Anesthesiology
66:453-464, 1987

A Comparison of the Cerebral Protective Effects of Isoflurane and Barbiturates during Temporary Focal Ischemia in Primates

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Isoflurane has protective properties during experimental global brain ischemia or hypoxia. However, this has not been evaluated in the more common case of focal ischemia, *e.g.*, as caused by middle cerebral artery occlusion (MCAO). The authors therefore compared the effects of isoflurane, thiopental, and N_2O/fentanyl anesthesia on neurologic and neuropathologic outcome in baboons subjected to 6 h of transorbital left MCAO. Prior to MCAO, animals were assigned to one of three groups: Group 1 (n = 7) received isoflurane (in O_2/air) in concentrations sufficient to maintain deep burst suppression on the EEG (2.0% ± 0.5% inspired, mean ± SD); group 2 (n = 6) received thiopental (O_2/air) in doses adequate to maintain similar EEG suppression (3.6 ± 0.7 g total); and group 3 (n = 6) received 60% N_2O/40% O_2 and fentanyl (25 μg/kg load, 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion). Efforts were made to keep mean arterial pressure (MABP) between ≈80 and 100 mmHg, using nitroprusside/hydralazine or phenylephrine/metaraminol, with Pa_{CO_2} at ≈30 mmHg. The selected anesthetic was established 45 min before MCAO, was maintained until 1 h after clip removal, and in decreasing concentrations for 5 h. Neurologic status was scored for 7 days and formalin-fixed brains were later sectioned for determination of infarction volume. Six of seven group 1 (isoflurane) animals were hemiplegic, and 7/7 had verified infarctions. By contrast, 4 of 6 group 2 (thiopental) animals were normal, with 2/6 having infarctions. Outcome in group 3 (N_2O/fentanyl) was intermediate between groups 1 and 2 (3/6 hemiplegic, 4/6 with infarctions). Differences in the infarction rates between groups 1 and 2 was significant ($P < 0.05$), while a similar comparison of neurologic outcome scores achieved a P value of 0.055. Infarctions in group 1 were more hemorrhagic in character than in group 3 (groups 1 and 2 could not be meaningfully compared). These results must be considered in light of differences in MABP during the occlusion period; MABP in group 1 was ≈80 mmHg in spite of vasopressor use, while that in group 2 was ≈100 mmHg (in spite of vasodilators). Nevertheless, they fail to demonstrate any protective value of isoflurane anesthesia, at least when compared with thiopental. (Key words: Anesthesia, neurosurgical. Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: thiopental; fentanyl. Anesthetics, volatile: isoflurane. Brain: EEG; evoked potentials. Brain ischemia: protection. Monitoring: electroencephalagram; evoked potentials. Surgery, cerebrovascular.)

This paper is accompanied by an editorial. Please see: Michenfelder JD: Does isoflurane aggravate regional cerebral ischemia? ANESTHESIOLOGY 66:451-452, 1987.

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Received from the Divisions of Neurological Surgery, Neurology, and Neuropathology, Barrow Neurological Institute, Phoenix, Arizona, and the Department of Anesthesiology, Neuroanesthesia Research University of California, San Diego School of Medicine, La Jolla, California. Accepted for publication November 14, 1986.

The views of the authors are their own and are not to be construed as reflecting the position of the Department of the Army or the Department of Defense.

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IN 1983, NEWBERG AND MICHENFELDER reported that isoflurane anesthesia prolonged survival time in mice subjected to severe hypoxia, and also slowed the development of cerebral ischemic changes (lactate accumulation, ATP depletion, etc.) during severe hemorrhagic hypotension in dogs.[1] Based upon these and other studies, it has been suggested that isoflurane may provide some degree of clinically useful cerebral protection.[1-5] If this were proven to be true, isoflurane would be a valuable agent for cerebrovascular surgery because its effects might be more easily titrated and reversed than those of intravenous drugs, such as the barbiturates. However, available animal experiments with isoflurane have dealt only with models of global cerebral ischemia or hypoxia. In contrast, most neurosurgical procedures entail a risk of focal ischemia (*e.g.*, carotid endartectomy, aneurysm clippings, etc.), and there are problems associated with extrapolating results obtained with one form of ischemia to another. For example, halothane anesthesia increases hypoxic survival in mice,[6] reduces cerebral metabolism,[3,7] and slows hemispheric metabolic deterioration during trimethaphan-induced hypotension (in the presence of carotid occlusion[8]). However, it is associated with larger infarcts and poorer neurologic outcome in models of focal ischemia.[9,10] Therefore, before isoflurane is employed for protective purposes during neurosurgery, it is imperative that its effects be examined during relevant circumstances.

With these considerations in mind, we have employed a model of focal cerebral ischemia,[11-13] produced by the temporary (6 h) transorbital occlusion of the proximal middle cerebral artery (MCA) in baboons, to evaluate the effects of deep isoflurane anesthesia on neurologic outcome and infarct size. The results obtained in these animals were compared with those observed in animals anesthetized with thiopental, and with a N_2O/fentanyl combination.

Methods

Nineteen wild-captured adult male baboons (Papio anubis, Charles River Research Primates, P.O. Box 416, Port Washington, New York, 11050) weighing 17–24 kg (21.4 ± 1.6 kg, mean ± SD) were studied. The animals were examined by a veterinarian upon arrival in Phoenix, and again as needed. Routine chemistries and blood counts were obtained, the animals were screened for parasites and tuberculosis, and were housed in quarters that met American Association for Accreditation of Laboratory Animal Care (ALAC) approval. All experiments were approved by the Animal Welfare Committee of the Barrow Neurological Institute. The animals were allowed free access to water and food (Wayne Monkey Diet, Continental Grain Company, Chicago, Illinois), with supplemental feedings of fresh fruit. Preoperatively, all animals were judged to be normal by the same neurologist who scored them after occlusion. Both food and water were withheld for 12 h prior to use of the animal.

