Anesthetic Choice of Halothane Versus Propofol Impact on Experimental Perioperative Stroke

Anish Bhardwaj, MD; Alejandro F. Castro III, BA; Nabil J. Alkayed, MD, PhD; Patricia D. Hurn, PhD; Jeffrey R. Kirsch, MD

Background and Purpose—It is not known whether preischemic exposure to anesthetic agents affects the amount of damage from transient focal ischemia that occurs after cessation of the anesthetic. We compared the effect of prior exposure to halothane or propofol on infarction size after transient middle cerebral artery occlusion (MCAO) induced in the awakening animal to test the hypothesis that anesthetic type and exposure duration would independently affect the amount of brain injury.

Methods—Male Wistar rats (weight, 200 to 300 g) were anesthetized briefly with halothane for placement of hemodynamic instrumentation. Twenty-four hours later, rats were treated with either a short (approximately 1 hour) or long (8 hours) duration of inhaled halothane (1% to 2%) or intravenous propofol (10 mg/kg bolus, 30 mg/kg per hour infusion). Each cohort (n=8 per group) was then subjected to 2-hour MCAO by the intraluminal suture technique. All anesthesia was discontinued once MCAO was achieved. Infarct volume was measured at 22 hours of reperfusion. In a second cohort, regional cerebral blood flow (CBF) was measured ([14C]iodoantipyrine autoradiography) at end-occlusion in short-duration halothane (n=5) or short-duration propofol (n=5) anesthesia groups and in corresponding surgical shams (n=3 each).

Results—Pericranial temperature, PaO2, Paco2, and blood pressure were controlled and not different among groups before or during occlusion. MCAO resulted in a similar immediate reduction in laser-Doppler flow signal after discontinuation of anesthesia in the awakening animals. Infarct volume was smaller in rats exposed to short-duration halothane in cortex (87.5±16.6 mm3) (mean±SEM) and caudoputamen (38.3±13.7 mm3) compared with rats exposed to short-duration propofol (cortex, 177.5±16.9 mm3; caudoputamen, 47.8±2.9 mm3). Infarct volume was not different in long-duration halothane versus long-duration propofol treatment. Absolute cortical or caudoputamen intraischemic CBF was not different between short-duration halothane or short-duration propofol treatment.

Conclusions—These data demonstrate that short-duration halothane exposure before MCAO in the awakening animal attenuates infarction volume compared with propofol. This protection by halothane is not mediated through preservation of intraischemic CBF. Longer durations of halothane exposure may activate secondary injury pathways, which negate the protective effects of short-term halothane preischemic treatment. (Stroke. 2001;32:1920-1925.)

Key Words: anesthesia ■ cerebral ischemia ■ halothane ■ propofol ■ stroke

Anesthesia-linked neuroprotection has been extensively investigated in transient focal1,2 and global3,4 ischemia in a variety of animal models. These agents uniformly alter neural activity and electric conduction and have diverse effects on cerebral blood flow (CBF) and metabolism.5,6 Inhalational anesthetics such as halothane have been shown to reduce ischemic tissue damage by a variety of cellular mechanisms7–11 and to produce cerebral vasodilation,5,12,13 in part, via a nitric oxide (NO)–mediated mechanism.14–17 Non-volatile agents such as propofol (2,6-di-isopropyl phenol) have also been shown to prevent neuronal injury in animal models of transient global1 and focal cerebral ischemia.18 Propofol reduces CBF and cerebral metabolic rate19,20; however, its neuroprotective properties may be linked to activation of γ-aminobutyric acid (GABA)A receptors3 or through inhibition of synaptic glutamate21 and catecholamine release.4 While there is considerable evidence for ischemic neuroprotection by such anesthetic agents, there is little information concerning the possibility that anesthetic agents affect outcome from middle cerebral artery occlusion (MCAO), which is induced after cessation of the anesthetic agent. Delayed or lasting effects of anesthetics could be important in both clinical and experimental neuronal injury that occurs after emergence from anesthesia. For example, if cerebrovascular reactivity or excitatory neurotransmitter levels do not return to basal conditions on emergence from anesthesia, then such

