Comparison of the Effects of Isoflurane and Thiopental on Neurologic Outcome and Neuropathology after Temporary Focal Cerebral Ischemia in Primates

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In an attempt to determine whether one anesthetic might be clearly advantageous over another in clinical situations of temporary focal ischemia, isoflurane or thiopental (in concentrations producing equal suppression of cerebral function as measured by the electroencephalogram) were studied for their effects on neurologic outcome and cerebral infarct size in pigtailed monkeys exposed to temporary focal ischemia produced by 5 h of middle cerebral artery occlusion (MCAo). Burst suppression was produced for 15 min before MCAo and maintained throughout the ischemic period by 2.18 ± 0.11% (mean ± SE) end-expired isoflurane or 135 ± 18 mg · kg⁻¹ thiopental. Mean arterial pressure was supported with phenylephrine and maintained at approximately 90 mmHg in both groups throughout the ischemic period. At the end of the ischemic period, the isoflurane or thiopental was discontinued, allowing the animals to awaken. Intensive care was provided as needed. Neurologic function was scored for 8 days at the end of which surviving animals were killed and the brains were fixed in formalin and then examined for infarct size. There was no significant difference in final neurologic outcome between the animals receiving isoflurane and those receiving thiopental as determined by the Mann-Whitney rank sum test. Neurologic deficit scores ranged from normal (one of eight in the group receiving isoflurane and three of nine in the group receiving thiopental) to death resulting from brain injury (three in the isoflurane group and five in the thiopental-treated group). There also was no significant difference in infarct size between the two groups. Infarct size correlated with neurologic outcome (Spearman rank correlation coefficient, ρ = 0.74). From this study it is concluded that in situations of temporary focal ischemia when blood pressure is equally maintained, there is no difference in neurologic outcome or in cerebral infarct size when cerebral function is suppressed either by isoflurane or by thiopental anesthesia. (Key words: Anesthesia; neurosurgical. Anesthetics, intravenous; thiopental. Anesthetics, volatile: isoflurane. Brain: EEG; ischemia; protection. Monitoring: electroencephalogram. Surgery: cerebrovascular.)

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It has been shown that both thiopentalk and isoflurane² produce a dose-related decrease in cerebral function as detected by the electroencephalogram (EEG), with an attendant decrease in cerebral oxygen metabolism (CMR_o₂), with maximal metabolic depression occurring with the onset of an isoelectric EEG. Nehls et al.³ have recently reported that thiopental in doses sufficient to produce burst suppression on the EEG provided better neurologic outcome and significantly less cerebral infarction than did comparable doses of isoflurane in baboons exposed to temporary focal ischemia produced by 6 h of middle cerebral artery occlusion (MCAo). Because it was assumed that thiopental and isoflurane produced comparable global cerebral metabolic suppression, the authors hypothesized that thiopental but not isoflurane produced favorable changes in regional cerebral blood flow to contribute to the results. However, the results of that study may have been influenced not only by differences in the anesthetic but also by the significant differences in mean arterial pressure (MAP) and by the use of vasodilating drugs in the animals receiving thiopental and vasoconstricting drugs in the animals receiving isoflurane. It is important to determine whether one anesthetic agent is clearly advantageous in situations of temporary focal cerebral ischemia that can occur clinically. Therefore, the purpose of the present study was to compare the effects of isoflurane and thiopental on neurologic outcome and cerebral infarct size in primates exposed to temporary focal ischemia (5 h middle cerebral artery occlusion) while equally maintaining MAP and limiting the number of vasoactive drugs.

Methods

STUDY SUBJECTS AND PREISCHEMIC PREPARATION

Nineteen unmedicated adult pigtailed macaque monkeys (Macaca nemestrina) of either sex, weighing 3.6–4.4 kg and ranging in age from 2.5 to 3 yr, were wild-captured for the study (Charles River Research Primates, P. O. Box 416, Port Washington, New York 11050). All animals were examined by a veterinarian and screened for parasites and tuberculosis. The experimental protocol was ap-
proved by the Animal Care and Use Committee and the Research Committee of the Mayo Clinic. The animals were allowed free access to food and water. Twenty-four hours before the experiment the animals received their last feeding but were allowed water up to the time of the experiment. Feedings were withheld for 24 h because pigtailed macaque monkeys can and will sequester food in their cheek pouches for up to 12 h.