On the morning of the experiment, each animal was sedated with an intramuscular dose of ketamine (100–200 mg) and acepromazine (5–10 mg) to allow removal from the cage and insertion of a peripheral intravenous catheter in a saphenous vein. Anesthesia was then induced with approximately 8 mg/kg of thiopental, and an intravenous infusion of normal saline was started (1 l of normal saline was administered during the first hour of the study. The rate was then decreased to maintain a total of 80 ml/h thereafter [including fluids given as catheter flushes, for cardiac output determinations, and as drug infusions]). An oral endotracheal tube was placed by direct vision, pancuronium bromide (4 mg) was administered intravenously, and mechanical ventilation was begun with a tidal volume of 400 ml and a rate adjusted to initially maintain Pa_{CO_2} = 33–38 mmHg, using an inspired gas mixture of 1.5% isoflurane in 60% N_2O/O_2. A single 1 g dose of cephapirin was given intravenously. The left femoral artery and vein were then percutaneously catheterized and a Swan-Ganz™ catheter was advanced from the femoral vein into the pulmonary artery. (Note: left-sided vessels were chosen to avoid the possible complication of a "false" right lower extremity paresis secondary to nerve injury [since left MCA occlusion would be expected to lead to a right hemiparesis/plegia.]) Both catheters were continuously flushed with heparin-free saline to maintain patency, and the catheter insertion sites were infiltrated with 0.5% bupivacaine. The animal was then turned prone and the head fixed in a stereotactic frame (sphinx position, interaural line approximately 12 cm above the mid-chest). The inspired concentration of isoflurane was decreased to 0.8% (in the same 60% N_2O/40% O_2 mixture), and gold cup electrodes were affixed to the shaven scalp for acquisition of EEG and evoked potential response signals (see below).

Using sterile technique, the MCA was approached through the left orbit after infiltration with 1% lidocaine containing 1:200,000 epinephrine. The intraorbital contents were removed and hemostasis was achieved with bipolar coagulation and bone wax. Pa_{CO_2} was then reduced to ≈30 mmHg by increasing respiratory rate, and a portion of the posterolateral wall of the orbit adjacent to the optic canal and superior orbital fissure was removed with a drill. After complete hemostasis was confirmed, the dura and arachnoid were incised to expose the proximal portion of the MCA, and arachnoidal adhesions surrounding the vessels were removed in preparation for MCA occlusion.

Monitoring

All animals underwent continuous monitoring of mean arterial blood pressure (MABP), right atrial pressure (RAP), and mean pulmonary artery pressure (MPAP). These values were recorded at established intervals and are expressed as electrical means at end-expiration. Cardiac output (CO) determinations (measured by the thermodilution technique) were made hourly. EEG and evoked potential data were acquired with an Interspec "Neurotrac™" device (Interspec Co., Conshocken, Pennsylvania) with two channels of EEG continuously displayed as a compressed spectral array (CSA). The approximate electrode locations were at F3-C3 and F4-C4. At set intervals, power spectrum and raw EEG tracings were also recorded. Median nerve somatosensory evoked potentials (MNSEP's) were obtained (using the same bipolar EEG montage) by averaging the cortical response to 512 repetitions of 20–25 mA stimuli delivered at a rate of 6/s *via* needle electrodes inserted subcutaneously into the contralateral wrist. End-tidal expired concentration of CO_2 was continuously monitored, and arterial blood was intermittently sampled for determination of blood gases, *p*H, hematocrit, electrolytes, and glucose. Core temperature (measured using the thermister on the pulmonary artery catheter) was maintained between 36.5 and 37.5° C using heated humidification and warming blankets, and by adjusting room temperature.

Experimental Protocol

The general experimental protocol is summarized in figure 1. All animals received identical treatment up to the point of orbital exenteration, when the first set of

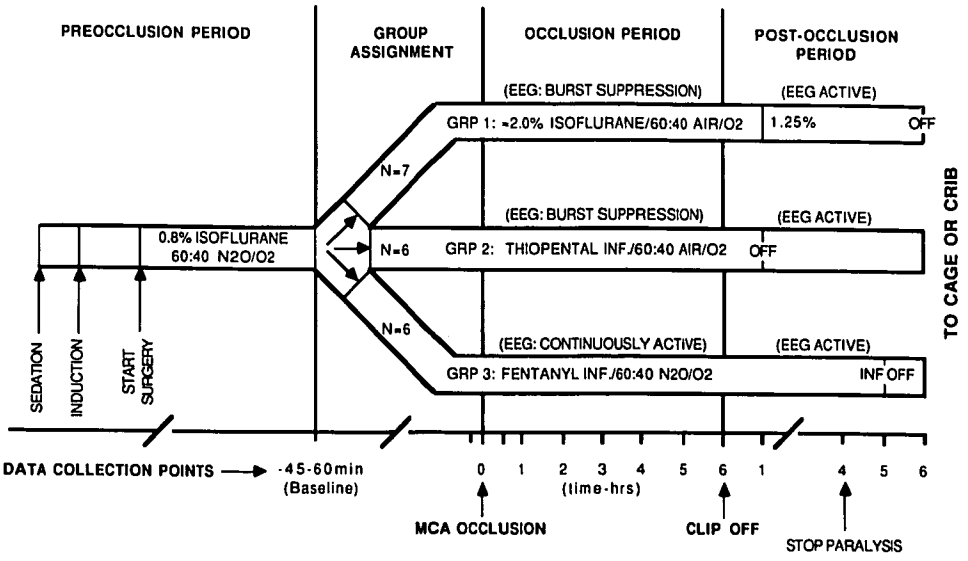

FIG. 1. Schematic summary of experimental protocol. Please note that the time base is not linear, except during the occlusion period. All animals were treated in an identical fashion until the time of group assignment.

data ("baseline") were collected (hemodynamic and electrophysiologic data, as well as hematologic variables). During the retroorbital craniectomy, but prior to opening the arachnoid membrane, the animal was assigned to one of three experimental groups: group 1—isoflurane; group 2—thiopental; and group 3—N_2O/fentanyl.

Group 1–Isoflurane (n = 7): Following acquisition of baseline data, the inspired concentration of isoflurane was increased to 2.5%, and N_2O was replaced with O_2/air (FI_{O_2} = 0.4). Over the next 45 min (during the bony dissection), the inspired isoflurane concentration was adjusted to produce an EEG pattern of burst suppression (2–6 bursts/min). Phenylephrine was infused in an effort to maintain MABP in the range of 80–100 mmHg. If cardiac output decreased below baseline values and hypotension persisted, a metaraminol infusion was added (all group 1 animals required vasopressor therapy during the MCA occlusion period). Ventricular dysrhythmias were treated with intravenous lidocaine (1 mg/kg) and propranolol (0.5–1 mg), if necessary.

Group 2—Thiopental (n = 6): After baseline data collection, both isoflurane and N_2O were discontinued and the animals ventilated with O_2/air (FI_{O_2} = 0.4). An intravenous infusion of thiopental was started at approximately 560 mg/h (70 ml/h of an 8 mg/ml solution of thiopental in saline). Incremental 40 mg boluses of thiopental were also given over the next 30–45 min, to achieve a burst suppression pattern similar to that produced with isoflurane. The infusion was thereafter adjusted to maintain this pattern. Sodium nitroprusside was used in an effort to maintain mean arterial pressure in the same 80–100 mmHg range. (All group 2 animals required antihypertensive therapy during thiopental administration). Supplemental therapy with hydralazine (5–10 mg) was begun if nitroprusside doses above 10 mg/h were necessary. As in group 1, ventricular dysrhythmias were treated with lidocaine and, if needed, propranolol.