Received January 24, 2001; final revision received April 12, 2001; accepted April 18, 2001.
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Stroke is available at http://www.strokeaha.org

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anesthetic sequelae would alter outcome from postoperative (postanesthetic) stroke. Similarly, anesthetic agents could act as preconditioning stimuli in animal models, such that repeated episodes of anesthesia protect the brain from vulnerability when stroke is induced. The clinical import of delayed or persistent anesthetic actions is applicable to a patient population that has poor cerebrovascular reserve and is prone to cerebrovascular occlusive events undergoing surgical procedures under anesthesia, eg, carotid endarterectomy, aneurysmal clipping, or neuroradiological interventions such as stent placements for occlusive carotid or vertebrobasilar disease and intracranial angioplasty. Thus, neurological outcome in high-risk patients with preexisting cerebrovascular disease after surgical procedures may depend on the type of anesthetic used during the procedure.

We tested the hypothesis that the extent of ischemic brain injury in the awake rat is dependent on the type and duration of anesthetic exposure before the onset of MCAO. The observation that short-duration halothane, but not propofol, administration protects the brain from injury in the awakening rat opens the possibility that anesthetics have value as preconditioning agents to prevent subsequent brain injury.

Materials and Methods

General Preparation and Animal Surgery

The experimental protocol was approved by the Institutional Animal Care and Use Committee and conforms to the National Institutes of Health guidelines for the care and use of animals in research. Animals were randomized to treatment group in all protocols. All experiments were conducted by a single individual (A.F.C.). Adult male Wistar rats (weight, 200 to 300 g) were anesthetized with halothane (4% induction; 1% to 2% maintenance in oxygen-enriched air) and allowed to breathe spontaneously via a snout mask. With the use of aseptic surgical techniques, catheters were inserted into the right femoral artery and vein to monitor arterial blood pressure and arterial blood gases and to administer fluids and drugs. All catheters were exteriorized in the posterior mid-thorax and suture-fixed on a stainless steel swivel, allowing free movement of the rat in its cage. An infusion of heparinized (20 U/mL) 0.9% saline at 0.5 mL/h was administered to ensure catheter patency. Laser-Doppler flowmetry (LDF) was measured with a chronically implanted Perimed probe within a retaining sleeve. An area 2 to 3 mm in diameter in the right parietal bone (2 mm posterior and 6 mm lateral to bregma) was thinned with a high-speed drill for placement of the retaining sleeve, which was cemented with dental acrylic. Rectal and temporalis muscle temperatures were monitored and maintained within a normothermic range (36°C to 37°C) with a heating lamp throughout the surgical procedures. Rats were then allowed to emerge from anesthesia and allowed free access to food and water. Total anesthetia time was limited to 30 to 45 minutes.

Transient Focal Cerebral Ischemia and Reperfusion

Twenty-four hours after instrumentation, rats began treatment with short (approximately 1 hour) or long (8 hours) durations of either inhaled halothane (n=8 per group) or propofol (10 mg/kg IV bolus, followed by 30 mg/kg per hour IV infusion; n=8 per group). The LDF probe was fixed into the retaining sleeve, and the signal was allowed to stabilize over a 30-minute period before baseline measurements were obtained. All rats were treated with atropine methyl bromide (2 mg/kg IP) to minimize bronchial secretions. Reversible MCAO (2 hours) was produced by the intraluminal suture technique, as previously described. Successful MCAO was documented by an abrupt decrease in LDF signal to at least 40% of preischemic values. The total time taken for surgical preparation and initiation of focal ischemia under anesthesia was 45 to 60 minutes. After MCAO, the neck wound was closed, allowing approximately 10 mm of the nylon suture to be exposed outside the closed incision. All surgical wounds were infiltrated with 0.25% bupivacaine. The anesthetic agent was then discontinued, and the rat was allowed to emerge and move freely about the home cage. At the end of 2 hours of ischemia, reperfusion was produced by withdrawal of the intraluminal suture with rats in the unanesthetized state; this was associated with rapid restoration of the LDF signal. LDF measurements were averaged in 5-minute epochs at 15, 30, 60, 75, 90, and 120 minutes after the onset of MCAO and 15 minutes of reperfusion. At 22 hours of reperfusion, rats were deeply anesthetized with 5% halothane and decapitated. The brain was harvested and sliced into seven 2-mm-thick coronal sections for staining with 1% triphenyltetrazolium chloride in saline at 37°C for 30 minutes, as previously described. Infarct volume was measured with digital imaging (MTI Series 68 Video Camera) and image analysis software (SigmaScan Pro, Jandel). The infarcted area was numerically integrated across each section and over the ipsilateral hemisphere. Infarct volumes were measured in cerebral cortex and the caudoputamen complex and expressed as a percentage of the ipsilateral structure, as previously described.