The experimental protocol is summarized in figure 1. For induction of anesthesia, each animal was removed from the cage and placed in an air-tight box with a flow-through of halothane in air. Once the animal was anesthetized, each received 1 mg pancuronium im to facilitate tracheal intubation. Ventilation was controlled and 0.25% halothane in air was administered while each animal was shaved for surgery. A peripheral iv 20-g catheter was inserted into each forelimb for fluid and drug administration. The animal was then moved to the operating room. Ventilation was controlled with a Harvard Pump® with a tidal volume of 65–100 ml and a rate (10–15 breaths/min) adjusted to maintain $P_aCO_2$ at 33–37 mmHg (normal $P_aCO_2$ = 45 mmHg for macaque monkeys). Anesthesia was maintained at 1.2% end-expired halothane in oxygen (adjusted to maintain $P_aO_2$ at 170–190 mmHg) with the balance being nitrogen. All inspired gases were administered through a heated humidifier. Each animal received a bolus of 50 ml normal saline followed by a continuous infusion at the rate of 4 ml·kg$^{-1}$·h$^{-1}$.

All surgery was performed under aseptic conditions. A catheter was inserted into the right femoral artery via a cutdown for pressure monitoring and blood sampling. This was continuously flushed with heparin-free saline to maintain patency. Body temperature was measured with a rectal thermometer and maintained at 37–38°C with heating pads and heat lamps.

The animal was placed in a sphinx position, and the head was fixed in a stereotactic frame allowing unobstructed access to the right orbit. A midline scalp incision was made for insertion of disk electrodes cemented to the exposed skull to minimize muscle artifact. A two-lead, single-channel, frontoparietal EEG was recorded from each hemisphere on a Grass® EEG recorder (model 8-10B).

With the use of the operating microscope, the right middle cerebral artery (MCA) was approached through the orbit. The intraorbital contents were removed and hemostasis was achieved with bipolar coagulation and bone wax. The halothane was then discontinued. Once the end-expired halothane concentration reached 0.6%, 10 animals received 1.2% (end-expired) isoflurane and nine animals received 20 mg (5 mg·kg$^{-1}$) thiopental iv. The posterolateral wall of the orbit was removed and hemostasis was again achieved. The dura mater and arachnoid were incised to expose the MCA, and all arachnoidal adhesions surrounding the vessels were removed. Once end-expired halothane was less than 0.15%, burst suppression on the EEG was achieved by increasing the concentration of inspired isoflurane to those animals receiving isoflurane or by administering additional 20-mg boluses of thiopental to those animals receiving thiopental. Burst suppression was maintained by either adjusting the isoflurane concentration or a continuous infusion of 2% thiopental in normal saline. An infusion of 0.8% phenylephrine in normal saline was used as needed to maintain MAP at 85–90 mmHg. Continuous monitoring included MAP, heart rate, EEG, rectal temperature, end-expired $P_aCO_2$, end-expired halothane, and end-expired isoflurane concentrations (mass spectrometry). Arterial blood gases with base deficit, hemoglobin (Hb), blood glucose, and lactate were measured during the steady state control period of burst suppression on the EEG preischemia; at 0.5, 1, 2, 3, 4, and 5 h during ischemia; and at 0.5 h posts ischemia; then hourly until tracheal extubation. Sodium bicarbonate

![Diagram](attachment:file.png)
was given if the base deficit decreased greater than 5 mEq/l from the control value.

ISCHEMIC PERIOD

When burst suppression had been maintained for 15 min, the MCA was occluded at its origin with a temporary Mayfield clip. Occlusion was verified by injecting a 0.5-ml bolus of methylene blue into the left forelimb iv catheter and observing flow of dye into the right internal carotid artery but not into the right MCA past the clip. The orbit was then moistened with sterile saline and covered. Occlusion was maintained for 5 h. Isoflurane concentration and thiopental administration were adjusted to maintain burst suppression on the EEG. As in the preischemic period, PaCO₂ was maintained in the range of 33–37 mmHg, PaO₂ was maintained in the range of 170–190 mmHg, and MAP was maintained at 85–90 mmHg with the phenylephrine infusion. Acidosis was treated with sodium bicarbonate. Benzathine penicillin 150,000 units, procaine penicillin 150,000 units, and gentamicin 0.2 mg · kg⁻¹ were given during the first hour of ischemia.