Group 3—N_2O/Fentanyl (n = 6): After the collection of baseline data, the administration of isoflurane was stopped, and ventilation was continued with N_2O in oxygen (FI_{O_2} = 0.4). A loading dose of fentanyl (25 μg/kg) was administered over 5–10 min, and an infusion of fentanyl in saline was started at a rate of 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$. No changes in the rate of narcotic infusion were made thereafter. MABP was kept between 80–100 mmHg, using phenylephrine/metaraminol or nitroprusside/hydralazine according to the same criteria as in groups 1 and 2. Dysrhythmias were also treated in a similar fashion. Although the EEG was monitored and recorded in this group, it was not used to guide fentanyl infusion rates (which were kept constant).

All groups: A minimum of 45 min elapsed between the collection of baseline data and stabilization with the selected anesthetic, although surgery proceeded during this time.†† Following this period, hemodynamic and electrophysiologic data were collected, along with the measurement of arterial blood gases ("Pre-Clip"). The arachnoid was then opened and the MCA occluded at its origin (proximal to the lenticulostriate arteries) with a temporary Heifetz clip. Occlusion was verified by injecting a 3 ml bolus of methylene blue dye into the pulmonary artery, and observing through the operating microscope that dye appeared in the internal carotid and anterior cerebral arteries, but did not flow into the MCA distal to the clip.

†† A Puritan Bennett volatile agent analyzer was available during experiments in four animals from groups 2 and 3 (but only one animal from group 1). In each of these group 2 and 3 animals, end-tidal expired isoflurane concentrations were ≤0.1% ≈30 min after stopping isoflurane administration.

The orbit was then filled with warm saline and covered with a temporary dressing.

Occlusion was maintained for 6 h in all animals. In groups 1 and 2, inspired isoflurane concentrations or thiopental infusions were adjusted to maintain the desired burst suppression pattern on the EEG, while the fentanyl infusion was maintained at a constant rate in group 3 animals. The Pa_{CO_2} was kept in the range of 25–30 mmHg, pancuronium was given at a rate of 2 mg/h, and an attempt was made to maintain mean arterial pressure between 80 and 100 mmHg, as noted above. All hemodynamic, blood gas, and electrophysiologic data were recorded at 0.5, 1, 2, 3, 4, 5, and 6 h after vessel occlusion, while electrolytes, glucose, and hematocrit were measured at 3–4-h intervals.

Immediately after data collection at t = 6 h, occlusion was again verified by methylene blue injection. The clip was then removed, and reflow into the MCA was confirmed by a final injection of methylene blue. The dural opening was covered with Gelfoam™, the orbit filled with methyl methacrylate cement, and the lid sutured closed.

No changes were made in the anesthetic, fluid, or ventilatory parameters until 1 h following clip removal. At this point, the Pa_{CO_2} was increased into the normocarbic range (35–38 mmHg), and maintenance fluids were changed to D5/0.45 NS with 20 mEq KCl per liter (still at 80 ml/h). In group 1 animals, the inspired isoflurane concentration was decreased to 1.25%, while, in group 2 animals, the thiopental infusion was halted (fig. 1). No changes were made in the anesthetic parameters in group 3. Data were recorded at 0.5, 1, 2, and 4 h after clip removal. Vasopressor or vasodilator infusion rates were adjusted to maintain the blood pressure within the limits used during occlusion, and paralysis and mechanical ventilation were continued until 4 h following clip removal. At this time, the administration of pancuronium was halted and the pulmonary artery catheter removed. The subsequent disappearance of neuromuscular blockade was checked using the same median nerve stimulator that had been used to obtain MNSEP data. At 5 h after clip removal, weaning from the ventilator was started (fentanyl administration was stopped in group 3) and considered successful if the Pa_{CO_2} could be maintained below 40 mmHg during spontaneous ventilation. Six hours after clip removal, isoflurane (group 1) and N_2O (group 3) administration was discontinued, and, following confirmation of normocapnia and normotension, the arterial catheter was withdrawn and the EEG leads removed. When airway reflexes were adequate, the trachea was suctioned and the animal extubated and returned to a cage. Since animals in the thiopental group awoke more slowly from anesthesia, they were left intubated and transferred to a crib for further observation. They were turned from side to side and suctioned periodically until awakening, which occurred between 12 and 16 h after clip removal. During this period, they breathed only humidified room air.

On occasion, an animal would awaken very suddenly (in all of the groups). Given their size and strength, this posed a serious threat to all laboratory personnel. Therefore, a single intravenous dose of ketamine (50–100 mg) was sometimes administered to reestablish sufficient sedation to permit safe transfer to the cage.

Intravenous maintenance fluids (D5/0.45 saline + 20 mEq K^+/l) were continued at a rate of 60 ml/h until oral intake resumed. Animals that developed seizures (a total of three) were given a loading dose of 500 mg of phenytoin intravenously and continued on phenytoin either intravenously or orally until they were killed.

Evaluation

The animals were examined at postoperative days 2 and 7 by a neurologist who was unaware of which anesthetic the animals had received. Particular attention was paid to level of consciousness, motor function, facial symmetry, and visual fields. Additionally, the animals were examined daily by regular laboratory personnel. The results of the final examination on day 7 were converted into a simple five-point neurologic deficit score (NDS): NDS = 0: normal; NDS = 1: minimal detectable abnormality, *e.g.*, preferential use of the left arm, but without evidence of weakness during more vigorous activity; NDS = 2: weakness (paresis) of the right upper and/or lower extremity; NDS = 3: paralysis (plegia) of the right upper and/or lower extremity (although in retrospect, no animal was ever monoplegic); NDS = 4: paralysis accompanied by a reduction in the level of consciousness; and NDS = 5: death (in animals with a previous score of 4). The score assigned to each animal was not determined by simple observation, but involved an attempt to elicit motor activity. In most animals with scores of 3 or less, this could be done by placing an apple slice on the top of the cage and observing standing, reaching, and use of the hands as needed to retrieve the fruit. In less active animals, the apple was placed within the cage. If no response occurred, a blunt pole was used to gently prod the animal into movement.

