Anesthesiology
59:23–28, 1983

The Cerebral Metabolic Effects of Isoflurane at and above Concentrations that Suppress Cortical Electrical Activity

L. A. Newberg, M.D., J. H. Milde,† J. D. Michenfelder, M.D.‡*

The effects of 1.4–6.0% end-expired isoflurane on cerebral metabolism and hemodynamics were examined in dogs. A dose-related decrease in cerebral oxygen consumption (CMR_{O_2}) occurred until there was suppression of cortical electrical activity as reflected by the onset of an isoelectric electroencephalogram. This occurred at an end-expired concentration of 3% isoflurane when the mean CMR_{O_2} was 2.02 ml · 100 g^{-1} · min^{-1}. Thereafter, increasing concentrations of isoflurane to 6% had no further effect on the CMR_{O_2}. Brain biopsies taken at the end of the study revealed normal concentrations of ATP and phosphocreatine and a normal energy charge. Despite a normal cerebral energy state, there was a mild, dose-related, cerebral lactic acidosis (up to 2.84 μmol/g) that accompanied a mild systemic acidosis. It is concluded that the cerebral metabolic changes produced by isoflurane are secondary to an effect on cortical electrical activity, that abolition of this activity can be produced in dogs by a clinically relevant concentration of isoflurane (3%) without marked systemic hemodynamic effects, and that concentrations of isoflurane necessary to abolish cortical activity have no direct toxic effect on cerebral metabolic pathways. (Key Words: Anesthetics, volatile: isoflurane. Brain: blood flow; electroencephalogram; metabolism; oxygen consumption.)

PREVIOUS STUDIES from this laboratory[1,2] have suggested that anesthetics in clinical concentrations produce cerebral metabolic depression only to the extent that they alter cortical electrical activity. This has been demonstrated with thiopental, which produces a dose-related decrease in cerebral metabolism that is correlated to its effect on cortical electrical activity.[3] Thiopental has no apparent direct or toxic effect on the metabolic pathways necessary for the maintenance of cellular integrity.[3] However, halothane, in a concentration at (4.5%) and up to two times that sufficient to abolish cortical electrical activity (9.0%), produces a dose-related and presumably toxic alteration in oxidative phosphorylation.[4] Isoflurane is unique among the volatile anesthetics in that an isoelectric electroencephalogram (EEG) can be produced in man with a clinically relevant end-expired concentration (2.4%).[5] Like other volatile anesthetics, isoflurane produces a dose-related reduction in the cerebral metabolic rate.[6] This effect is nonlinear, the major decrease in metabolic rate occurring when the EEG changes from an "awake" to an "anesthetic" pattern.[7] The cerebral metabolic effects of higher concentrations of isoflurane, including that required to produce an isoelectric EEG, have not been investigated.

This study was designed to determine whether isoflurane, like thiopental, reduces cerebral metabolism only in relation to decreased cortical electrical activity or whether, like halothane, it has any direct toxic effects on cellular metabolic pathways. In a dog model similar to that used for the prior studies of thiopental and halothane, we examined the cerebral metabolic effects of progressively increasing concentrations of isoflurane, including that necessary to abolish cortical electrical activity (3%) to a maximum of twice the concentration necessary to suppress electrical activity (6%).

Methods

Cerebral metabolic studies were done in nine unmedicated fasting mongrel dogs weighing 13–17 kg. Anesthesia was induced and maintained with isoflurane, 1.4% end expired, in oxygen, 50%, and nitrogen. Succinylcholine (40 mg) was given intravenously to facilitate endotracheal intubation and continued thereafter at an infusion rate of 150 mg/h to maintain muscle paralysis. Ventilation was controlled by a Harvard pump, adjusted to maintain normocarbia. Cannulae were inserted into a femoral artery, for pressure measurements and blood sampling, and into a femoral vein for fluid and drug administration. Blood collected during the cerebral blood flow measurements was returned via the femoral vein. A peripheral intravenous catheter was placed for the administration of maintenance fluid, isotonic saline, infused at a rate of 75 ml/h. Esophageal and parietal epidural thermistor probes were placed to monitor temperature, which was maintained near 37°C with either heating lamps and pad or ice packs. Biparietal EEG was recorded continuously from electrodes cemented to the skull.