POSTISCHEMIC PERIOD

After 5 h of ischemia, the clip was removed from the MCA. Reflow through the MCA was confirmed by injection of 0.5 ml methylene blue and observation of flow of dye through the internal carotid artery and into the MCA. After the observation of reflow, the thiopental infusion was discontinued in the animals receiving thiopental, and the isoflurane concentration was decreased to 1.2% end-expired in the animals receiving isoflurane. At this time, the phenylephrine infusion was decreased as determined by the MAP. The dural opening was covered with Gelfoam®; the orbit was layered with oxycecl® and cotton and filled with methyl methacrylate cement; and the eyelid was sutured closed.

At the end of the surgical procedure (approximately 15 min after removal of the MCA clip) the isoflurane was discontinued. Neuromuscular blockade was reversed in all animals with 0.07 mg · kg⁻¹ neostigmine and 0.012 mg · kg⁻¹ glycopyrrolate. Animals that received isoflurane were given 0.1 mg · kg⁻¹ morphine sulfate for analgesia. Ventilator support of ventilation was discontinued when spontaneous ventilation was considered adequate with maintenance of PaO₂ greater than 60 mmHg and PaCO₂ less than 45 mmHg while the animal was breathing room air. When the animal had carinal and pharyngeal reflexes and stable hemodynamics, the trachea was extubated. The animals receiving isoflurane were weaned from the ventilator and their tracheas extubated approximately 30 min after the isoflurane was discontinued. The animals receiving thiopental were weaned from the ventilator 240 min after the end of the procedure, but their tracheas were not extubated until they were awake or, for those remaining in coma, were able to adequately maintain their airway (2–25 h after the end of the procedure). The intravenous fluid infusion (normal saline) was maintained until oral intake (5% dextrose in water and/or oranges) was resumed.

NEUROLOGIC EVALUATION

Each animal was evaluated daily for 8 days postischemia by an observer (J.D.M.) blinded to the anesthetic each animal had received. The neurologic evaluation used was similar to that of Nehls et al.³ Animals were scored according to level of consciousness, motor function, facial symmetry, and visual fields. A 0–5-point scoring system was used to obtain a neurologic deficit score (NDS) each day. (NDS = 0: normal; NDS = 1: minimal detectable weakness such as preferential use of right forelimb; NDS = 2: mild–moderate weakness [paresis] of the left upper and/or lower extremity or significant left facial weakness; NDS = 3: paralysis of the left upper and/or lower extremity; NDS = 4: paralysis accompanied by a reduction in level of consciousness [not necessarily coma]; NDS = 5: death resulting from brain injury.)

At 8 days postischemia, after the final neurologic evaluation, each animal was anesthetized with im ketamine (15 mg · kg⁻¹) and killed by iv injection of KCl. The brain was excised and fixed in 10% formalin for a minimum of 12 days. Each brain was individually examined by an observer (J.D.M.) who had no knowledge of the animal, the neurologic deficit score, or anesthetic that it had received. The size of each cerebral hemisphere was measured by volume displacement before sectioning into 5-mm coronal slices. Each slice was grossly examined for infarct size with a grid; the total size of infarct was computed and expressed as percentage of that hemisphere's volume.⁵ For animals dying before 8 days, the brains were removed within 2 h of death and fixed as above, and other vital organs were examined for evidence of injury.

EXCLUSIONS

Animals that did not meet all preestablished protocol criteria were excluded from the study immediately. Exclusion was based on the following: a preischemic blood glucose level greater than 200 mg · kg⁻¹; evidence of incomplete MCAO; severe cardiopulmonary complications such as pulmonary edema resulting in the inability of the animal to maintain a PaO₂ greater than 60 mmHg and/or a PaCO₂ less than 45 mmHg while spontaneously breathing room air; a MAP less than 80 mmHg for more than 60 min or less than 50 mmHg at any time. Two animals, both of which received isoflurane, were discarded from the study, one before ischemia and one after isch-
emia for failure to maintain an MAP greater than 80 mmHg despite massive doses of phenylephrine. Therefore, the results are reported for 17 animals.