Regional CBF Measurements

End-ischemic CBF was measured in additional cohorts by quantitative [14 C]iodoantipyrine ([14 C]IAP) autoradiography, as described previously. As in the previous experiments, rats were instrumented for physiological measurements, then 24 hours later they were subjected to MCAO or sham occlusion with short-duration halothane (n=5), short-duration propofol anesthesia (n=5), or surgical sham procedure (n=3). As before, anesthesia was discontinued once successful MCAO was confirmed by LDF, then the rats were allowed to awaken in a restraining chamber. At 2 hours of MCAO, arterial blood pressure and blood gases were measured. Then 40 µCi of [14 C]IAP (New England Nuclear) in 0.8 mL of isotonic saline was infused intravenously for 45 seconds. During infusion, fifteen 10- to 20-µL samples of free-flowing arterial blood from the femoral artery catheter were collected in heparin-coated sample tubes. With the intraluminal suture still in place, the rat was decapitated 45 seconds after the start of infusion. One postdecapitation arterial blood sample was also collected. The brain was quickly removed and frozen at −50°C in 2-methylbutane on dry ice. Each brain was sectioned by cryostat into 20-µm-thick coronal sections at −20°C and thaw-mounted onto cover glasses. Sections were apposed for 1 week to film (Kodak, Bio-Max MR) with 1 C standards. The concentrations of [14 C]IAP in blood samples were determined by liquid scintillation spectrometry (Beckman, model 3801) after decolorization with 0.2 mL of tissue solubilizer (Soluene-350, Packard Instruments Co). Autoradiographic images representing 5 different coronal levels (+2.2, +0.2, −1.8, −3.8, and −5.8 mm from bregma, 6 to 9 images at each coronal level) were digitized, and CBF was determined with the use of image analysis software, as previously described. Two methods of analysis were used to determine CBF. First, discrete areas were measured by sampling 0.08-mm² squares within those regions most vulnerable to MCAO: frontal and parietal cortex and medial and lateral caudoputamen. Flow rates were then averaged from squares assessed from 6 to 9 consecutive brain slices at each of 3 coronal levels (+2.2, +0.2, and −1.8 mm from bregma). In the second method, tissue areas for increasing incremental ranges of flow rates were determined by digital image scanning for selected slices spanning the entire ischemic hemisphere. These areas were then averaged over 3 images from each brain level (+2.2, +0.2, −1.8, −3.8, and −5.8 mm from bregma) and numerically integrated across the 5 coronal levels to obtain tissue volume with CBF of 0 to 20 mL/min per 100 g and increasing increments.

Statistical Analysis

All values are expressed as mean±SEM. Two-way ANOVA was used to detect differences between groups and over time for each individual variable. One-way ANOVA was used to detect differences over time in both groups when the 2-way ANOVA demonstrated a significant effect of time or group by time interaction. Post...
Selected Physiological Variables at Baseline (Preischemia), During Ischemia, and at 15 Minutes of Reperfusion (Postischemia) in Treatment Groups With Short and Long Exposure to Halothane or Propofol (n=8 per Group)

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<tr>
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MABP indicates mean arterial blood pressure. Values are mean±SEM.

hoc comparisons were conducted with the Newman-Keuls test. The criterion for statistical significance was \( P<0.05 \).