After heparinization (300–400 units/kg intravenously), the sagittal sinus was exposed, isolated, and cannulated as previously described[8] for direct measurement of cerebral blood flow (CBF) by a square-wave electromagnetic flow meter (EP 300 API, Carolina Medical Electronics).[9] The sagittal sinus primarily drains the anterior, superior, and lateral portions of the cerebral

* Research Fellow in Anesthesiology.
† Research Assistant.
‡ Professor of Anesthesiology.
Received from the Department of Anesthesiology, the Mayo Clinic, and the Mayo Medical School, Rochester, Minnesota. Accepted for publication January 4, 1983. Supported in part by Research Grant NS-07507 from the National Institute of Health, Public Health Service, and a grant from Ohio Medical Anesthetics.
Address reprint requests to Dr. Newberg: Mayo Clinic, Rochester, Minnesota 55905.

0003-3022/83/0700/0023 $01.10

TABLE 1. Hemodynamic and Metabolic Effects of Phenylephrine at 1.4% Isoflurane

	Control	Phenylephrine (11 ± 1 μg/min)	P
Pa_{O_2} mmHg	244 ± 7	260 ± 13	NS
Pa_{CO_2} mmHg	40 ± 1	41 ± 1	NS
pH units	7.36 ± 0.01	7.35 ± 0.01	NS
BB^+ mEq/l	44 ± 1	43 ± 0	NS
Pss_{O_2} mmHg*	62 ± 4	56 ± 2	NS
Hb g/dl	12.3 ± 0.7	12.9 ± 0.7	NS
Glucose mg/dl	110 ± 5	100 ± 6	NS
Lactate μmol/ml	2.0 ± 0.3	1.8 ± 0.1	NS
L/P	12 ± 0	14 ± 1	NS
MAP mmHg	107 ± 6	122 ± 5	<0.01
Heart rate beats/min	106 ± 17	109 ± 15	NS
CBF ml · 100 g^{-1} · min^{-1}	91 ± 10	68 ± 10.5	<0.01
CVR mmHg · ml^{-1} · 100 g · min	1.2 ± 0.1	2.0 ± 0.3	<0.02
CMR_{O_2} ml · 100 g^{-1} · min^{-1}	2.83 ± 0.11	2.84 ± 0.18	NS

Values are means ± SEM for five dogs.
P values obtained by Student's t test for paired data.
NS = not significant.
* Sagittal sinus blood P_{O_2}.

hemispheres, approximately 54% of the total brain weight.[10] Blood oxygen contents were calculated from measurement of oxyhemoglobin concentration (CO oximeter, IL 282) and oxygen tension (IL electrodes).[11] Blood glucose, lactate, and pyruvate contents were determined by standard enzymatic techniques.[12,13] Cerebral metabolic rates for oxygen (CMR_{O_2}) were calculated as the product of CBF and the arterial–sagittal sinus blood oxygen content difference. Cerebral vascular resistance (CVR) was calculated as the ratio of mean arterial pressure (MAP) to CBF. Inspired and end-expired concentrations of isoflurane were measured with an infrared analyzer (Beckman Medical Gas Analyzer LB-2) calibrated for isoflurane.

In five dogs, control values were obtained with 1.4% end-expired isoflurane. Mean values for CBF, CMR_{O_2}, and CVR were calculated from 6–11 sequential measurements repeated at intervals of 3–4 min. Mean values for blood glucose, lactate, and pyruvate concentrations were obtained from three sequential measurements at 10-min intervals. Because pilot studies had revealed the necessity for phenylephrine support of the blood pressure in the dogs exposed to the greater concentrations of isoflurane (>3%), the same five dogs were given phenylephrine as a continuous infusion in a dose sufficient to raise the MAP approximately 15 mmHg (mean dose = 11 ± 1 μg/min). Control values then were repeated as above for comparison.