PILOT STUDIES

To determine what duration of MCAo would produce a wide range of neurologic deficits, pilot studies were performed on nine pigtailed monkeys. Three pigtailed monkeys each were exposed to 3, 4, or 5 h of temporary focal ischemia during isoflurane anesthesia in concentrations sufficient to produce burst suppression on the EEG. After 3 h of focal ischemia, two monkeys were normal (NDS = 0; no measurable infarct) and one had an NDS = 3 (2% infarct). Similarly, after 4 h of ischemia, two monkeys were normal (NDS = 0; no measurable infarct) and one had an NDS = 3 and a 3% infarct. After 5 h of ischemia, one monkey had an NDS = 1 with a 3% infarct, one monkey had an NDS = 3 with a 9% infarct, and one monkey died (NDS = 5) with an 8% infarct. In addition, two pilot studies were done in pigtailed monkeys receiving thiopental in doses sufficient to produce burst suppression on EEG to determine the effect of this dose of thiopental on MAP and to determine the need for vasoactive agents during the periischemic period. In these two animals, MAP was maintained at 90–95 mmHg throughout the ischemic period (1–3 h) without the use of vasoactive drugs.

STATISTICAL ANALYSIS

Individual final neurologic deficit scores and individual infarct sizes were compared for each group by the Mann-Whitney rank sum test. The rank of final neurologic deficit scores was compared with the rank of infarct sizes by the Spearman rank correlation. Hemodynamic values and laboratory values for the group receiving isoflurane were compared with the values for the group receiving thiopental by a repeated measure analysis of variance (ANOVA). When differences were found, these were tested for significance with the use of the Newman-Keuls test.

RESULTS

HEMODYNAMIC VALUES

Hemodynamic values obtained in the steady-state control period preischemia, values averaged over the 5-h period of ischemia, and values obtained at the time of extubation are presented in table 1. The MAP of animals receiving isoflurane was maintained at 89 ± 3 mmHg preischemia and 88 ± 1 mmHg throughout the ischemic period with a phenylephrine infusion, the average total dose being 9.0 ± 2.5 mg·kg⁻¹ given throughout the period of deep isoflurane anesthesia. The MAP of the animals receiving thiopental was 92 ± 8 mmHg preischemia and 91 ± 3 mmHg throughout the ischemic period. Seven of nine animals receiving thiopental required phenylephrine, but the mean phenylephrine dose (0.8 ± 0.5 mg·kg⁻¹) was significantly less than that given to the animals receiving isoflurane. At the time of tracheal extubation, MAP was 109 ± 5 mmHg for the animals receiving isoflurane and 94 ± 10 mmHg for the animals receiving thiopental without the use of phenylephrine. There were no significant differences in MAP either with time or between the two groups during the study. There also were no clinically significant differences in heart rate or temperature between the two groups.

The average end-expired isoflurane concentration required to maintain burst suppression on the EEG preischemia was 2.34 ± 0.19%. This concentration decreased to
2.18 ± 0.11% isoflurane during the ischemic period. The average dose of thiopental given over 6.5 h was 135 ± 18 mg·kg⁻¹ and ranged from 67 to 233 mg·kg⁻¹. The dose of thiopental required by each animal to produce burst suppression did not correlate with neurologic outcome or infarct size.

BLOOD GASES AND CHEMISTICS

Laboratory values obtained during the preischemic period, values averaged throughout the period of ischemia, and values obtained at the time of extubation are presented in Table 2. Arterial blood gases of the animals receiving isoflurane or thiopental were similar preischemia and during the ischemic period. However, those receiving isoflurane hyperventilated (spontaneous breathing) significantly more than those receiving thiopental at the time of tracheal extubation. This resulted in significantly lower PaCO₂ and significantly higher PaO₂ in the animals in the isoflurane-treated group, although all values were within the normal physiologic range. Blood glucose levels were significantly lower both preischemia and throughout ischemia in the animals receiving thiopental than in those receiving isoflurane, although blood glucose remained within the normal physiologic range in all animals. There was no relationship between the blood glucose level either preischemia or during ischemia and final neurologic outcome (Fig. 2). Blood lactate levels were significantly higher in the animals receiving isoflurane than in the animals receiving thiopental beginning 1 h after the onset of ischemia and remained so at the time of extubation. There was no significant difference in the amount of sodium bicarbonate given to each group to treat acidosis (6.2 ± 1.3 mEq to the animals receiving isoflurane and 4.6 ± 1.3 mEq to the animals receiving thiopental).