After the final examination, the animals were killed by KCl injection under deep thiopental anesthesia. The brains were removed and fixed in 10% formalin for a minimum of 2 weeks. After adequate fixation, the brains were serially sectioned in 9-mm slices in a coronal plane. The use of a sectioning frame (Brain Macrotome, Lipshaw, Detroit, Michigan 48201) assured similar planes of sectioning and uniform thickness. Each slice was photographed in color with a reference scale. Color enlargements were marked for infarct size by a neuropathologist who was unaware of which treatment protocol had been used for each animal. In each slice, the area of the infarct

and of each hemisphere was determined using a Videoplan computer image analysis system (Carl Zeiss, Inc., One Zeiss Drive, Thornwood, New York 10594), which allowed the calculation of total infarct volume (by summing data from each slice). The percent of each hemisphere that was infarcted was computed by dividing the total volume of infarction by the total volume of the respective hemisphere. In addition, the character of each infarct was scored with regard to degree of hemorrhage present (0 = absent, 1 = mild, 2 = moderate, or 3 = severe).

In animals dying before the end of the 7-day period, the brains were removed within 2–6 h of death, and processed as above.

Statistics

Changes in hemodynamic and biochemical variables within each anesthetic group over time (relative to the "Pre-clip" measurement) were examined using a repeated measures ANOVA, with further intergroup comparisons at any given point in time being carried out with additional one-way ANOVA testing, followed by Newman-Keuls testing where indicated.

The incidence of pathologically verified infarction (infarct *vs.* no infarct, regardless of size) among the three groups was examined using a 2×3 contingency table and χ^2 testing, with 2×2 subdivision and Fisher's exact testing as needed. Comparison of infarction volumes, hemorrhage scores, and neurologic deficit scores were performed using a three-way nonparametric method (Kruskal-Wallis test). When indicated, pairwise comparisons were performed using the nonparametric modification of the Tukey test as described by Dunn.[14] Note that, since we were concerned about the size and character of the infarcts that were present, tests to compare infarction volumes and hemorrhage scores could be performed only after deleting those animals in which no infarct was present. Hence, n-values were appropriately adjusted; *e.g.*, in group 2 (thiopental) only two infarcts occurred, and, hence, n = 2 (rather than n = 6) for comparisons of infarct volume and hemorrhage scores.

Results

There were no operative deaths or technical failures, and no animal was discarded. Methylene blue injections confirmed MCA occlusion (and later reflow) in all animals. The desired EEG picture was achieved in all group 1 and group 2 animals. The average inspired isoflurane concentration used to maintain deep burst suppression was 2.0% ± 0.5%, while the average total dose of thiopental given over 7 h was 3625 ± 679 mg (164 ± 31 mg/kg) and ranged from 2820–4900 mg. Total fentanyl dose was 890 ± 56 μg (43 μg/kg).

Selected laboratory values for the groups are shown in table 1. There were no significant intergroup differences at any point in time during the study. Both potassium and glucose concentrations increased in all groups during the post-occlusion period, coincident with a change in maintenance fluids from normal saline to D5/0.45 NS with KCl. However, again there were no intergroup differences (*e.g.*, 6 h after clip removal, blood glucose concentrations were 150 ± 9, 157 ± 15, and 161 ± 25 in groups 1, 2, and 3, respectively). No animal required either vasopressors or vasodilators by 6 h after clip removal (*i.e.*, at the time of extubation or transfer from the OR), and all were normocarbic (or, more commonly, hypocarbic) (table 1) with spontaneous ventilation.

Hemodynamic Values

Hemodynamic values at selected times during the experiment are presented in table 2. There were no significant intergroup differences in any variable during the baseline period (not shown), nor were there any intergroup differences in RAP, MPAP, or CO at any time. However, in spite of the use of vasopressors in all group 1 animals and vasodilators in all group 2 (thiopental) animals, MABP was significantly lower in group 1 (isoflurane) compared with group 2 animals at all times after the entry into the group (from the Pre-Clip period onward until after reperfusion). Vasopressors were required in three animals in group 3 (N_2O/fentanyl), while the remaining three animals required vasodilators. There were no differences in MABP between group 3 and either groups 1 or 2.

Neuropathologic and Neurologic Outcome

Neuropathologic data (infarction volume and hemorrhage scores) and neurologic deficit scores are shown in table 3, and a typical infarction is shown in figure 2 (from an animal in group 1). Infarctions were found in seven of seven group 1 (isoflurane) animals, compared with only two of six animals in group 2 (thiopental), and four of six in group 3. The difference in the incidence of infarction between groups 1 and 2 was significant ($P = 0.021$). However, neither comparisons of group 1 or 2 *versus* group 3 (N_2O/fentanyl) achieved significance ($P = 0.19$ and $P = 0.24$, respectively). A three-way comparison of infarct volumes showed no significant differences. However, comparison of hemorrhage scores indicates that infarctions in group 1 were significantly more hemorrhagic in character than those occurring in group 3 ($P = 0.027$). No significant differences could be detected in hemorrhage scores between either groups 1 or 3 *versus* group 2 (although the comparison, as well as that of infarction volumes, is of limited value because of the small number of infarctions in group 2).

Neurologic deficit data are summarized in figure 3. Only one of seven animals in group 1 (isoflurane) was

TABLE 1. Selected Laboratory Values

	Pre-clip	3 h Clip On	1 h Clip Off	6 h Clip Off
Pa_{O_2} (mmHg)				
Group 1 (isoflurane)	218 ± 18	210 ± 29	206 ± 26	179 ± 22
Group 2 (thiopental)	172 ± 27	174 ± 34	173 ± 28	194 ± 22
Group 3 (N_2O/fentanyl)	201 ± 34	196 ± 28	184 ± 38	191 ± 12
Pa_{CO_2} (mmHg)				
Group 1	27 ± 3	27 ± 4	29 ± 3	31 ± 6
Group 2	26 ± 4	29 ± 3	29 ± 4	33 ± 3
Group 3	26 ± 3	28 ± 5	28 ± 3	29 ± 6
*p*H				
Group 1	7.49 ± 0.02	7.45 ± 0.03	7.35 ± 0.05	7.39 ± 0.02
Group 2	7.49 ± 0.06	7.47 ± 0.02	7.45 ± 0.04	7.38 ± 0.03
Group 3	7.48 ± 0.04	7.43 ± 0.06	7.43 ± 0.05	7.40 ± 0.07
Hct (%)				
Group 1	35 ± 3	38 ± 4	37 ± 4	—
Group 2	35 ± 1	36 ± 2	36 ± 3	—
Group 3	33 ± 4	36 ± 4	36 ± 4	—
Na^+ (mEq/l)				
Group 1	146 ± 3	147 ± 3	147 ± 2	—
Group 2	149 ± 4	147 ± 4	148 ± 4	—
Group 3	147 ± 3	149 ± 3	148 ± 5	—
K^+ (mEq/l)				
Group 1	3.3 ± 0.4	4.1 ± 0.6	5.3 ± 0.5	5.9 ± 0.9
Group 2	3.4 ± 0.2	4.1 ± 0.9	4.1 ± 1.0	4.3 ± 0.1 (n = 3)
Group 3	3.8 ± 0.8	3.9 ± 0.7	4.2 ± 0.6	6.0 ± 0.7
Glucose (mg/dl)				
Group 1	88 ± 31	91 ± 22	100 ± 27	150 ± 9
Group 2	75 ± 19	79 ± 24	96 ± 34	157 ± 15
Group 3	66 ± 17	86 ± 13	111 ± 22	161 ± 25