Following control measurements, the isoflurane was increased abruptly to 3% end expired and then to 6% end expired. After each step increase in isoflurane, measurements were repeated at 5-min intervals over a 30-min period for determination of CBF, CVR, and CMR_{O_2}, and at 15-min intervals for blood glucose, lactate, and pyruvate concentrations. At 3% isoflurane, MAP was maintained above 70 mmHg with the transfusion of dextran 75 (mean = 50 ml) and infusion of phenylephrine (mean = 19 μg/min), amounts that did not differ significantly from those used with 1.4% isoflurane. At 6% isoflurane, increases in dextran 75 transfusion (mean = 280 ml) and phenylephrine infusion (mean = 66 μg/min) were required for maintenance of the same MAP.

To evaluate the possibility that cardiopulmonary bypass (CPB), which was necessary to support circulation in the previous studies of thiopental and halothane, might introduce artifactual cerebral effects, a sixth dog was placed on partial cardiopulmonary bypass using the technique as described in the previous studies.[3,4] Control measurements and step increases in isoflurane were as in the other five dogs. Partial bypass was initiated with a flow of 1.47 $l \cdot min^{-1} \cdot m^2$. Because of marked vasodilation observed on partial CPB, the MAP could be maintained only by increasing the bypass flow rates (to a maximum of 2.9 $l \cdot min^{-1} \cdot m^2$ at 6% isoflurane), performing a transfusion of 1500 ml dextran 75, and increasing the phenylephrine infusion to 150 μg/min at 6% isoflurane. Because of the difficulties encountered in maintaining this one dog and because of the gross nonphysiologic interventions that were required to do so, additional studies using CPB were abandoned.

In three additional dogs, the effects of isoflurane at concentrations other than 3 and 6% were examined. Control values were obtained at 1.4% end-expired isoflurane, while the animals received 9–12 μg/min phenylephrine as a constant infusion. Thereafter, increases in isoflurane were accomplished in one to three steps ranging from 3 to 5.5% end-expired isoflurane. Measurements were obtained at each step as above.

In each of the nine studies, after the last measurements were obtained, the dura overlying the cerebral hemispheres was excised and four sequential cerebral

TABLE 2. The Effect of Isoflurane on Systemic Blood Values and Hemodynamics

	End-expired Concentration of Isoflurane		
	1.4%	3%	6%
Pa_{O_2} mmHg	271 ± 13	267 ± 8	277 ± 9
Pa_{CO_2} mmHg	40 ± 1	38 ± 1	38 ± 1
*p*H units	7.38 ± 0.02	7.40 ± 0.02	7.32 ± 0.03*
BB^+ mEq/l	44 ± 1	45 ± 1	40 ± 1*
Hb g/dl	14.0 ± 0.3	13.9 ± 0.8	12.2 ± 0.3†
Glucose mg/dl	99 ± 6	87 ± 5	121 ± 22
Lactate μmol/ml	3.13 ± 0.5	2.70 ± 0.4	3.96 ± 0.6
Pyruvate μmol/ml	0.221 ± 0.032	0.167 ± 0.018†	0.153 ± 0.012*
L/P	14 ± 1	17 ± 2	25 ± 2†
MAP mmHg	112 ± 8	85 ± 4†	77 ± 3†
Brain temp °C	37.0 ± 0	37.0 ± 0	37.0 ± 0
Phenylephrine μg/min	11 ± 1	19 ± 3	66 ± 11*

Mean ± SEM in six dogs.
* Significantly different from 1.4% and 3% value $P < 0.05$.
† Significantly different from 1.4% and 3% value $P < 0.05$.

cortical biopsy specimens were taken at 2-min intervals.[14] Each sample was analyzed as described by Lowry *et al.*[15] for adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) for calculation of the energy charge (EC),[16] and for phosphocreatine (PCr), glucose, lactate, and pyruvate.