**Results**

All physiological variables (eg, pericranial temperature, PaO2, PaCO2, blood pressure) were maintained in a normal range during ischemia (Table). In all groups, MCAO resulted in a similar immediate reduction in LDF signal between groups (short-duration halothane, 22±3%; long-duration halothane, 24±4%; short-duration propofol, 34±5%; long-duration propofol, 27±5% of baseline). Within 15 minutes (30 minutes into the period of ischemia) of cessation of anesthetic administration, rats from both groups appeared as if the global effects of these drugs had completely resolved (were awake and moved freely). Removal of the intraluminal suture in awake animals resulted in a rapid and complete return of the LDF signal to nonischemic values (Figure 1). Infarct volume in the short-duration halothane group (cortex, 24±4% of ipsilateral cortex; caudoputamen, 46±5% of ipsilateral caudoputamen complex) was significantly smaller \( (P<0.05) \) than that in the short-duration propofol group (cortex, 47±4%; caudoputamen, 61±4%). Preischemic short-duration halothane treatment resulted in smaller caudoputamen infarct relative to long-duration halothane (66±5%), but cortical damage was equivalent (35±5%) in both groups. There were no differences between long-duration halothane and long-duration propofol groups (Figure 2).

To evaluate the role of potential differences in ischemic CBF between the short-duration halothane and short-duration propofol groups, both absolute end-occlusion CBF and the pattern of blood flow distribution were examined during ischemia, after the rats emerged from anesthesia. At 2 hours of MCAO, absolute CBF was not different between treatment groups in the areas sampled within the MCA territory, ie, frontal and parietal cortex and medial and lateral caudoputamen (Figure 3). Furthermore, there were no differences in blood flow distribution at 2 hours of MCAO across the ischemic hemisphere in short-duration halothane versus short-duration propofol groups (Figure 4).

**Discussion**

The main findings of this study are as follows: (1) short-duration halothane (<1 hour), but not equivalent propofol
exposure, decreases brain vulnerability to subsequent focal ischemic insult initiated shortly before cessation of the anesthetic; (2) the relative beneficial effect of preischemic exposure to halothane is lost with prolonged anesthetic exposure; and (3) the mechanism of protection by preischemic short-duration halothane exposure does not appear to involve an alteration in cerebral perfusion at end-ischemia. Thus, preischemic anesthetic administration affects neurological outcome in a manner that is dependent on the anesthetic agent used and the duration of preischemic exposure. The doses of anesthetic used in our experiments are comparable to those previously used.6 Equipotence of halothane and propofol at these doses was estimated by the presence of comparable physiological parameters (blood pressure and PaCO₂ during spontaneous ventilation), response to tail-clamp stimulus, and no differences in the appearance of the righting reflex after cessation of anesthetic administration.21 Halothane concentration (1% to 2%) was adjusted to maintain comparable depth of anesthesia, as dictated by these physiological parameters. The beneficial effect of short preischemic treatment with halothane does not appear to be due to an alteration in percent reduction of cerebral perfusion during or after reperfusion from intraluminal carotid artery occlusion. We used LDF as a measure of cortical cerebral perfusion. While LDF is not a measure of CBF, it provides a rapid, noninvasive, and continuous assessment of blood flow velocity and reflects relative changes in CBF.23,28 A fixed LDF probe-adapter device embedded in the skull achieved spatial continuity of recording and reduction in movement artifact in the awake animal without hemodynamic compromise.