NEUROLOGIC OUTCOME AND NEUROPATHOLOGY

The time of death (in hours postischemia), the final neurologic deficit score, and the percentage of the right cerebral hemisphere showing infarction are presented in Table 3. The final NDS score for each animal is presented in Figure 3. There was no significant difference in final NDS between animals receiving isoflurane and those receiving thiopental as determined by the Mann-Whitney rank sum test. NDS scores within each group ranged from normal (one of eight in the group receiving isoflurane and three of nine in the group receiving thiopental) to death resulting from brain injury (three of eight in the group receiving isoflurane and five of nine in the group receiving thiopental). Figure 4 plots the rank order of neurologic deficit scores against the rank order of infarct sizes. The range of infarct size for each group was similar and correlated with the final neurologic deficit scores (Spearman rank correlation coefficient, rₚ = 0.74). The animals that were inconsistent with this correlation were...
TABLE 3. Neurologic Damage (Function and Neuropathology)

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<tr>
<th>Monkey</th>
<th>Time of Death (Hours Postischemia)</th>
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FIG. 4. Correlation between rank of infarct size and the rank of neurologic deficit scores $r_s = 0.74$.

brain injury not lung injury, based on postmortem examination.

**Discussion**

The results of the present study demonstrate similar neurologic outcome and similar infarct size after 5 h of focal ischemia with reperfusion during either deep isoflurane or thiopental anesthesia. In both groups the anesthetics were administered in doses sufficient to produce burst suppression on the EEG. Previous studies have demonstrated that there is a dose-related decrease in cerebral function and a parallel decrease in cerebral metabolism with both isoflurane and thiopental. When cerebral function is decreased to burst suppression or isoelectricity on the EEG, the decrease in cerebral metabolism is at the maximum produced by an anesthetic. If cerebral metabolic suppression is the major determinant of neurologic outcome during focal cerebral ischemia, then it is hypothesized that equivalent metabolic suppression by either isoflurane or thiopental should provide equivalent neurologic outcome after focal ischemia. However, Nehls et al. reported better neurologic outcome and less cerebral infarction with thiopental anesthesia than with isoflurane anesthesia in baboons subjected to 6 h of temporary focal ischemia and hypothesized that thiopental produced favorable changes in regional cerebral blood flow (CBF), which contributed to the better outcome. In their study, hypertension developed in animals receiving thiopental requiring treatment with sodium nitroprusside and hydralazine, but these animals had significantly higher MAP (100–109 mmHg) preischemia and throughout the ischemic period than those receiving isoflurane (83–89 mmHg) that became hypotensive, requiring phenylephrine and metaraminol.

Ischemia interferes with normal cerebrovascular reactivity such that autoregulation is abolished. Changes in MAP may affect CBF in the ischemic area. In awake

![Fig. 3. Final neurologic deficit score (NDS) for each animal receiving isoflurane or thiopental. The vertical bars are arranged in order of increasing deficit, the order for the Mann-Whitney rank sum test.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931370/)

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cynomolgus monkeys subjected to 4 h of MCAo, induced hypertension with phenylephrine increased CBF 40% in the ischemic hemisphere but had no effect in nonischemic zones. This resulted in improved neurologic status both during ischemia and 2 weeks after ischemia and decreased infarct size at autopsy. In baboons anesthetized with alpha-chloralose subjected to MCAo, increasing the MAP by 44% with metaraminol significantly increased cortical blood flow in the area of ischemia and significantly improved the somatosensory evoked potentials recorded from that area. The authors concluded that disorders of neuronal electrical activity (cerebral function) produced by ischemia could be restored by increased cerebral perfusion in the area where autoregulation was lost. In a report of patients with recent ischemic strokes, pharmacologic elevation of blood pressure improved CBF in those regions with the most reduced regional CBF. Unfortunately, vasopressor therapy was not continued beyond the length of the CBF measurement so no clinical effects were noted. In a study of patients in whom vasospasm and a documented decrease in CBF developed after clipping of anterior circulation cerebral aneurysms, induced hypertension by phenylephrine produced a significant increase in CBF and an improvement in neurologic function. Based on this evidence, it is reasonable to conclude that the differences in neurologic outcome and infarct size reported in the Nehls et al. study may have been influenced not only by proposed differences in the cerebral hemodynamic and metabolic effects of isoflurane and thiopental but also by significant differences in blood pressure and differences in the use of vasodilating and vasoconstricting agents.