In the six dogs exposed to 1.4, 3, and 6% isoflurane, values were compared at each concentration by analysis of variance, and significant differences were tested by the Bonferroni *t* test for paired data. Regression equations relating cerebral concentrations of ATP, PCr, and lactate; the cerebral energy charge; and the cerebral lactate/pyruvate ratio (L/P) to end-expired isoflurane concentrations were calculated by the method of least squares. Cerebral concentrations of metabolites at each isoflurane concentration were also compared with normal values from a previous study[9] by Student's *t* test for unpaired data. Systemic and cerebral values obtained at 1.4% isoflurane before and after the administration of phenylephrine were compared and significant differences were identified by Student's *t* test for paired data.

Results

The hemodynamic and metabolic effects produced by phenylephrine during the control period are summarized in table 1. There was no change in the arterial blood gases, glucose, acid-base status, or hemoglobin. The mean 15 mmHg increase in MAP produced by phenylephrine was reflected in a markedly increased CVR, while CBF fell. However, phenylephrine produced no change in the CMR_{O_2}.

In the only dog done with partial cardiopulmonary bypass, the increased requirement for fluid and phenylephrine to support the MAP did not affect the cerebral hemodynamic and metabolic variables, and these data were combined, therefore, with the data from the five dogs studied without cardiopulmonary bypass.

In these six dogs, throughout the exposure to isoflurane, the arterial blood gases remained unchanged, although a mild metabolic acidosis occurred at 6% isoflurane as indicated by significant decreases in pH, buffer base, and pyruvate and an increase in the L/P ratio (table 2). The MAP progressively decreased, despite increases in the infusions of phenylephrine and Dextran 75, the latter producing a significant hemodilution at 6% isoflurane.

With increasing concentrations of isoflurane, the CMR_{O_2} decreased until an abrupt change in the EEG was observed. Consistently, at an end-expired concentration of 3%, the EEG changed from the high-amplitude slow wave pattern of deep anesthesia to either an

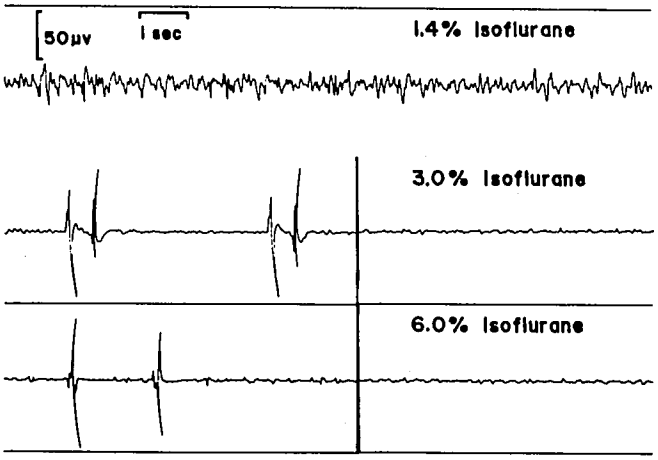

FIG. 1. EEG in a single dog during the administration of 1.4%, 3%, and 6% end-expired isoflurane. An EEG pattern of deep anesthesia can be seen during 1.4%. At 3% and 6% isoflurane, rhythmic spikes separated by periods of isoelectric silence (left) or an isoelectric EEG (right) occur.

TABLE 3. The Effect of Isoflurane on Cerebral Metabolism and Circulation

	End-expired Concentration of Isoflurane		
	1.4%	3%	6%
CMR_{O_2} (ml·100 g^{-1}·min^{-1})	2.81 ± 0.12	2.02 ± 0.12*	2.05 ± 0.06*
CBF (ml·100 g^{-1}·min^{-1})	63 ± 9.1	64 ± 8.7	67 ± 5.2
CVR (mmHg·ml^{-1}·100 g·min)	2.00 ± 0.3	1.45 ± 0.19	1.18 ± 0.1*
Pss_{O_2} (mmHg)†	57 ± 6	65 ± 5	67 ± 3

Mean ± SEM for six dogs.
* Significantly different ($P < 0.05$) from 1.4% value.
† Sagittal sinus blood P_{O_2}.

isoelectric EEG or an isoelectric pattern with superimposed spikes occurring at a rate of 10–60/min (fig. 1). In individual dogs, at and above isoflurane concentrations of 3%, either or both of these patterns were variably observed but did not correlate with any change in CMR_{O_2}. Once the change in EEG occurred (at 3% isoflurane), increasing concentrations to as high as 6% isoflurane did not alter the CMR_{O_2}. The "basal" CMR_{O_2} produced at 3% isoflurane was 2.02 ml·100 g^{-1}·min^{-1} and at 6% isoflurane was 2.05 ml·100 g^{-1}·min^{-1} (table 3, fig. 2).

