Barbiturate Protection in Acute Focal Cerebral Ischemia

BY ALLAN L. SMITH, M.D.,* JULIAN T. HOFF, M.D., SURL L. NIELSEN, M.D., AND C. PHILIP LARSON, M.D.

Abstract

We have found that anesthetic technique modifies the neurological and pathological sequelae of unilateral middle cerebral artery and internal carotid artery occlusion in dogs. Occlusion was performed in seven groups of six dogs during each of the following anesthetic regimens: light (0.8%) halothane, "awake," deep (1.9%) halothane, deep halothane with mean arterial pressure reduced to 55 torr, pentobarbital (56 mg per kilogram), light halothane plus 40 mg per kilogram thiopental begun just before cerebral artery occlusion, and light halothane plus 40 mg per kilogram thiopental begun 15 minutes after occlusion. Body temperature, arterial PCO₂, PO₂, pH, and blood pressure (except as noted above) were maintained normal. Neurological examinations were performed daily. On the seventh day the dogs were killed and their brains removed for pathological study. Hemiparesis occurred in five of six dogs under light halothane and five of six awake dogs; a mean of 10.8% and 9.6%, respectively, of their right hemispheres were infarcted. In the deep halothane groups, all of the normotensive and five of the six hypotensive dogs became severely hemiplegic; mean infarction size was 28.2% and 34.1%, respectively. Only one of the 18 dogs who received a barbiturate sustained a neurological deficit — a transient unilateral weakness. Means of 1.4%, 2.7%, and 0.1% of the right hemisphere were infarcted in the barbiturate animals. The protective action of barbiturates in canine acute focal cerebral ischemia suggests that they should be considered for anesthesia in surgery requiring cerebral vessel occlusion and perhaps even for treatment of acute stroke.

Introduction

Increasing numbers of patients with cerebrovascular disease are subjected to corrective surgical procedures such as carotid artery thromboendarterectomy, cerebral aneurysm ligation, and cerebral artery bypass. The temporary or permanent occlusion of cerebral vessels required by these procedures incurs a high risk of brain damage. It is of manifest importance to discover those factors which might lessen the short-term and long-term hazards of cerebral vessel occlusion. Although the effects of arterial P CO₂ (P aCO₂) and blood pressure have been reported, there has been no direct inquiry into influence of anesthetic technique on the occurrence of neurological damage. Accordingly, we compared the pathological and neurological sequelae of experimental cerebral artery occlusion in animals, produced during each of seven anesthetic techniques. We have found that anesthesia which includes barbiturate may significantly decrease the incidence of cerebral infarction.

Methods

The right internal carotid and middle cerebral arteries were permanently clipped through a temporal burr hole in each of 42 dogs. These dogs were divided into seven groups of six
animals. Each group differed in anesthetic management as follows:

Group 1: Light halothane* (0.8% end-tidal).

Group 2: “Awake.” Halothane, given for initial surgery, was discontinued three minutes before vessel occlusion.

Group 3: Deep halothane (1.9% end-tidal).

Group 4: Deep halothane-hypotension. Five minutes before cerebral vessel clipping, halothane was increased to reduce mean arterial blood pressure to 50 to 60 torr and pressure was held at that level for one hour. Halothane then was decreased to 0.8% end-tidal and blood pressure restored to a mean of at least 110 torr.

Group 5: Pentobarbital. Anesthesia was induced with 25 mg per kilogram pentobarbital intravenously. Just before vessel clipping, sufficient additional drug was given to reduce EEG frequency to less than 1 Hz.

Group 6: Light halothane plus thiopental pretreatment. Halothane (0.8%) was maintained throughout the study. Twenty milligrams per kilogram thiopental were given rapidly intravenously immediately before vessel clipping and an additional 20 mg per kilogram were given slowly over the ensuing two hours.

Group 7: Light halothane plus thiopental posttreatment. A constant background of 0.8% halothane was maintained. Fifteen minutes after vessel clipping, we gave 20 mg per kilogram thiopental rapidly intravenously. An additional 20 mg per kilogram were administered slowly over the next two hours.

