetized with 1.0 MAC of either anesthetic demonstrated a burst suppression pattern with no evidence of spike or seizure activity. The data suggest that the effects of sevoflurane on cerebral blood flow, cerebral metabolic rate for oxygen, intracranial pressure, and the electroencephalogram are indistinguishable from those of equivalent concentrations of isoflurane in the rabbit. (Key words: Anesthetics, volatile: isoflurane; sevoflurane. Brain: blood flow; intracranial pressure; oxygen consumption.)

SEVOFLURANE (fluoromethyl 2,2,2-trifluoro-1-{trifluoromethyl}ethyl ether) is a pleasant-smelling volatile anesthetic with a blood/gas partition coefficient of 0.60.[1] Anesthetic induction with this agent is typically rapid and smooth.[2] Although sevoflurane is now being used clinically in Japan, the American company with the patent rights to sevoflurane has decided against marketing sevoflurane in the United States at this time. The main reasons for this are that sevoflurane is slightly unstable in the presence of soda lime or baralyme and releases fluoride ion *in vivo*.[3,4] Nonetheless, other characteristics of sevoflurane suggest that it may be an ideal anesthetic for use in neurosurgery, where its low blood-gas solubility coefficient could promote faster awakening and its non-irritating odor would be less likely to produce coughing or straining on induction or emergence. However, the cerebral effects of sevoflurane have not yet been adequately characterized in animal models. We, therefore, compared the effects of 0.5 MAC and 1.0 MAC of sevoflurane on intracranial pressure (ICP), cerebral blood flow (CBF), the cerebral metabolic rate for oxygen ($CMRO_2$), and the electroencephalogram (EEG) to the already extensively studied effects of isoflurane in the New Zealand white rabbit.

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Methods

Fourteen New Zealand white rabbits of either sex were anesthetized individually in a box with 4% halothane in oxygen. Following endotracheal intubation, halothane was discontinued and the animals were given a loading dose of morphine sulfate (MS), 10 mg/kg followed by an infusion of 2 $mg \cdot kg^{-1} \cdot h^{-1}$. Paralysis was maintained with a pancuronium (P) infusion of approximately 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$. This anesthetic technique has been previously described.[5] The animals were ventilated with 70% nitrous oxide (N_2O) in oxygen at a standard rate and tidal volume, and Pa_{CO_2} was maintained in the normal range at all times by adding CO_2 to the inspired gases. Following positioning in a stereotactic head frame, the surgical preparation was begun. All surgical incisions were preceded by infiltration of the operative site with 0.25% bupivacaine. An arterial catheter (PE 90) was positioned in the aorta *via* the left femoral artery for measurement of mean arterial pressure (MAP) and blood sampling for arterial blood gases (ABGs). The tissue atop the head was incised and reflected laterally to expose the skull. The sagittal sinus and confluence of sinuses were then exposed and a small catheter (PE-50) was placed directly into the saggital sinus for withdrawal of cerebral venous blood. CBF was measured with the hydrogen clearance technique.[6-8] Electrodes were stereotaxically placed in the sagittal sinus just posterior to the tip of the cerebral venous sampling catheter and in the parietal cortex bilaterally through small burr holes. $CMRO_2$ was determined as the product of CBF measured in the sagittal sinus and arterial/cerebral venous oxygen content difference. ICP was measured by placing a small needle through the atlanto occipital membrane into the cisterna magna. A bipolar fronto-occipital EEG was recorded at all times. Recorded variables included EEG,

TABLE 1. Mean Arterial Pressure, Blood Gas Values, and Angiotensin II Doses (Mean ± SD)

	MS/N_2O		0.5 MAC		1.0 MAC		MS/N_2O	
	Sevoflurane	Isoflurane	Sevoflurane	Isoflurane	Sevoflurane	Isoflurane	Sevoflurane	Isoflurane
MAP	94 ± 5	88 ± 10	90 ± 5	84 ± 8	91 ± 7	84 ± 7	95 ± 5	85 ± 9
pH	7.41 ± .06	7.48 ± .05	7.41 ± .04	7.46 ± .07	7.41 ± .05	7.46 ± .09	7.39 ± .06	7.42 ± .09
Pa_{CO_2}	38 ± 3	37 ± 3	37 ± 2	37 ± 1	37 ± 3	37 ± 2	37 ± 3	39 ± 3
Pa_{O_2}	151 ± 11	146 ± 14	146 ± 14	161 ± 16	144 ± 17	162 ± 14	148 ± 9	159 ± 21
Angio dose	Not required	Not required	.047 ± .026	.06 ± .06	.09 ± .07	.17 ± .16	Not required	Not required

MAP = mean arterial pressure; MAP, Pa_{O_2}, Pa_{CO_2} expressed in mmHg.