The CBF remained constant (63–67 ml·100 g^{-1}·min^{-1}) at all concentrations of isoflurane, despite a decrease in MAP from 112 to 77 mmHg; accordingly, the CVR also decreased from 2.00 to 1.18 mmHg·ml^{-1}·100 g·min (table 3). The adequacy of cerebral oxygen delivery was reflected by the maintenance of the CBF and high oxygen tensions in the sagittal sinus blood (table 3).

A normal cerebral metabolic state was demonstrated at the end of the study by the cerebral tissue assays for ATP and PCr and by the calculated energy charge (EC) (table 4). However, increasing concentrations of isoflurane produced a mild dose-related cerebral lactic acidosis up to 2.84 μmol/g at 6% (fig. 3).

Discussion

In previous studies done in this laboratory, a constant infusion of thiopental produced a dose-related reduction in CMR_{O_2} until the onset of an isoelectric EEG, indicative of cessation of cortical electrical activity. At a mean dose of 72 ± 10 mg/kg thiopental, the CMR_{O_2} reached a plateau at 2.2 ml·100^{-1}·min^{-1}. Thereafter, doubling the infusion rate to a mean total dose of 177 ± 10 mg/kg thiopental did not further alter CMR_{O_2} or adversely affect the cerebral energy state.[3] However, this relationship of CMR_{O_2} to EEG activity is not common to all anesthetics. Halothane is the only volatile anesthetic that has been examined at clinical concentrations and at concentrations sufficient to abolish electrical activity (4.5%).[4] Unlike doubling thiopental, doubling the halothane concentration (9%) produced a dose-related decrease in CMR_{O_2} to 1.4 ml·100 g^{-1}·min^{-1} that was unrelated to cortical electrical activity. At the greater concentrations, oxidative phos-

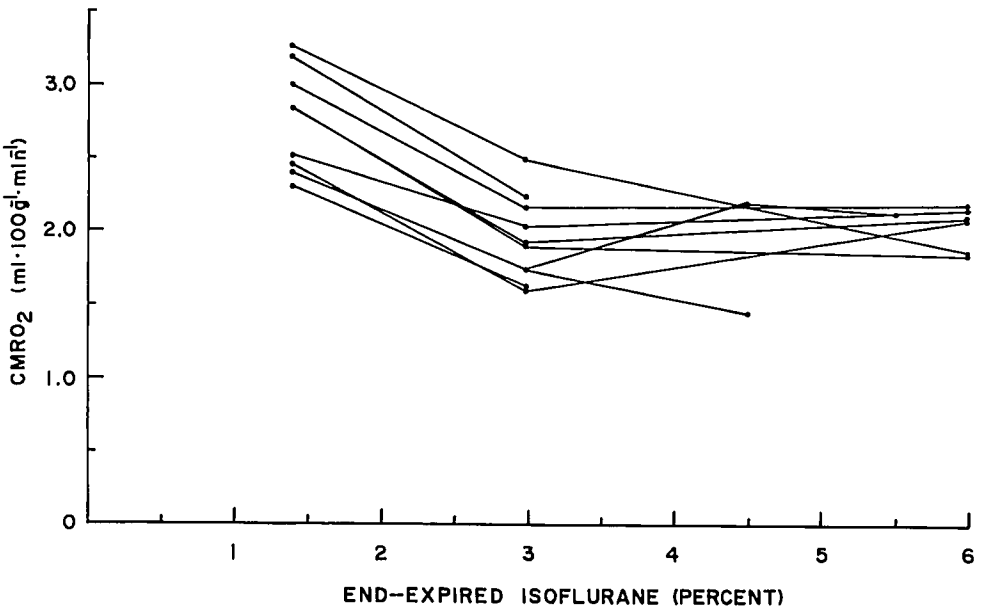

FIG. 2. Individual CMR_{O_2} values obtained at increasing concentrations of isoflurane. EEG activity abruptly changed at 3% isoflurane.