Anesthesia was induced with halothane, except in pentobarbital animals. The trachea of each dog was intubated and the animals were ventilated with 30% O2-70% N2. An intravenous infusion was begun in a peripheral vein and a plastic cannula was placed percutaneously into a femoral artery for pressure measurements and blood sampling. End-tidal Pco2 was continuously monitored with an infrared analyzer and maintained at 36 to 41 torr throughout the study. Arterial Pco2, Paco2, and pH were measured hourly and base deficits greater than 5 mEq per liter were corrected by slow intravenous administration of NaHCO3. Arterial blood pressure was continuously transduced and recorded on a polygraph together with the end-tidal Pco2. Phenylephrine was infused as needed to maintain mean arterial blood pressure above 110 torr in all except Group 4 animals. Inspired and end-tidal halothane concentrations were measured by infrared analysis. The electroencephalogram was recorded from a pair of left fronto-occipital leads. Rectal temperatures were maintained at 38°C by surface warming.

We began surgery only after blood pressure and end-tidal halothane and CO2 concentrations had been stable for at least 15 minutes. A 15 mm right temporal burr hole was made and the dura opened. The internal carotid artery was permanently occluded with a Scoville clip placed between the origins of the posterior communicating and anterior cerebral arteries. The middle cerebral artery was clipped just distal to the origin of the anterior communicating artery. The dura was not closed, but the overlying muscles and skin were approximated. Mechanical ventilation and anesthesia were maintained for six hours after vessel ligation in all dogs but those of the “awake” group, and they were then permitted to awaken. If spontaneous ventilation did not maintain arterial PaO2 above 60 torr and PaCO2 below 50 torr when breathing air, ventilator therapy was continued.

On the day of surgery, 500 ml 5% dextrose and 1,000 ml saline were given intravenously. Animals unable to drink postoperatively were given 500 ml Ringer’s lactate daily. All dogs were treated postoperatively with intramuscular penicillin, 105 units, and streptomycin, 0.75 gm, daily.

We scored motor function (table 1) daily for seven days in each animal. The dogs were then killed with pentobarbital. The brain was removed and clip placement verified. Pathological evaluation was performed by one of us (SLN), who did not know which anesthetic had been given. The fixed brain was cut into 3-mm thick coronal sections. A grid with 2-mm squares, placed over each section, was used to estimate percent of infarcted and normal tissue. Representative areas of normal and abnormal tissue were stained with hematoxylin-eosin and the abnormalities confirmed microscopically. Criteria for infarction included loss of normal cellular elements, infiltration with macrophages, and early vessel proliferation. The pathologist also attempted to predict the presence or absence of hemiparesis.

Infarction data were analyzed by the Wilcoxon rank test and neurological scores and experimental conditions with analysis of variance (P < 0.05).

Results

Blood gases, arterial pressure, body temperature, and ventilator time (table 2) differed among groups only as follows. Blood pressure in the halothane-hypotension group differed from that of all other groups; the 9 torr difference between Groups 6 and 7 just reached significance. Pentobarbital dogs had the longest ventilator time and awake dogs had the shortest ventilator time.

The neurological scores obtained daily for seven days were averaged and the means for the six overall scores for each treatment group were computed (table 3, fig. 1). Most animals with deficits improved one grade over the postoperative week. Thus, a score of 2.4 implies a dog that could not stand until the fourth day after vessel clipping. A score of greater than 3.0 indicates an animal that died. Five of six dogs whose cerebral vessels were clipped during light halothane anesthesia developed obvious neurological deficits. Equivalent deficits appeared in the “awake” animals.

<table>
<thead>
<tr>
<th>Neurological Evaluation Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological signs</strong></td>
</tr>
<tr>
<td>No neurological deficit</td>
</tr>
<tr>
<td>Walks with limp or circles to side of lesion</td>
</tr>
<tr>
<td>Walks poorly; stands, but cannot support body with right limbs held off ground</td>
</tr>
<tr>
<td>Cannot stand without support</td>
</tr>
<tr>
<td>Dead</td>
</tr>
</tbody>
</table>

*Halothane was supplied by Ayerst Laboratories.
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Mean neurological scores following seven anesthetic techniques.

Deep halothane was significantly worse than light halothane. All animals given deep halothane anesthesia became hemiparetic. Neurological signs also were severe in dogs made hypotensive with halothane. No neurological abnormalities occurred following deep pentobarbital anesthesia. Among the 12 animals given thiopental before or after vessel occlusion, only one had a neurological deficit. Barbiturates, compared with light halothane or "awake," significantly reduced or eliminated the neurological sequelae of middle cerebral artery and internal carotid artery clipping.