All values are mean ± SD. There were no significant intergroup differences. Note that three data points for serum K^+ at 6 h after clip removal were lost. Also, it should be noted that iv fluids were changed at 1 hr after clip removal to 5% dextrose in 0.45 N saline with 20 mEq/l of K^+.

TABLE 2. Selected Hemodynamic Values

	Pre-Clip	1 h Clip On	3 h Clip On	6 h Clip On	2 h Clip Off
MABP (mmHg)					
Group 1 (isoflurane)	89 ± 7	89 ± 6*	87 ± 5*	83 ± 4*	102 ± 5
[range]	[80–104]	[80–97]	[80–104]	[78–89]	[97–102]
Group 2 (thiopental)	100 ± 9	109 ± 11	100 ± 5	105 ± 5	105 ± 5
[range]	[84–110]	[98–130]	[89–110]	[99–112]	[97–110]
Group 3 (N_2O/fent.)	96 ± 10	97 ± 9	102 ± 7	93 ± 8	93 ± 9
[range]	[83–112]	[83–112]	[80–110]	[82–107]	[84–111]
RAP (mmHg)					
Group 1	6 ± 7	5 ± 5	6 ± 5	4 ± 5	4 ± 3
Group 2	4 ± 4	3 ± 2	4 ± 2	3 ± 2	4 ± 3
Group 3	5 ± 4	3 ± 3	1 ± 2	2 ± 4	3 ± 4
PAP (mmHg)					
Group 1	12 ± 6	13 ± 5	13 ± 6	13 ± 5	16 ± 7
Group 2	9 ± 1	12 ± 4	13 ± 5	13 ± 3	15 ± 4
Group 3	13 ± 4	11 ± 5	11 ± 3	11 ± 4	11 ± 5
C.O. (l/min)					
Group 1	3.6 ± 0.9	3.6 ± 1.1	4.0 ± 0.9	3.9 ± 1.0	5.0 ± 1.4
Group 2	3.4 ± 0.9	3.9 ± 1.5	3.2 ± 0.7	3.2 ± 0.8	3.2 ± 0.1
Group 3	2.6 ± 0.2	3.2 ± 0.3	3.4 ± 0.5	3.5 ± 0.7	3.4 ± 0.7
SVR ($mmHg \cdot l^{-1} \cdot min$)					
Group 1	25 ± 9	28 ± 8	21 ± 4*†	21 ± 7*	22 ± 9
Group 2	25 ± 11	26 ± 14	28 ± 10	29 ± 7	28 ± 10
Group 3	35 ± 6	30 ± 2	31 ± 8	27 ± 5	28 ± 4

Values are all mean ± SD.
* $P < 0.02$ for group 1 *vs.* group 2.
† $P < 0.05$ for group 1 *vs.* group 3.

No other significant differences were noted. [Note: range data are included under MABP to better define the intergroup differences].

TABLE 3. Neurologic Outcome and Neuropathology

Animal	NDS	Infarct Volume (% Hemisphere)	Hemorrhage Grade	MNSEP Change
Group 1—Isoflurane				
1.1	0	2.1	2	No
1.2	3	1.9	2	Yes
1.3	3	9.6	3	Yes
1.4	3	12.1	2	Yes
1.5	4	9.2	1	Yes
1.6	4	11.6	3	Yes
1.7	5	15.5	3	Yes
Group 2—Thiopental				
2.1	0	0.0	0	No
2.2	0	0.0	0	No
2.3	0	0.0	0	No
2.4	0	0.0	0	No
2.5	3	7.1	0	Yes
2.6	3	12.0	2	Yes
Group 3—N_2O/Fentanyl				
3.1	0	0.0	0	No
3.2	1	0.0	0	No
3.3	1	0.7	0	No
3.4	3	4.6	2	Yes
3.5	3	6.4	1	Yes
3.6	5	15.3	0	Yes

See text for definitions of Deficit and Hemorrhage Grades, and Infarct Volumes. Animal numbers are arranged in order of increasing neurologic deficit, to coincide with figure 1, and do not reflect experimental sequencing.

normal (although a "silent" infarct was present) (table 3), compared with four of six in group 2 (thiopental). Statistical evaluation demonstrated that the difference in scores between groups 1 and 2 achieved a level of $P = 0.055$ (after corrections for multiple comparisons). There were no significant differences between groups 1 and 3 or groups 2 and 3 ($P > 0.5$).

One animal in each of the three groups had a witnessed seizure. All were hemiplegic (NDS = 3).

EEG

Thiopental and isoflurane anesthesia precluded a detailed evaluation of the EEG during the period of MCA occlusion, thus making any careful examination of the relationship between EEG change and outcome impossible. In some animals, it was possible to note a degree of left-right asymmetry during the residual "bursts" of electrical activity. Such asymmetry occurred during the occlusion period in five of the seven group 1 (isoflurane) animals and in two of six group 2 (thiopental) animals. Asymmetry was also observed in five of six animals in group 3. Of particular interest was the finding that such asymmetry was often not noted until late in the occlusion period, with a median time to appearance (all groups) of ≈2.5 h (range 30 min to ≈6 h [more accurate determination of the time to asymmetry was very difficult]).