TABLE 4. Brain Biopsy Values Following Exposure to Isoflurane

	PCr (μmol/g)	ATP (μmol/g)	EC	Lactate (μmol/g)	L/P
Control (n = 7)*	3.07 ± 0.17	2.14 ± 0.10	0.92 ± 0.01	1.04 ± 0.14	17 ± 1
3% isoflurane (n = 1)	3.32	1.99	0.94	0.95	13
4.5% isoflurane (n = 1)	3.91	2.13	0.94	1.78	15
5.5% isoflurane (n = 1)	3.58	2.19	0.94	2.73	22
6% isoflurane (n = 6)	3.41 ± 0.13	2.13 ± 0.07	0.93 ± 0.004	2.84 ± 0.27†	20 ± 4

Mean ± SEM.
* Normal values without exposure to isoflurane from a previous study.[9]
† Statistically different from control $P < 0.05$.

phorylation was altered, as demonstrated by progressive decreases in the cerebral tissue concentrations of ATP and phosphocreatine and large increases in cerebral lactate to 15 μmol/g. *In vitro* studies have also demonstrated that halothane (>2%) directly altered mitochondrial electron transport and respiratory control.[17]

The purpose of this study was to determine the cerebral metabolic effects of isoflurane at the concentration and at double the concentration that abolishes cortical electrical activity as reflected by the EEG. In man, electrical activity ceases at an alveolar concentration of 2.4% isoflurane.[5] This study demonstrates that in dogs a flat EEG (with or without superimposed spikes) occurs at an end-expired concentration of 3% isoflurane.

Isoflurane progressively decreased the cerebral metabolic rate for oxygen only until cortical electrical activity ceased as evidenced by an isoelectric EEG. Despite doubling the concentrations of isoflurane to 6% (end expired), CMR_{O_2} was maintained at a constant rate, the "basal" rate presumably required for the maintenance of cellular integrity. This basal metabolic rate (2.05 ml · 100 $g^{-1} \cdot min^{-1}$) was similar to that obtained in dogs when thiopental abolishes EEG activity (2.2 ml · 100 $g^{-1} \cdot min^{-1}$),[3] to that calculated from rates of cerebral ATP depletion and lactate accumulation in dogs during the initial minutes of complete cerebral anoxia (2.0 ml · $100^{-1} \cdot min^{-1}$),[1] and to *in vitro* CMR_{O_2} values reported for unstimulated human gray matter (2.2 ml · 100 $g^{-1} \cdot min^{-1}$).[18]

There was no evidence that isoflurane altered normal oxidative phosphorylation. The cerebral energy stores of ATP and PCr and the energy charge remained constant and within normal limits for each concentration of isoflurane. There was a small dose-related increase in cerebral lactate levels, although the greatest lactate (2.84 μmol/g) was markedly less than that observed with high halothane concentrations (7–15 μmol/g). This was accompanied by a mild systemic acidosis, which possibly accounted for the cerebral lactic acidosis. Thus, it appears that in concentrations necessary to suppress cortical electrical activity, isoflurane, unlike halothane but like thiopental, has no direct toxic effect on cerebral metabolism.

Isoflurane is a recognized potent systemic vasodilator and can produce a dose-related fall in MAP. In the present study, at concentrations of isoflurane above 3%, maintenance of MAP > 70 mmHg required infusion of phenylephrine. Phenylephrine has been used in clinical studies of isoflurane to maintain the MAP.§ It was reported previously to have no effect on CBF[19] and CMR_{O_2}[20] and also was used in a study of cerebral autoregulation.[21] A comparison of cerebral values at 1.4% end-expired isoflurane in this study before and after the infusion of phenylephrine demonstrated a significant decrease in CBF with an increase in CVR during the phenylephrine infusion. However, CMR_{O_2} remained unchanged.