A mean of about 10% of the right hemisphere was infarcted in light halothane or awake dogs (table 4, fig. 2). Infarctions were three times more extensive in deeply anesthetized halothane animals, with either normal or decreased blood pressure. Infarctions were small or absent in the three barbiturate groups, except for one animal who also had a Class 1 neurological deficit. Although there was considerable variability in

![Figure 1](http://stroke.ahajournals.org/)

FIGURE 1

Mean neurological scores following seven anesthetic techniques.

![Figure 2](http://stroke.ahajournals.org/)

FIGURE 2

Mean percents of right hemisphere infarcted following cerebral artery occlusion.
TABLE 3

Neurological Sequelae of Cerebral Artery Occlusion

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Mean neurological scores*</th>
<th>Individual scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light halothane</td>
<td>1.1 ± 0.4</td>
<td>2.6, 2.4, 0.6, 0.7, 0.4, 0</td>
</tr>
<tr>
<td>&quot;Awake&quot;</td>
<td>1.0 ± 0.3</td>
<td>0.1, 0.7, 1.0, 1.0, 2.1, 0</td>
</tr>
<tr>
<td>Deep halothane</td>
<td>2.4 ± 0.3</td>
<td>2.0, 2.9, 1.7, 1.6, 3.7, 2.6</td>
</tr>
<tr>
<td>Deep halothane-hypotension</td>
<td>2.2 ± 0.6</td>
<td>1.3, 2.9, 1.4, 3.9, 0.0, 3.7</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>0</td>
<td>0, 0, 0, 0, 0, 0</td>
</tr>
<tr>
<td>Light halothane + thiopental, preocclusion</td>
<td>0.05 ± 0.05</td>
<td>0, 0, 0, 0, 0, 0</td>
</tr>
<tr>
<td>Light halothane + thiopental, postocclusion</td>
<td>0</td>
<td>0, 0, 0, 0, 0, 0</td>
</tr>
</tbody>
</table>

*± SE analysis of variance shows F = 9.6 (P < 0.005) and least significant difference = 0.91 at the P < 0.05 level.

Discussion

The data indicate that barbiturates reduce the injury produced by acute arterial occlusion. Either profound pentobarbital anesthesia or addition of a moderate dose of thiopental to halothane anesthesia protected against neurological deficit and/or cerebral infarction. The fact that halothane to deep levels did not prevent injury — but rather caused its increase — suggests that deep anesthesia per se is not protective. The lack of protection with light halothane anesthesia also suggests that anesthesia, by itself, is not the means by which the barbiturates act.

Since other workers have found that removing the clips several hours after placement prevents neurological lesions, it is not surprising that thiopental was protective even when begun 15 minutes after arterial occlusion. The duration of the postocclusion period in which barbiturates may protect remains to be established.

Previous studies of brain halothane uptake suggest that brain tissue halothane content in the "awake" dogs fell to less than 0.2% of an atmosphere by five minutes after vessel clipping. Thus, our "awake" group would seem to be a reasonable approximation to "true" awake. The effect of light halothane did not differ from "awake," but deep halothane anesthesia resulted in a higher incidence of hemiparesis and infarction than either light or no halothane. The deleterious effect of deep halothane may be a threshold phenomenon, which does not appear during light anesthesia. Alternatively, the adverse effects of light halothane may have been obscured by the large variability of the results.

As might have been anticipated, deep halothane with hypotension was no better, and perhaps worse, than deep halothane without hypotension. Pressures of 50 to 60 torr are below the autoregulatory range of dog cerebral vasculature. Thus, despite the vasodilatory effect of halothane, we would expect cerebral blood flow (CBF) to be subnormal even in regions with intact vasculature. CBF in borderline perfused areas would be further reduced and must have been lower than flows consistent with survival for

TABLE 4

Pathological Sequelae of Cerebral Artery Occlusion

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Mean percent of right hemisphere infarcted*</th>
<th>Individual percents of right hemisphere infarcted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light halothane</td>
<td>10.8 ± 5.2</td>
<td>22.6, 30.0, 0.5, 1.9, 10.0, 0.5</td>
</tr>
<tr>
<td>&quot;Awake&quot;</td>
<td>9.6 ± 7.4</td>
<td>0.1, 0.0, 10.4, 0.5, 46.0</td>
</tr>
<tr>
<td>Deep halothane</td>
<td>28.2 ± 9.9</td>
<td>1.9, 51.0, 0.5, 22.3, 58.1, 35.4</td>
</tr>
<tr>
<td>Deep halothane-hypotension</td>
<td>34.1 ± 7.7</td>
<td>25.1, 47.0, 38.0, 53.1, 10.4, 41.1</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>1.4 ± 0.8</td>
<td>3.4, 0.4, 49.0, 0.0, 0</td>
</tr>
<tr>
<td>Light halothane + thiopental, preocclusion</td>
<td>2.7 ± 2.5</td>
<td>0.0, 0.5, 0.5, 15.0, 0</td>
</tr>
<tr>
<td>Light halothane + thiopental, postocclusion</td>
<td>0.1 ± 0.1</td>
<td>0.0, 0.0, 0.0, 0, 0</td>
</tr>
</tbody>
</table>