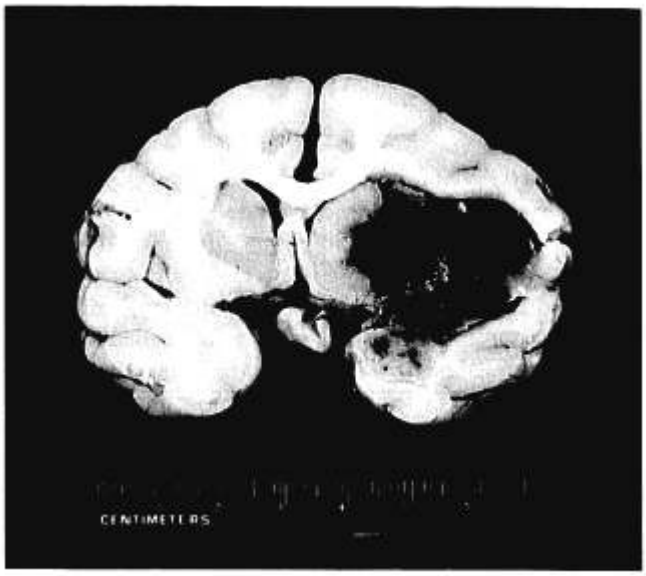

FIG. 2. Unstained coronal brain section of an animal in group 1 (isoflurane), with a typical hemorrhagic infarction. Note that the cortical areas are relatively spared.

EVOKED POTENTIALS

Readily recognizable MNSEP waveforms were seen in all animals prior to MCA occlusion, even after the administration of high-dose isoflurane or thiopental. This typically consisted of a negative potential with a latency of ≈9.50–10.5 ms (presumably of cervical or medullary origin, and which was essentially unaffected by either anesthetic administration or MCA occlusion), followed by an "N1-P1" complex with an initial N1 latency of approximately 12–14 ms (fig. 4). Occlusion-induced

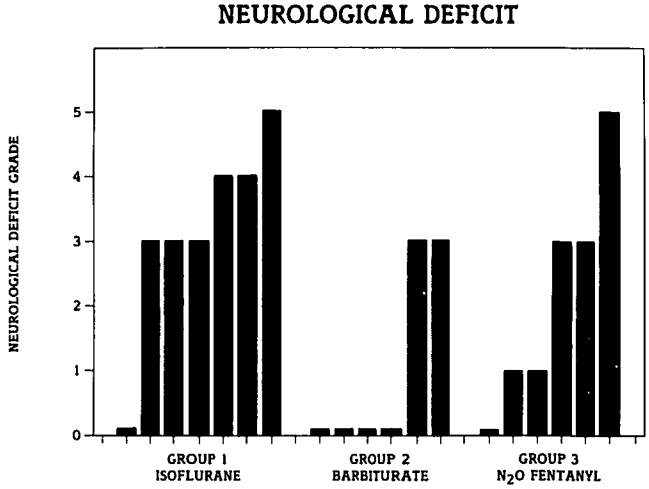

FIG. 3. Neurologic deficit scores for the three groups. See text for details of the scoring system, and statistical evaluation. Note that bars are arranged in order of ascending deficit within each group (as in table 3), and the order does not reflect experimental order.

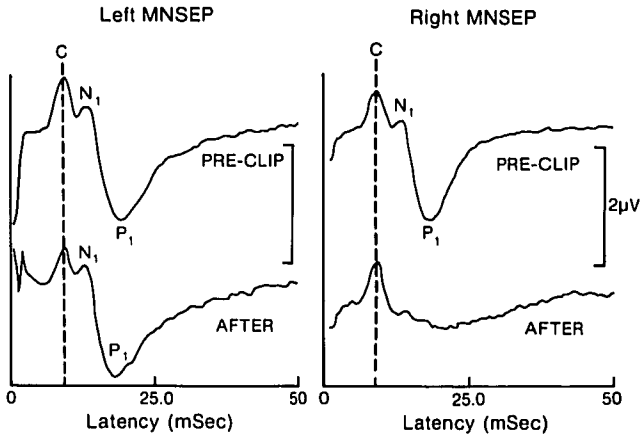

FIG. 4. Typical cortical responses to left and right median nerve stimulation. In each, the top curve was obtained after stabilization with the selected anesthetic (isoflurane in this animal), while the bottom was recorded ≈2 h after MCA occlusion. In all curves, a cervical or medullary response is visible (labeled C, dashed line) with a latency of ≈10.5 ms. This peak did not change with MCA occlusion. However, the N_1-P_1 response to right median nerve stimulation has disappeared in the lower right trace (after occlusion).

changes, when they occurred, were obvious, and were characterized by either a dramatic reduction in amplitude (>75%) or complete loss of the cortical N1-P1 complex over the hemisphere ipsilateral to the occlusion (fig. 4). The magnitude of these alterations made determination of latency changes either difficult or impossible.

Unlike the EEG, the relationship between MNSEP changes during occlusion and eventual neurologic outcome was very good (table 3). All animals showing an intraoperative loss of MNSEP's had final NDSs of 3 or more, while all animals with persistantly normal MNSEP's were clinically normal (scores of 0 or 1) to examination at day 7. Chi square analysis of MNSEP changes *versus* the presence of infarction was highly significant ($X_c^2 = 12.06$, $0.001 < P < 0.01$, all groups combined). However, two of these animals had "silent infarctions" demonstrated at autopsy (one each in groups 1 and 3). Only one animal was noted to have any recovery (minimal) of MNSEP waveforms after clip removal, but nevertheless still suffered an infarction.

The delay between initial MCA occlusion and the appearance of MNSEP changes was similar to that noted with the EEG, and varied between 30 min and 5 h.

Discussion

The brain is exquisitely vulnerable to ischemic injury, and despite an intense search for methods to protect it, particularly during surgical procedures, there is currently no widely accepted drug or technique that can consistently provide such protection. Barbiturates have been shown to reduce infarct size and improve neurologic outcome in animal models of cerebral ischemia,[9,10,12,13,15-22] and these agents are currently considered by many to be the protective agents of choice. However, their administration in large doses is not without risk.[23] Additionally, they prolong the postoperative emergence period, delaying neurologic evaluation and extending the requirements for intubation, mechanical ventilation, and intensive care support.

Recently, attention had been directed towards isoflurane. As a volatile anesthetic, concentrations can be easily altered and actions rapidly terminated. Cerebral blood flow and blood volume increases are less than those produced by halothane,[3,24-27] and clinically acceptable concentrations result in profound depression of the cortical EEG.[2,3,28,29] More importantly, such EEG-depressant concentrations decrease $CMRO_2$ by about 50%,[2,3,30] a value which equals that seen with the barbiturates.[31,32] Recently, Newberg and Michenfelder[1] have shown that isoflurane anesthesia could prolong survival in mice subjected to profound hypoxia, and could slow the deterioration of several cerebral metabolic variables during hemorrhagic shock in dogs. All of these observations have prompted intense speculation about the clinical protective value of this agent.