The EEG changes were notable with increasing concentrations of isoflurane. At 3% end-expired isoflurane, the EEG pattern changed abruptly to an isoelectric pattern or an isoelectric pattern with superimposed rhythmic high amplitude spikes occurring 10–60 per minute. The spikes did not appear in all dogs and were not related to isoflurane concentration or CMR_{O_2}. There was no spike response to hand clapping, no EEG seizure activity, and no motor activity (in dogs not receiving succinylcholine). This pattern is similar to that reported by Joas *et al.*,[22] who detected spiking activity at 3.0–3.7% end-expired isoflurane in hyperventilated dogs. The significance of the spike pattern is unknown. It has been demonstrated with other fluorinated ethers (methoxyflurane and fluroxene) and has been demonstrated in dogs, cats, and humans.[5] Whether this represents direct cortical irritation by isoflurane, cortical irritability secondary to suppression of ascending inhibitory pathways from the midbrain, or midbrain irritability superimposed on an isoelectric cortex is unknown. Possibly, the appearance of the spikes does represent a nonspecific toxic effect of isoflurane, the metabolic or functional consequences of which were not demonstrable by this study.

The cerebral metabolic rates for oxygen measured at 1.4% and at 3% end-expired isoflurane did not differ

§ Murphy FL, Kennel EM, Johnstone RE, et al: The effects of enflurane, isoflurane, and halothane on cerebral blood flow and metabolism in man, Abstracts of Scientific Papers. Annual Meeting of the American Society of Anesthesiologists, 1974, p 61.

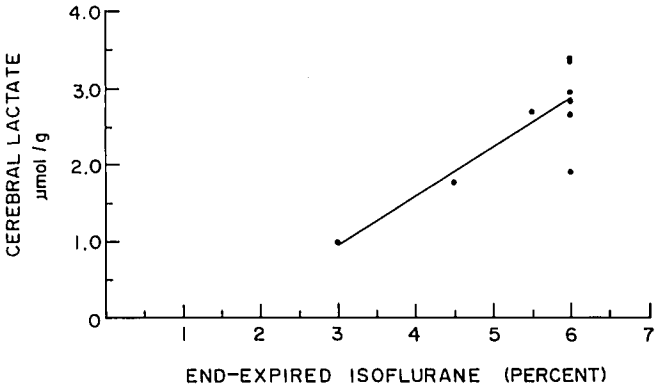

FIG. 3. Cerebral tissue lactate concentration obtained at the final isoflurane concentration, with the calculated linear regression line. Cerebral lactate concentration = 0.64% (end-expired isoflurane) + 0.98. R = 0.82

significantly from those reported in a 1977 study from this laboratory using the same dog model.[7] However, the CMR_{O_2} at 1.4% in both of these studies was significantly less than that reported in a 1974 study.[6] Reasons for this discrepancy are not obvious but possibly include less accurate measurement of isoflurane concentrations in the earlier study, differences in surgical techniques, or the effect in the earlier study of a period of relative awakefulness with increased circulating catecholamines on cerebral metabolism. Whatever the reason for the discrepancy, this again emphasizes the potential error in using historic controls for comparison purposes.

The present results demonstrate that suppression of cortical electrical activity and maximal nontoxic depression of CMR_{O_2} can be produced in dogs at 3% end-expired isoflurane. Like thiopental, but unlike halothane, greater concentrations (up to two times) do not further alter CMR_{O_2} and have no adverse effect on the cerebral energy state. If these observations can be extrapolated to man, maximal nontoxic CMR_{O_2} depression should occur at 2.4% end-expired isoflurane,[5] a concentration that is tolerated hemodynamically by normal man.[23,24]

Assuming that cerebral metabolic depression without toxicity relates to brain protection, a potential clinical use of isoflurane is that of cerebral protection in circumstances currently cited as appropriate for barbiturate therapy.