*± SE
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FIGURE 3
Coronal section of a dog brain showing 35% infarction of the right hemisphere

an hour. Return to normal perfusion pressure would not save these areas of brain.

Protection against cerebral hypoxia has been suggested previously for both barbiturates and halothane. In these studies, survival was recorded after either the entire brain or the whole animal was subjected to severe ischemia and/or anoxia. Severe ischemia or anoxia should produce major cardiorespiratory alterations, which may modify the likelihood of an insult. Since anesthetics alter cardiorespiratory responses to anoxia, it is difficult to know whether the previously reported "protection" resulted from salutary effects of anesthetics on the brain or on other organ systems. In the present study, we controlled variables which affect cerebral hemodynamics (arterial P\textsubscript{CO\textsubscript{2}}, P\textsubscript{O\textsubscript{2}}, pH, blood pressure, and body temperature). Thus, we studied specific brain protection of anesthetics, rather than some indirect manifestation of anesthetic action. This may explain why we found halothane not to be salutary. The protective effect of barbiturates that we observed is consistent with earlier studies.

The mechanism of barbiturate protection may be on a macroscopic (flow to large regions) or microscopic (capillary, cell) level. First consider the macroscopic level. Differences in sequelae following the seven anesthetic techniques may relate to regional cerebral blood flow (rCBF) alterations. Cerebral vasodilators, which act only on normal brain blood vessels, may divert ("steal") blood flow from ischemic tissue. In contrast, cerebral vasoconstrictors, which again act on normal vessels, may increase rCBF to ischemic areas ("inverse steal"). Hypocapnia is an example of the latter phenomenon. In a canine preparation similar to ours, smaller infarctions followed middle cerebral artery occlusion during hypocapnia than during normocapnia. Excluding the hypotensive group, the severity of neurological sequelae (tables 3 and 4) was directly related to the expected CBF. Thiopental plus halothane (doses similar to ours) halves CBF. Pentobarbital probably reduces CBF by at least this much. Light halothane increases CBF about 10% and 2.1% halothane more than doubles CBF. Although the flow data are consistent with the steal-inverse steal hypothesis, all data are not. Other workers have not found steals or inverse steals with carbon dioxide. Hypocarbia is associated with greater lactate production in ischemic brain than normocarbia. Furthermore, our laboratory was not able to document the steal phenomenon during either light or deep halothane anesthesia in the dog middle cerebral artery occlusion preparation. Using the Xenon washout technique, we found that rCBF to the ischemic region was always increased by deep halothane anesthesia.

Although we could not document steals, rCBF in intact brain areas still may affect ischemia in occluded areas, because CBF alters intracranial pressure (ICP) through its effect on intracranial blood volume. Increases in CBF raise ICP; halothane decreases ICP and barbiturates decrease ICP. Perhaps the raised ICP of halothane decreased effective cerebral perfusion pressure (arterial-ICP) or predisposed to cerebral edema. Barbiturates would have the opposite effect, i.e., a reduction in ICP.

Depression of cerebral oxygen consumption (CMRO\textsubscript{2}) may have a role in barbiturate protection but cannot be the only factor. Both halothane and barbiturates decrease CMRO\textsubscript{2}. Furthermore, there is evidence to suggest that the reduction in CMRO\textsubscript{2} during anesthesia reflects decreased cerebral activity rather than a decrease in oxygen required to maintain cellular integrity.