The current experiments were undertaken to examine the protective potential of isoflurane during focal cerebral ischemia. We chose a temporary MCA occlusion model to simulate the clinical situation of intraoperative occlusion of a major vessel. A primate model was employed for clinical relevance, and we chose 6 h for the duration of ischemia, as this typically produces a high proportion of moderate infarcts in this well-characterized model.[11-13,33] Since "protection" was considered to be of greater interest than "therapy," the selected agents were administered prior to vessel occlusion. Both isoflurane and thiopental were titrated to maintain an EEG picture of deep burst-suppression, since this is associated with near maximal degrees of cerebral metabolic suppression with these agents.[2,31,32] (Since clear-cut EEG endpoints are not readily apparent with a N_2O-fentanyl anesthetic, these animals received only a fixed μg/kg dose. While this was not strictly a "control" group, this anesthetic is associated with lesser degrees of cerebral metabolic suppression than either the isoflurane or thiopental anesthetics used, and is also a commonly employed neuroanesthetic.) Because extreme changes in blood pressure may play a role in determining the extent of infarction, we elected to treat the animals with vasopressors and/or vasodilators in an attempt to maintain mean arterial pressures in the 80–100 mmHg range. Combinations of agents were employed (*e.g.*, nitroprusside and hydralazine, phenylephrine/metaraminol) to avoid toxic concentrations of any one drug, and to better maintain other hemodynamic variables (*e.g.*, cardiac output, systemic resistance, venous pressures,

etc.) at acceptable levels (*i.e.*, MABP supported with phenylephrine alone leads to profound vasoconstriction and a reduction in cardiac output. Since metaraminol acts as a mild inotrope in the baboon, its use acts to avoid this difficulty). To minimize the confusion of introducing the effects of hemodilution,[33-36] we did not employ volume loading for the treatment of hypotension, although it might have reduced the need for vasopressors.

Several aspects of the experimental design and/or execution can be criticized. Throughout the study, and in all groups, a variety of drugs were used other than the selected anesthetics. This was particularly true prior to group assignment, when all animals received doses of ketamine/acepromazine, thiopental, pancuronium, lidocaine, and, slightly later, methylene blue. Some of these have known central nervous system effects. However, these drugs were given to all animals (in all groups), and were given in small doses; *e.g.*, the dose of ketamine/acepromazine produces sedation (not anesthesia) for only $\approx$1 h, while the induction dose of thiopental will yield only about 15–30 min of anesthesia. Furthermore, such polypharmacy is clinically common, and we do not believe it influences the clinical applicability of the results. All animals also received several hours of isoflurane/N_2O anesthesia prior to group assignment. However, inspired isoflurane concentrations were held at 0.8% during the preparatory phase, with adequate anesthesia assured by the use of N_2O and local infiltration. We believe that adequate time was allowed for the elimination of these agents (particularly isoflurane in groups 2 and 3) prior to clip placement. This was verified directly in four animals. Additional concern might be directed toward the terminal portion of the experiments, since differences were present between the groups in terms of postoperative care. This was particularly true of group 2 (thiopental). Isoflurane and N_2O/fentanyl-treated animals were returned to their cages at approximately 6 h after clip removal, whereas barbiturate animals were kept in a crib for 6–8 h more, until ready for extubation. However, during this additional time period, the barbiturate animals received no special care other than periodic turning and tracheal suctioning, and we also do not feel that this difference materially affects the results.

A much more important criticism can be directed at intergroup differences in vasopressor/vasodilator use. It could be argued that, since nitroprusside, hydralazine, neosynephrine, metaraminol, propanolol, and lidocaine all have CNS effects, their use should be avoided. However, when attempting to compare drugs as hemodynamically dissimilar as isoflurane, thiopental, and N_2O/fentanyl, this prohibition may be unreasonable (particularly given the high anesthetic doses employed). For example, isoflurane in EEG suppressant doses is commonly used for the induction of hypotension,[37] and pilot studies indicated that MABP's of $\approx$40 mmHg could be expected with isoflurane in the concentrations used, at least in the absence of hemodynamic support. Conversely, baboons given thiopental were invariably hypertensive (MABP 120–130 mmHg) in the abscence of vasodilator drugs, while N_2O/fentanyl animals had widely variable pressures. We would then have been confronted with a comparison between the effects of isoflurane + profound hypotension, *versus* thiopental + hypertension. We felt this to be unacceptable (although it would perhaps be a valuable experiment in its own right). Instead, we attempted to replace one variable (MABP) with another (vasoactive drug use), and opted for equivalent EEG patterns, comparable fluid volumes, hematocrits, blood glucose concentrations, arterial blood gases, *p*H and electrolytes, and similar MABPs, rather than for identical pharmacologic treatment.

Unfortunately, this goal was not entirely met, since significant differences in MABP were present between groups in spite of attempts at control. In practice, it simply proved impossible to maintain arterial pressure within tighter limits than those obtained, at least without resorting to much higher doses of vasoactive drugs. During the period of MCA occlusion, and extending until 1 h after clip removal (perhaps the most important reperfusion period), MABP in group 2 (thiopental) animals averaged 16 $\pm$ 4 mmHg higher than in group 1 (isoflurane), and 8 $\pm$ 5 mmHg higher than group 3 (all data points are included in these numbers, not just the selected values reported in table 2). It is, therefore, possible that these observed differences in MABP may have had an effect upon outcome, independent of the anesthetics themselves. However, for blood pressure to be the sole factor which determined the outcome differences between groups, it would be necessary to postulate a very steep "dose-response" relationship between blood pressure and outcome, particularly between groups 1 and 2 (a 100% *vs.* 33% incidence of infarction associated with a 16 mmHg MABP difference). Studies with this model in awake baboons show that while sustained phenylephrine-induced hypertension(MABP > $\approx$130 mmHg) can produce some improvement in neurologic function (during occlusion), it had no effect on the incidence of subsequent infarction, nor on final neurologic outcome.[38] However, the only episode of clinically notable hypertension (a MABP rise to 130 mmHg in a group 2 baboon) was corrected within 20 min. Conversely, hypotension, if it leads to a reduction in CBF, can reduce tolerance to focal ischemia.[38] However, none of the animals in the current experiments were hypotensive, with the lowest MABP noted at any point in the study being 78 mmHg just before clip removal in one isoflurane-treated animal. Furthermore, an attempt to correlate outcome with blood pressure in individual animals revealed no relationship when animals were

grouped according to outcome (independent of anesthetic). Those with good outcomes (neurologic deficit scores of 0–2) had MABP's that were statistically the same as those with poor outcomes (grades 3–5). Furthermore, within groups 2 and 3 (groups with animals having both good and bad outcomes) animals with good outcomes could not be distinguished from those with bad outcomes on the basis of arterial pressure alone. This analysis does not, obviously, rule out some interaction between anesthetic agent, blood pressure, vasoactive drugs, and outcome, and does not eliminate the possibility that intergroup differences in MABP/drugs may have magnified the outcome differences (particularly between isoflurane and thiopental treatments). It would obviously have been preferrable to have maintained closer pressure between the groups, and our results must be interpreted in view of this difficulty.