Angio = Angiotensin II, Angiotensin II doses expressed in $\mu g \cdot kg^{-1} \cdot min^{-1}$.

ICP, CBF (sagittal sinus and cortical), $CMRO_2$, temperature (servo-controlled to 37° C), mean arterial pressure (MAP), end-tidal (ET) CO_2, ET volatile anesthetic, and arterial blood gases.

Following the surgical preparation, animals were left undisturbed for 30 minutes. In all animals, this insured an ET halothane concentration of <.08%. However, it must be emphasized that the MS/N_2O anesthetic was continued at all times during the experiment. CBF was then measured and all variables recorded. Animals were randomly assigned to receive either isoflurane or sevoflurane (one agent/animal). The anesthetic was introduced over 10 min initially to achieve a 0.5 MAC ET¶ concentration. Once this level was achieved, 10 min was allowed to pass before measurements of CBF and $CMRO_2$ were repeated. The ET anesthetic level was then increased to 1.0 MAC for at least 10 min, and all measurements were repeated. During the period of volatile anesthetic administration, MAP was maintained at pre-volatile anesthetic levels with intravenously administered angiotensin II. Following measurements at 1.0 MAC, the volatile anesthetic was discontinued. Thirty minutes later, all measurements were repeated during the MS/N_2O background anesthetic only.

MAP, Pa_{O_2}, Pa_{CO_2}, *p*H, sagittal sinus CBF (SSCBF), cortical CBF, $CMRO_2$, and ICP were compared within groups with a repeated measures analysis of variance and corrected paired *t* tests where appropriate. The magnitude of the ICP changes within groups (MS/N_2O) was compared between groups with an unpaired *t* test. For all statistical comparisons, $P < .05$ was considered statistically significant.

Results

Pa_{O_2}, Pa_{CO_2}, *p*H, and MAP were not different within groups during any of the three anesthetic states (MS/N_2O, MS/N_2O + 0.5 MAC, MS/N_2O + 1.0 MAC) (table 1). Neither mean SSCBF nor cortical CBF were altered by the administration of either 0.5 or 1.0 MAC of either agent (table 2). However, three animals receiving sevoflurane did demonstrate approximately 50% increases in SSCBF, but not cortical CBF. $CMRO_2$, however, decreased with both 0.5 MAC and 1.0 MAC administration; the decrease during 1.0 MAC administration (approximately 50%) was statistically significant for both agents (fig. 1). ICP increased significantly during both 0.5 and 1.0 MAC administration of either anesthetic (fig. 2). ICP increases were seen in all animals, even in those animals in which measured SSCBF was lower during volatile anesthetic administration than during the MS/N_2O control period. The magnitude of the ICP increases was not different between groups. Following discontinuation of both anesthetics, ICP and $CMRO_2$ returned to pre-volatile anesthetic levels in all animals (figs. 1, 2). The EEG of animals equilibrated at 1 MAC of either agent demonstrated a burst suppression pattern which was indistinguishable by visual examination between groups (fig. 3).

TABLE 2. CBF and $CMRO_2$ Responses to Sevoflurane or Isoflurane (Mean ± SEM)

	MS/N_2O	0.5 MAC	1 MAC	MS/N_2O
CBF Responses				
Sagittal sinus				
Sevoflurane	74 ± 9	86 ± 16	95 ± 22	61 ± 11
Isoflurane	81 ± 12	78 ± 12	82 ± 10	71 ± 9
Cortex				
Sevoflurane	69 ± 8	67 ± 11	65 ± 11	67 ± 10
Isoflurane	72 ± 7	65 ± 8	59 ± 7	68 ± 7
$CMRO_2$ Responses				
Sevoflurane	5.29 ± 0.89	4.53 ± 0.70	2.49 ± 0.62*	4.72 ± 0.94
Isoflurane	5.95 ± 0.89	4.27 ± 0.76	3.01 ± 0.62*	5.88 ± 0.61

CBF = Cerebral blood flow expressed in ml blood · 100 grams of $brain^{-1} \cdot min^{-1}$; $CMRO_2$ = Cerebral metabolic rate for oxygen expressed in ml oxygen · 100 grams of $brain^{-1} \cdot min^{-1}$.