In an attempt to control these differences in the present study, a primate species was chosen in which hypertension did not occur in response to thiopental and MCAo and the use of vasoactive drugs was restricted to phenylephrine. However, some minor differences between the two groups occurred with respect to phenylephrine dose, hemodilution, lactate production, and blood glucose. All animals receiving isoflurane and seven of nine of those receiving thiopental required phenylephrine for support of the blood pressure, although the mean phenylephrine dose in animals in the isoflurane-treated group (9 mg · kg⁻¹) was greater than 10 times that of the animals in the thiopental-treated group (0.8 mg · kg⁻¹). Phenylephrine produces a pressor response with different effects in the major vascular beds. The vasoconstrictive effect of phenylephrine is antagonized by pressoreceptor reflexes in most vascular beds. The cerebral vessels are not under the influence of these pressoreceptor reflexes so that in normal cerebrovasculature, cerebrovascular resistance is increased disproportionately more than MAP and CBF decreases in areas of normal CBF. It is unknown whether this action of phenylephrine on normal cerebral vessels might redirect CBF from normal brain to areas of ischemia. Although it is assumed that regional CBF in the ischemic area was primarily influenced by MAP, regional CBF may have been proportionately affected by the differences in phenylephrine dose used to support the MAP in the two groups. In a study of swine undergoing cardiopulmonary resuscitation, there was a significant improvement in regional CBF when the animals were given 10 mg · kg⁻¹ phenylephrine but not when the animals were given 1 mg · kg⁻¹ phenylephrine, although nonsignificant differences in aortic blood pressure existed. If this effect was present in the present study, it might have more favorably affected the animals receiving isoflurane than those receiving thiopental.

To avoid the effect of hemodilution, all animals received the same maintenance dose of normal saline. Intravenous fluids were not given to treat hypotension. The amount of fluid given by the phenylephrine infusion to the animals receiving isoflurane approximated the total fluid given for both the thiopental infusion plus or minus the phenylephrine infusion to the animals receiving thiopental. It has been reported that moderate normovolemic hemodilution produced by decreasing the hematocrit from 40–48% to 21–32% by the administration of saline to rabbits before 15 min of complete cerebral ischemia resulted in a significant improvement in CBF after reperfusion. In cats hemodilution with saline to lower the hematocrit by 45% did not improve CBF in the area of the ipsilateral MCA during MCAo but did improve CBF in the contralateral hemisphere. In patients following superficial temporal artery to middle cerebral artery anastomosis, normovolemic hemodilution with 5% human serum albumin to lower hematocrit from 40 to 33% produced a significant increase in CBF in both the bypassed region and in the contralateral MCA region. It was hypothesized that this observed increase in CBF with hemodilution results from a reduction in blood viscosity. The observed 1.3 mg · dl⁻¹ difference in Hb in the present study between the group receiving isoflurane (Hb = 9.9–10.8 mg · dl⁻¹) and the group receiving thiopental (Hb = 8.6–9.5 mg · dl⁻¹) probably had little effect on CBF in the region of ischemia during the MCAo. However, after release of the clamp the small difference in Hb, if it had any effect, would have increased CBF to the ischemic area more in the animals receiving thiopental than in the animals receiving isoflurane, favoring more improvement in the group receiving thiopental.

The significantly higher blood lactate levels in the animals receiving isoflurane may result from the decreased peripheral perfusion secondary to the greater amounts of phenylephrine given to maintain MAP to the animals receiving isoflurane. This increased lactate is most likely from poorly perfused muscle. Lactate crosses the blood–brain barrier by a carrier-mediated mechanism. In nor-
moxia the brain can consume 4–6% of the arterial lactate for energy substrate. However, during ischemia the brain excretes lactate. In the conditions of the present study, an increase in arterial lactate probably had little effect on cerebral metabolism and CBF.