Given the caveats noted above, it is nevertheless apparent that the current experiments do not support the idea that isoflurane provides protection during focal cerebral ischemia, at least when compared with thiopental. Baboons in the isoflurane group had more frequent infarcts than animals in group 2, and their neurologic outcome scores were worse (although a P value of only 0.055 was achieved). Furthermore, while there were no significant differences between isoflurane and N_2O/fentanyl groups in terms of neurologic outcome and infarction incidence, there was a significant difference in the character of the infarcts, with those in isoflurane-treated baboons being more hemorrhagic in character.

At first glance, it is difficult to explain isoflurane's lack of therapeutic benefit in light of its cerebral metabolic depressant properties, and in view of its protective effects in situations of hypoxia and incomplete global cerebral ischemia.[1] The results of the present study are reminiscent of earlier experiments in dogs and primates in which halothane was shown to cause larger infarcts and more severe neurologic deficits,[9,10] in spite of the fact that it too reduces $CMRO_2$,[3,7] provides some protection against hypoxia[6] and against hemispheric ischemia.[8] These observations suggest that abolishing electrical activity and reducing $CMRO_2$ are not the only factors of importance in terms of providing protection during focal ischemia. Barbiturates and isoflurane are both protective during incomplete global ischemia (*e.g.*, hypotension), and both have similar metabolic properties. However, the differences observed here suggest that there are additional properties of barbiturates that become important during focal ischemia—properties that isoflurane does not possess. One such effect of the barbiturates may involve the redistribution of cerebral blood flow (CBF) during focal ischemia, such as noted by Branston *et al.*[39] These authors found that, after the administration of methohexital, flow in nonischemic areas decreased, but that, conversely, local CBF increased in ischemic regions. A similar phenomenon was noted by Feustel *et al.*, who observed increases in the oxygenation of ischemic tissue following the administration of pentobarbital.[40] Such a redistribution of flow (*i.e.*, an inverse steal) might play a protective role in focal ischemia, but would not be important during global ischemia or hypoxia. While isoflurane is not associated with the same degree of cerebral vasodilation as halothane,[3,27] it also does not produce the reduction in CBF seen with the barbiturates (in nonischemic tissue). This failure to vasoconstrict normal vessels may thus prevent a favorable redistribution of CBF during focal ischemia.

A second potentially relevant difference between the actions of barbiturates and isoflurane may be in their relative effects on regional metabolic activity. Most available data concerning the effects of isoflurane on cerebral metabolism have look predominantly at cortical structures.[3,30] However, Maekawa *et al.*[41] have demonstrated autoradiographically that isoflurane produces a greater reduction in the metabolic rate for glucose (CMRG) in cortical structures than in subcortical regions. This contrasts with the more uniform depression of cerebral glucose metabolism seen with at least one barbiturate, pentobarbital.[42] The infarcts observed in the current study were predominatly located deep within the hemisphere, involving the basal ganglia/thalamus, with minimal involvement of the cortex (fig. 3). This type of infarction might not be prevented by isoflurane if its metabolic depressant actions were predominantly cortical. However, the aforementioned studies were both performed in rats, and technical differences make direct comparisons impossible. Such a possibility must, therefore, remain highly speculative. Additional actions, such as free radical scavenging[43,44] and the attenuation of free fatty acid release,[45] may also account for the superior cerebral protection afforded by barbiturates. Barbiturates may further improve outcome by reducing the edema associated with ischemic injury.[46] Such properties may be highlighted in our model where the long period of ischemia may allow harmful byproducts to accumulate. However, none of these additional properties have so far been demonstrated for isoflurane.

One additional observation made in the course of this study deserves comment, although it does not directly relate to protection. This concerns the clinical implications of the collected electrophysiologic data. The profound electrical suppression produced by both isoflurane and thiopental resulted in the EEG being of little value for detecting cerebral ischemia. By contrast, MNSEP recordings persisted in a readily recognizable form, despite the presence of these drugs, and appeared to correlate well with the occurrence of infarction. This would appear to support the predictive value of SEP recording during human cerebrovascular surgery, as noted by Symon *et al.*,[47]

and suggests that, under these circumstances, such a monitoring modality is of greater value than the raw or processed EEG. However, it should be noted that MNSEP changes (and EEG changes when they could be distinguished) frequently did not occur until several hours after clip application. While the reasons for this delay may be subject to debate, the practical implication is clear. If MNSEP's are to be used clinically in an attempt to prevent ischemic injury due to either intentional or inadvertent cerebrovascular occlusion, monitoring may need to be continued until long after the period that most physicians consider to be the time of maximal risk. The failure to observe an electrophysiologic change shortly after vessel occlusion does not mean that "all is well."

Our findings must not be carelessly interpreted. They do not imply that isoflurane is an inappropriate anesthetic for routine cerebrovascular surgery (carotid endarterectomies, aneurysm repairs, etc.), for the induction of hypotension, or for other neurosurgical procedures, such as intracranial tumor removals. In such situations, cerebral protection may be of little importance, and anesthetic techniques are best selected on the basis of changes in cerebral blood flow, blood volume, and intracranial pressure, and, because of their effects on blood pressure, cardiorespiratory function, etc. In fact, current evidence suggest that isoflurane may offer some significant advantages in some of these situations, at least when compared with other volatile agents. However, our results failed to demonstrate any protective value for isoflurane anesthesia during prolonged temporary focal ischemia, at least when compared to thiopental. We fully recognize that other results might be obtained with different anesthetic concentrations (*e.g.*, lower isoflurane doses), or with different approaches to hemodynamic control. However, until further studies contradict the current findings, we believe that this study (as well as numerous other experiments) suggests that the barbiturates remain the drugs of choice when intraoperative pharmacologic cerebral protection is desired. The use of isoflurane for such a purpose cannot currently be recommended.

The authors would like to thank Dr. Peter A. Raudzens for his assistance with intraoperative electrophysiology, and Linda C. Todd for her invaluable technical and editorial help. The isoflurane used for these studies was donated by Anaquest.

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