References

1. Michenfelder JD, Theye RA: The effects of anesthesia and hypothermia on canine cerebral ATP and lactate during anoxia produced by decapitation. ANESTHESIOLOGY 33:430–439, 1970
2. Michenfelder JD, Theye RA: Cerebral protection by thiopental during hypoxia. ANESTHESIOLOGY 39:510–517, 1973
3. Michenfelder JD: The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. ANESTHESIOLOGY 41:231–236, 1974
4. Michenfelder JD, Theye RA: In vivo toxic effects of halothane on canine cerebral metabolic pathways. Am J Physiol 229:1050–1055, 1975
5. Stockard JJ, Bickford R: The neurophysiology of anesthesia, A Basis and Practice of Neuroanesthesia. Edited by Gordon E. Amsterdam, Excerpta Medica, 1975, pp 3–46
6. Cucchiara RF, Theye RA, Michenfelder JD: The effects of isoflurane on canine cerebral metabolism and blood flow. ANESTHESIOLOGY 40:571–574, 1974
7. Stulken EH Jr, Milde JH, Michenfelder JD, Tinker JH: The nonlinear responses of cerebral metabolism to low concentrations of halothane, enflurane, isoflurane, and thiopental. ANESTHESIOLOGY 46:28–34, 1977
8. Michenfelder JD, Messick JM Jr, Theye RA: Simultaneous cerebral blood flow measured by direct and indirect methods. J Surg Res 8:475–481, 1968
9. Artru AA, Michenfelder JD: Canine cerebral metabolism and blood flow during hypoxemia and normoxic recovery from hypoxemia. Journal of Cerebral Blood Flow and Metabolism 1:277–283, 1981
10. Takeshita H, Michenfelder JD, Theye RA: The effects of morphine and N-allyl-normorphine on canine cerebral metabolism and circulation. ANESTHESIOLOGY 37:605–612, 1972
11. Theye RA: Calculation of blood O_2 content from optically determined Hb and HbO_2. ANESTHESIOLOGY 33:653–657, 1970
12. Bergmeyer HV: Methods of Enzymatic Analysis. New York, Academic Press, 1974, p 1196
13. Lowry OH, Passoneau JV: A Flexible System of Enzymatic Analysis. New York, Academic Press, 1972, pp 194–195
14. Kramer RS, Sanders AP, Lesage AM, Woodhall B, Sealy WC: The effect of profound hypothermia on preservation of cerebral ATP content during circulatory arrest. J Thorac Cardiovasc Surg 56:699–709, 1968
15. Lowry OH, Passoneau JV, Hasselberger FX: Effect of ischemia or known substrates and cofactors of the glycolytic pathway in brain. J Biol Chem 239:18–30, 1964
16. Atkinson DE: The energy charge of the adenylate pool as a regulatory parameter. Interaction with feedback modifiers. Biochemistry 7:4030–4034, 1968
17. Cohen PJ: Effects of anesthetics on mitochondrial function. ANESTHESIOLOGY 39:153–164, 1973
18. McIlwain H: Biochemistry and the Central Nervous System. Third edition. Boston, Little, Brown, and Company, 1966, pp 36–47
19. Chikovani O, Corkill G, McLeish I, Ong S, Beilin D: Effect on canine cerebral blood flow of two common pressor agents during prolonged halothane anesthesia. Surg Neurol 9:211–213, 1978
20. Smith AL, Wollman H: Cerebral blood flow and metabolism: effects of anesthetic drugs and techniques. ANESTHESIOLOGY 36:378–400, 1972
21. Smith AL, Neigh JL, Hoffman JC, Wollman H: Effects of general anesthesia on autoregulation of cerebral blood flow in man. J Appl Physiol 29:665–669, 1970
22. Joas TA, Stevens WC, Eger EI: Electroencephalographic seizure activity in dogs during anesthesia. Br J Anaesth 43:739–745, 1971
23. Stevens WC, Cromwell TH, Halsey MJ, Eger EI, Shakespeare TF, Bahlman SH: The cardiovascular effects of a new inhalation anesthetic, Forane®, in human volunteers at constant arterial carbon dioxide tension. ANESTHESIOLOGY 35:8–16, 1971
24. Tarnow J, Bruckner JB, Eberlein HJ, Hess W, Patschke D: Haemodynamics and myocardial oxygen consumption during isoflurane (Forane) anaesthesia in geriatric patients. Br J Anaesth 48:669–675, 1976