* Denotes significant change from control (MS/N_2O) value.

¶ MAC of isoflurane had been previously determined in our laboratory in the rabbit as 2.05%.[9] MAC of sevoflurane was determined to be 3.70% (unpublished observation)

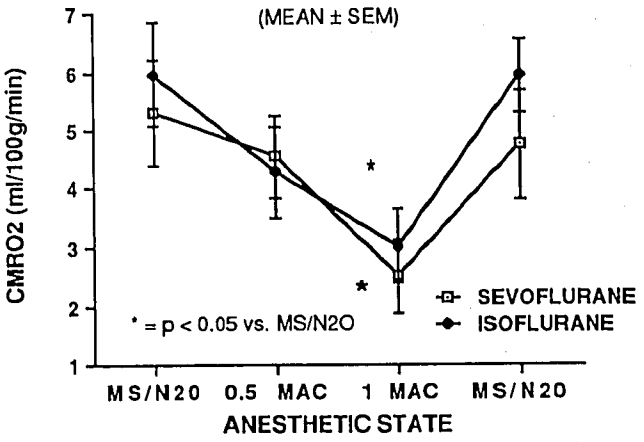

FIG. 1. $CMRO_2$ responses to sevoflurane or isoflurane. Asterisks denote significant change ($P < 0.05$) from control morphine/nitrous oxide state.

Discussion

The data demonstrate that the effects of sevoflurane on CBF, $CMRO_2$, ICP, and the EEG are similar to those of isoflurane when equipotent doses are compared in anesthetized rabbits.

The data obtained in the present study with isoflurane agree with previous studies in the rabbit, and other species as well.[5,10,11] That is, isoflurane does not alter CBF in concentrations of 1.0 MAC, but does predictably increase ICP and decrease $CMRO_2$. The effects of adding isoflurane to a MS/N_2O anesthetic on the EEG have been previously observed in our laboratory, and agree with the findings in the present study.[5]

The effects of sevoflurane on CBF and cerebral cortical oxygen consumption have been examined in isocapnic swine.[12,13] Manohar and Parks reported that 1 MAC sevoflurane decreased CBF compared to an awake non-anesthetized control state by approximately 20%, and that cerebral cortical O_2 consumption decreased by 50% during 1.0 MAC sevoflurane anesthesia. Unlike the present study, however, MAP was not maintained at pre-volatile anesthetic values, and this may explain why sevoflurane decreased CBF slightly in their model. The 50% reduction in cortical O_2 consumption agrees well with our finding of a 50% reduction in $CMRO_2$.

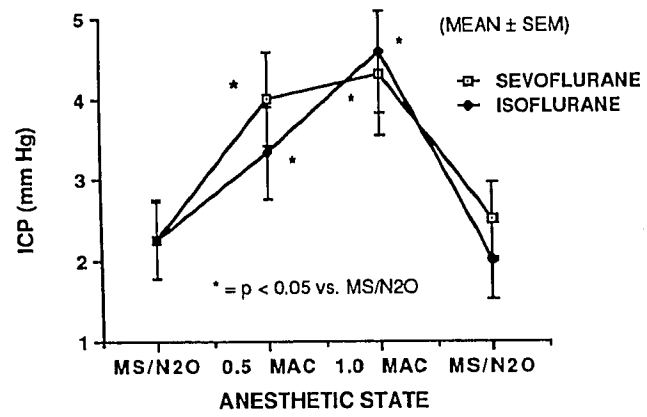

FIG. 2. ICP response to sevoflurane or isoflurane. Asterisks denote significant change ($P < 0.05$) from control morphine/nitrous oxide state.