The blood glucose level in the animals in the thiopental-treated group was significantly lower both preischemia and throughout ischemia than in those receiving isoflurane (table 2). Because the animals were equally exposed to food and fruit before ischemia, it is assumed that the thiopental infusion lowered the blood glucose level by an increase in blood insulin levels, by greater suppression of catecholamines, or by some other undetermined mechanism; and/or isoflurane increased blood glucose. In rats, thiopental in doses of 75–100 mg · kg⁻¹ injected i.p. reduced blood glucose concentration 65% accompanied by a significant increase in plasma insulin levels. Earlier studies have reported either no change or an increase in blood glucose concentration in humans after the administration of thiopental, but these studies used much smaller doses of thiopental (4–5 mg · kg⁻¹) and used nitrous oxide for anesthesia. Nitrous oxide has been reported to produce a hyperglycemic response in the presence of thiopental in patients. In the one study in which patients were given only thiopental (without nitrous oxide) there was a hypoglycemic response. In the present study, the administration of thiopental produced an average 15 mg · dl⁻¹ decrease in blood glucose before ischemia. Isoflurane has been associated with an increased blood glucose level. In rats anesthesia with 1 MAC isoflurane resulted in significantly higher plasma and brain glucose levels than did 1 MAC halothane or enflurane. Whether this was a result of less inhibition of the stress response (higher catecholamines producing higher plasma glucose), increased blood–brain barrier transport, or lower glucose use was not determined in that study. In humans the blood glucose level increased significantly from 77 ± 4 to 128 ± 9 mg/dl after the administration of 1.3 MAC isoflurane. This increase was significantly higher than the increase produced by 1.3 MAC halothane. In humans isoflurane anesthesia without the stress of surgery has been reported to decrease insulin secretion in response to glucose.

It has been shown that hypoglycemia may be detrimental to both normal and ischemic brains. However, neither EEG changes of ischemia nor changes in cerebral metabolites occur until the blood glucose level is less than 36 mg · dl⁻¹. It has also been reported that hyperglycemia existing before a severe ischemic event may be detrimental to the brain. The presumed mechanism for this is that, in the presence of ischemia, metabolism of glucose results in intracellular lactic acid accumulation, irreversible cell damage occurring when intracellular lactic acid concentration exceeds 20 μmol · g⁻¹. Glucose administration before ischemia has been reported to increase neurologic damage and was the reason why glucose administration was omitted from the present study. Even moderately increased blood glucose levels (180 mg · dl⁻¹) before ischemia have been reported to result in increased intracellular lactic acid and increased neurologic damage. Figure 2 demonstrates that the final neurologic deficit score was not related to the perischemic blood glucose. From the results of the present study it can be concluded that blood glucose within the range 40–145 mg · dl⁻¹ without acute change had no discernible effect on neurologic outcome.

It might be argued that the cerebral insult produced by 5 h ischemia in the pigtailed monkey was too severe to allow any cerebral protection by anesthetic agents because eight of 17 monkeys died. However, four of 17 monkeys were totally normal and one was very minimally damaged (NDS = 1). As previously stated, the goal was to produce an insult during isoflurane anesthesia with neurologic outcome comparable to the Nehls study so that any significant improvement produced by thiopental could be measurable. From our pilot studies it was concluded that the insult produced by 3–4 h ischemia during isoflurane was too mild. However, the range of neurologic damage resulting from 5 h of ischemia in pigtailed macaque monkeys during isoflurane anesthesia was as we expected from the results of the pilot studies. As such, we achieved our goal of approximating the same spectrum of neurologic injury as that reported by Nehls et al. for 6 h of ischemia in baboons.

It is concluded that in situations of prolonged but temporary focal ischemia during which suppression of cerebral function is maintained by either thiopental or isoflurane anesthesia and MAP is maintained, there is no difference in neurologic outcome or in the magnitude of cerebral infarction. Such equivalent results between isoflurane and thiopental may not be demonstrable with lesser (or greater) ischemic insults. For the degree of insult chosen, any differences that might exist between thiopental and isoflurane with regards to cerebral metabolic effects or distribution of regional CBF were not important in determining extent of neurologic injury. A seemingly logical reciprocal of our conclusion might be that isoflurane and thiopental are equally protective of the brain. However, protection was not demonstrated in the present study and therefore does not permit any clinical recommendations regarding the use of these anesthetics for the purpose of protecting the brain.

References

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