Barbiturate Protection in Cerebral Hypoxia

Allan L. Smith, M.D.*

Recent animal work has indicated that barbiturate anesthesia protects the brain against several types of hypoxic† insults. The goal of this paper is to review these data, to examine suggested mechanisms, and to consider possible clinical implications. Before doing so, I briefly review the effects of hypoxia on cerebral metabolism, as well as past experience with non-pharmacologic attempts to achieve cerebral protection with hyperventilation and hypothermia.

Cerebral Metabolism and Hypoxia

Glucose is the major (and usually sole) substrate from which the brain derives energy. Glucose first is metabolized to pyruvate. Normally, 5–8 per cent of the pyruvate is anaerobically converted to lactate and the remainder enters the Krebs cycle and is metabolized to CO₂ and H₂O. The latter reaction requires oxygen but yields 18 times more energy in the form of high-energy phosphate (\(\sim P\)) than the anaerobic pathway. In the absence of oxygen, \(\sim P\) production from the lactate reaction is insufficient to support the energy needs of the brain. Adenosine triphosphate (ATP) is the major form in which \(\sim P\) stored and is immediately available for neuronal energy requirements; phosphocreatine (PCr) serves as an additional store of \(\sim P\) which, in the presence of adenosine diphosphate (ADP), can be converted to ATP.

In mild cerebral hypoxia, lactate production increases in an effort to maintain energy stores, and lactate concentrations of brain tissue, CSF, and cerebral venous blood are elevated. Cerebral venous blood \(P_{O_2}\) may decrease, but this is not a reliable predictor of the severity of cerebral hypoxia. Errorneous interpretation is especially likely when hypoxia is patchy or regional, because local abnormalities are not reflected in average cerebral venous blood \(P_{O_2}\) as sampled from the jugular bulb or sagittal sinus. The increased lactate production resulting from mild cerebral hypoxia is often associated with a measurable increase in glucose consumption, but measurable decreases in cerebral oxygen consumption (CMR\(_{O_2}\)) are found only when cerebral hypoxia has become severe. Concentrations of high-energy phosphate stores in brain cells (particularly ATP) remain normal until hypoxia is extreme. However, neurons can often be metabolically “resuscitated” from a state in which ATP and PCr concentrations have decreased to unmeasurable levels.

The electroencephalogram (EEG) is often used both clinically and experimentally to quantitate the severity of cerebral hypoxia. In man, EEG slowing is seen at a \(P_{A_{O_2}}\) of 35 torr or when CBF is reduced to about 40 per cent of normal by ischemia. An isoelectric EEG (not caused by drugs or hypothermia) implies hypoxia severe enough to impair cortical function within a few minutes.

Forms of Cerebral Hypoxia

The metabolic effects of cerebral hypoxia and the efficacy of treatment depend in part on how the hypoxia was produced. Clinically, total cerebral ischemia usually is the result of cardiac arrest. The brain’s supply of both oxygen and glucose is interrupted and energy can only be obtained from existing stores of \(\sim P\) and from anaerobic metabolism of endogenous glucose and glycogen. Stores of these compounds are very limited, such that within three to five minutes of onset of circulatory arrest, ATP and PCr concentrations are reduced to near zero, lactate concentration plateaus at a high value, and energy production ceases.

Neurons can be revived as long as 8 minutes

*Assistant Professor of Anesthesia, University of California, San Francisco, California 94143.

†The term “hypoxia” is used here to encompass all forms of inadequate oxygen delivery to the brain, including arterial hypoxemia, ischemia, and circulatory arrest.

Accepted for publication May 5, 1977. Supported in part by USPHS Grant #GM-1-KO4-70770.

Address reprint requests to Dr. Smith: Department of Anesthesiology, San Francisco General Hospital, San Francisco, California 94110.
after total ischemia,25,47 but after longer periods it is unclear whether revival is limited by irreversible neuronal or vascular damage. Some investigators have reported that reperfusion of the brain following circulatory arrest is impeded by capillary microthrombi and/or perivascular swelling.3 This phenomenon, called "no reflow," has not been observed in all laboratories.27 However, rendering the brain bloodless during the period of arrest does seem to improve tolerance to circulatory arrest. Hossman studied cats and monkeys following anesthesia with pentobarbital (30 mg/kg).19 He found that biochemical and EEG recovery was possible after 60 minutes of circulatory arrest, when the brain was first perfused with saline solution. Biochemical recovery after 15 minutes of arrest was also obtained in rat brains cleared of blood by elevated intracranial pressure (ICP).46 Neither of these groups assessed the functional neurologic recovery of the animals. Even so, the data suggest that neuronal and, therefore, neurologic recovery may be possible in patients who sustain prolonged cardiac arrest, if the appropriate therapy can be devised.

Incomplete cerebral ischemia may result from cerebrovascular occlusion, cerebral-artery spasm, increased ICP, or arterial hypotension. With hypotension, autoregulation maintains CBF of normal man constant to perfusion pressures as low as 50–60 torr.25 Below that level, CBF decreases and, at arterial pressures of about 30 torr (in animals), global hypoxia is so severe that neuronal P concentration decreases and cell death is imminent.28 Such incomplete ischemia is associated with brain lactate levels higher than those found with complete ischemia because of a continuing (although reduced) supply of glucose.47 It is difficult to predict how severe a hypotensive stress the normal human brain will tolerate. A group of 42 healthy surgical patients was deliberately subjected to systolic pressures of 50 torr (heart level) for a mean of 39 minutes.14 Since head-up tilt was used, pressure at the base of the skull must have been lower. All patients recovered without neurologic deficit. Patients who have cerebrovascular disease do not tolerate hypotension as well as this. In these individuals, small decreases in perfusion pressure may produce profound regional decreases in CBF, causing dizziness, transient neurologic deficits, or even stroke.15

Regional cerebral ischemia has been studied in animals. Occlusion of the middle cerebral artery (MCA) for as long as two hours is tolerated by monkeys, without evidence of infarction.53 However, occlusion for more than four hours almost invariably causes stroke.53 This prolonged tolerance to regional ischemia produced by MCA occlusion is accounted for by collateral blood flow which, although inadequate to prevent ultimate infarction, does provide a significant period of potential reversibility. The findings suggest that, in man, there may be a period after appearance of stroke symptoms during which therapeutic intervention or surgical revascularization could be effective in preventing infarction.