The present data indicate that end-ischemic CBF was not different in the cortex or the caudoputamen complex in the 2 treatment groups. Similarly, the volume of hypoperfused...
tissue (<40 mL/100 g per minute) was not different between the halothane- and propofol-anesthetized rats. We did not determine regional CBF at other time points of reperfusion when hypoperfusion could have occurred. We have previously shown that during reperfusion (6 hours), regional CBF is characterized by large intraregional variability, and rCBF heterogeneity and patchy CBF recovery patterns have been well characterized by other investigators. Accordingly, effects on recovery of rCBF over time in the short-duration halothane versus short-duration propofol groups cannot be excluded. While the impact of anesthetic agents on CBF during anesthesia has been well studied, there are limited data on cerebrovascular effects after emergence from anesthesia. For example, inhalational anesthetics have been shown to have dose-dependent direct cerebral vasodilatory effects that are mediated partially by NO. Previous work to determine whether inhalational anesthetics increase NO activity in brain has produced variable results. Relatively little is known about delayed or residual cerebrovascular sequelae in the previously anesthetized brain.

Studies on ischemic neuroprotection with propofol have yielded mixed results. For example, propofol has been shown to exert neuroprotection in transient, but not permanent, focal ischemia. Others have found no differences in focal ischemic outcome with halothane and propofol anesthesia. Numerous mechanisms for the neuroprotective effect of propofol have been postulated, including decrement in CBF in conjunction with decreased cerebral metabolic rate for oxygen and reduced cerebral electric activity. The mechanism of reduced CBF with propofol remains unclear; however, a vascular origin is not likely because propofol causes vasodilation in isolated vessels. Propofol had no effect on subsequent postanesthetic cerebral vasodilator responses to hypercapnia in our previous study. Excitotoxic mechanisms may also play an important role and explain the findings of our study. While numerous studies have explored the effect of different anesthetics on the excitotoxic cascade leading to neuronal injury, none have studied these effects after emergence from anesthesia. For example, NO plays a dual role, enhancing CBF on the one hand but also exerting neurotoxic effects when present in large concentrations. Thus, prolonged exposure to halothane may further elaborate NO production that may exert excitotoxic effects, thereby exacerbating neuronal injury. Furthermore, halothane has been shown to modulate both excitatory and neuroinhibitory synaptic transmission in vitro, and the N-methyl-D-aspartate receptors have been shown to be more sensitive to the effects of halothane than other glutamate receptor subtypes. Thus, exposure to longer durations of halothane may result in activation of secondary pathways that negate the protective effects of short-term halothane exposure. Propofol, on the other hand, has been shown to exert neuroprotection via activation of the GABA_R receptors and suppression of sodium channels in the central nervous system, thereby inhibiting synaptic release of glutamate and sympathetic neurotransmission. Propofol has also been shown to exert protection in kainate-induced toxicity.

Irrespective of the mechanism(s), our study demonstrates that duration and type of anesthesia after emergence are important in ischemic outcome. The clinically oriented rationale for conducting this study was to determine whether anesthetic management was of importance if the majority of the ischemic insult occurred after cessation of the anesthetic agent. These data may be important in defining the optimal anesthetic for patients undergoing carotid endarterectomy or other vascular procedures who then emerge from anesthesia with a new neurological deficit. Our data suggest that the choice of anesthetic may be an important variable to consider for patients requiring a short operation in which the risk of cerebral ischemia is significant. However, our data cannot be used to determine the relative value of a general compared with a regional anesthetic when the risk of ischemia is high. Additional studies will be needed to further elucidate the mechanism of neuroprotection afforded by brief preischemic administration of halothane. In the heart, preconditioning with inhalational anesthetics results in tissue protection by a mechanism that involves activation of adenosine triphosphate–regulated potassium channels. Further studies will be needed to assess the role of these channels in the mechanism of ischemic protection by halothane in our model.

Acknowledgments

This work was supported in part by US Public Health Service, National Institutes of Health grant NS20020. Dr Bharwaj is supported in part by the Established Investigator Grant from the American Heart Association. Propofol (2%) was donated by Zeneca Ltd.

References


35. Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. *Proc Natl Acad Sci U S A*. 1990;87:1620–1624.

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*Stroke*. 2001;32:1920-1925
doi: 10.1161/01.STR.32.8.1920

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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