Several theories of the pathogenesis of irreversible anoxic-ischemic brain damage at the microscopic level...
have been advanced. We shall review some of these ideas very briefly and then speculate on their role in the protective action of barbiturates. While appearing to be competitive theories, each emphasizes different aspects of the same phenomenon, seen darkly through the glass of differing experimental preparations. Ames29 has suggested that the initial injury is at the capillary. The capillary injury, together with pericapillary swelling, is responsible for the "no-reflow" phenomenon, i.e., the failure of perfusion to reestablish itself after a period of temporary vascular occlusion. Once the capillary damage is advanced, cell death is inevitable. Others have emphasized the importance of CNS ultrastructure changes. Severe hypoxia causes microvacuolization of neurons, corresponding to mitochondrial swelling, before increased tissue water appears and swelling of astrocytic processes can obstruct capillaries.27-28 The role of both local pericapillary edema and intracellular edema in the irreversibility of ischemic damage also has been stressed by Meyer29 and Sundt;6 the latter failed to observe "no-reflow." Biochemical alterations of severe hypoxia include a progressive fall in neuronal high energy phosphates (ATP, phosphocreatine) and an increase in lactate concentration.30, 31 Thus, cells are doomed because they run out of energy and are poisoned by accumulation of acid metabolites. Finally, release of a toxic metabolite, such as serotonin, might contribute to a self-induced and self-perpetuated worsening of the hypoxic state.6, 25

Any hypothesis on the protective action of barbiturates must answer this question: How do barbiturates, which are given once and are thus a temporary measure, protect against brain infarction in permanent arterial occlusion? Permanent survival of the focal ischemic area implies that either a new source of perfusion must have become established within 6 to 24 hours of the occlusion or that remaining vasculature was sufficient once a temporary impairment to perfusion was reversed. Since such a rapid growth of vessels seems unlikely, we should look for a temporary impairment to perfusions that barbiturates could affect. It seems unlikely that barbiturates exert their salutary effects on the biochemical abnormalities of brain hypoxia. Although the drug decreases the rate of fall in brain ATP content during hypotension,24 it does not alter ATP depletion in arterial hypoxemia33 or asphyxia.34 Furthermore, the validity of ATP and lactate levels as quantifiers of brain cell viability has come to be questioned.34, 35

We believe that barbiturates protect principally by decreasing CBF and ICP. The lowered ICP would minimize pressure in cerebral capillaries and venules, thus maximizing perfusion pressure in ischemic areas. Cerebral vasodilators like CO2 have been found to aggravate cerebral edema.29 In contrast, the low CBF of barbiturate anesthesia would minimize cerebral edema, and might reduce capillary stasis and/or capillary damage. Cerebral edema could be the temporary factor, which contributes to irreversibility of hypoxic cell damage, but which is prevented by barbiturates. Decreased CMRO2 may be a secondary factor in barbiturate protection.

We compared neurological scores by computing means and using analysis of variance, because these techniques are more powerful for detecting differences among small groups (N = 6) than Chi square or the usual nonparametric measures. Treating an ordered scale as a continuous variable for purposes of statistical analysis is valid and appropriate in the case of the present data;28 actually the ordered scale approximates a continuous phenomenon. Since infarctions tended to be either very small or very large, the infarction data were not normally distributed. Kurtosis was always less than the normal value of 3, ranging from 1.0 to 2.9. Variances can be somewhat misleading in this situation and have been omitted from figure 2. We used the nonparametric Wilcoxon test5 for group comparison, since the t test or analysis of variance requires normally distributed data.

The severity of neurological signs in most animals was consistent with the extent of infarction, but a few animals suffered hemiparesis with small infarctions. Figure 4 shows the brain of one such dog. The infarction, though small, is located in the vital internal capsule. The excellent agreement of observed neurological signs with those predicted from autopsy data suggests that subjectivity did not affect the clinical evaluations.

We believe that barbiturates such as thiopental deserve a clinical trial as anesthetics or anesthetic supplements for surgical operations having a high risk of brain infarction, such as carotid artery thromboendarterectomy and cerebral artery aneurysm ligation. Thiopental is a commonly used anesthetic supplement and only modest doses would be required. Based on a canine induction dose for thiopental of 11 mg per kilogram29 and a human dose of 3 mg per kilogram, the dog dose for thiopental is three to four times the human dose. Our 40 mg per kilogram dog dose is thus equivalent to less than 1,000 mg thiopental in a 70 kg man. This dose could be started just before vessel ligation in surgical operations. A common way to provide good operating conditions for cerebral artery aneurysm ligation is to lower the blood pressure with deep halothane anesthesia. Results from the halothane plus hypertension group suggest that this may not be desirable. An equivalent degree of brain "shrinkage" and lowering of CBF might be obtained more safely with barbiturates.

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