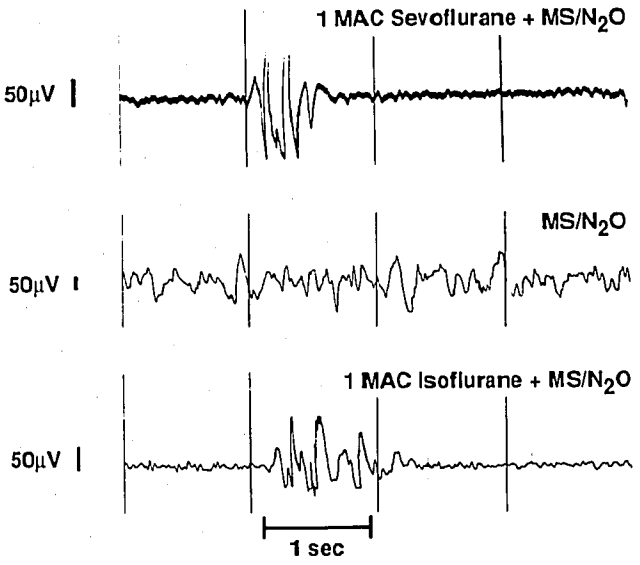

FIG. 3. EEG patterns representative of morphine/nitrous oxide, and either 1.0 MAC sevoflurane or isoflurane added to the morphine/nitrous oxide anesthetic.

It should also be emphasized that, although sevoflurane did not appear to alter CBF in the group as a whole in the present study, three animals did demonstrate increases in SSCBF (approximately 50%) in response to the administration of sevoflurane. In none of these animals did cortical CBF increase. This was not seen in the animals receiving isoflurane, and suggests that sevoflurane may increase subcortical CBF in some animals when administered under the conditions of this experiment.

As is the case with isoflurane, ICP increased during 0.5 and 1.0 MAC sevoflurane administration, despite no change in CBF. The magnitude of the ICP increases was not different between groups comparing ICP values recorded during the MS/N_2O control state with those recorded during either 0.5 or 1.0 MAC administration. Also, ICP increased in all animals receiving sevoflurane, and appeared unrelated to the individual animal's SSCBF response to the administration of sevoflurane. This may indicate that sevoflurane, like isoflurane, increases cerebral blood volume (CBV) independently of changes in CBF.[14,15]

A constant background anesthetic was necessary to insure that the acute effects of the administration of isoflurane and sevoflurane could be compared directly. The MS/N_2O anesthetic we selected provided a relatively high basal $CMRO_2$, suggesting that it is a "light" anesthetic state. The stability of the MS/N_2O anesthetic is attested to by the return of $CMRO_2$ and ICP to initial baseline values following discontinuation of the 1.0 MAC volatile anesthetic.

The determination of global $CMRO_2$ in this study, as the product of the arterial-cerebral venous oxygen content difference and CBF measured in the sagittal sinus (SSCBF), insured that the cerebral blood sampled for oxygen content traversed the same compartment from which the flow measurement was taken.[16] However, cortical CBF values during the MS/N_2O control state were nearly identical to those recorded in the confluence of sinuses, suggesting that the blood in the sagittal sinus was derived primarily from the cerebral cortices. The implication of this is that the 50% reduction of "global" $CMRO_2$ seen in the present study may primarily represent events in the cortex, rather than in whole brain. Further studies using more sensitive techniques, such as autoradiography, will be required to clarify regional flow-metabolism relationships during sevoflurane administration.

Small doses of angiotensin II were administered to support MAP at pre-volatile anesthetic levels to eliminate the possibility that differences in CBF or ICP responses to volatile anesthetic administration could be caused by volatile anesthetic-induced differences in MAP. The effects of angiotensin II on the cerebral vasculature are thought to be minimal.[17,18] Regardless of this, since both groups required similar doses of angiotensin II to maintain MAP, the effects should be similar in the two groups. Furthermore, the similarity of the angiotensin II doses at equi-MAC concentrations of isoflurane and sevoflurane suggests that sevoflurane and isoflurane are equally potent peripheral vasodilators or myocardial depressants in this model.

For the time being, it is unlikely that sevoflurane will be marketed in the United States. However, as its patent is due to expire soon, any company would then theoretically be able to manufacture and market sevoflurane, once approval of the Food and Drug Administration is obtained.

The present data indicate that the effects of sevoflurane on $CMRO_2$, ICP, CBF, and the EEG are similar to those of isoflurane in anesthetized rabbits, a drug that has already found wide acceptance in neuroanesthetic practice.

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