Arterial hypoxemia results in oxygen deprivation, but no deficit in glucose delivery or CO₂ removal. Compensation occurs primarily by an increase in CBF. At a PaO₂ of 35 torr in man, CBF is increased 32 per cent, and cerebral lactate production is elevated, but CMR₀₂ is unaffected.12 In animals, reducing PaO₂ to 20–25 torr does not affect ATP concentration, although PCr concentration decreases slightly.45 Thus, pure arterial hypoxemia is remarkably well tolerated. However, when even slight hypotension or ischemia occurs during severe hypoxemia, biochemical deterioration and cell death quickly ensue.31,42

Non-pharmacologic Cerebral Protection

Hypothermia

Hypothermia was among the first treatment modalities found to protect hypoxic brain. Protection probably results from the decrease in CMR₀₂, which, in man, is about 7 per cent per degree Celsius.48 Because of decreased energy requirements, the rate of neuronal ATP loss during circulatory arrest is slowed by hypothermia.53,59 The “safe” period of circulatory arrest is extended from approximately 4 minutes at 37 C to at least 35 minutes at 17 C.3

Hypothermia is also protective in arterial hypoxemia. Rats cooled to 27C and subjected to an otherwise lethal PaO₂ of 12 torr demonstrated only moderate cerebral lactacidosis and no decrease in ATP concentration.8 The authors suggested two mechanisms for the protection: a decrease in CMR₀₂ and a leftward shift of the O₂-dissociation curve. The latter effect would permit greater O₂ loading of hemoglobin, which apparently outweighs the detrimental effect of impaired O₂ unloading.

Rosenoff reported that the extent of cerebral infarction that followed MCA ligation in dogs was decreased by cooling to 22–24 C.40 Protection was still found when hypothermia was induced 15 minutes after vessel occlusion. Unfortunately, other investigators did not find protection in primates. Michenfelder reported that monkeys subjected to MCA occlusion and treated with hypothermia of 29 C for 48 hours suffered massive cerebral edema and died.35 Such a detrimental effect of hypothermia might be accounted
for by an increase in viscosity and/or impaired $O_2$ delivery due to increased binding of $O_2$ to hemoglobin at the tissue $P_{O_2}$. (Pulmonary $O_2$ loading during normoxia would be only slightly improved by hypothermia.) Therefore, a clinical trial of hypothermia for acute stroke would seem at best premature.

Hyperventilation

Hypocapnia as produced by hyperventilation constricts vessels and reduces CBF in normal brain. However, vessels distal to an incomplete arterial occlusion often are maximally dilated by hypoxia and unresponsive to changes in $P_{aCO_2}$. Thus, it was postulated that hyperventilation might shunt blood from normal to ischemic brain tissue. This phenomenon, called “inverse steal,” offered promise for treatment of stroke. Additionally, it has been suggested that hypocapnia might be beneficial by reducing intracranial pressure (ICP), by partial titration of cerebral lactic acidosis, and by a possible increased resistance of cerebral tissue to hypoxia per se. In the first reported animal study, dogs subjected to MCA occlusion during decreased $P_{aCO_2}$ had smaller infarctions than normocarbic controls. However, in subsequent studies neither monkeys nor cats were protected from infarction when hyperventilation was begun 25–60 minutes after vessel ligation. Furthermore, hyperventilation failed to alter the neurologic outcome in a group of 50 severe-stroke patients.

These latter observations dampened enthusiasm for using hyperventilation to treat stroke patients. However, decreased $P_{aCO_2}$ might still be protective during carotid endarterectomy since it could be instituted before carotid-artery clamping. No study comparing the neurologic morbidity associated with carotid endarterectomies during normal $P_{aCO_2}$ and decreased $P_{aCO_2}$ has been reported. Studies of CBF suggest that, on the average, hyperventilation is associated with less ischemia distal to the carotid clamp than normocarbia. However, ischemic CBF is not alleviated in all patients by hyperventilation, and an occasional patient's condition is even worsened. Since the “ideal” $P_{aCO_2}$ usually cannot be established for each individual patient, many compromise by using normal or only slightly decreased $P_{aCO_2}$ during endarterectomy.

Barbiturate Protection

While interest in both hypothermia and hyperventilation as possible techniques for cerebral protection has waned, there has, in recent years, been a growing interest in the potential protective effects of barbiturate anesthesia. Barbiturates have no important effect on the pathways of cerebral glucose metabolism and do not alter brain concentrations of ATP, PCr, lactate, and pyruvate. However, barbiturates do produce dose-related decreases in CBF and CMR$_{O_2}$. In man, sedation with thiopental, amytal, or phenobarbital in doses that did not cause loss of consciousness was not associated with alterations in CMR$_{O_2}$ or CBF. Thiopental, 0.5–1.6 g IV, reduced CMR$_{O_2}$ by 30 per cent; this dose produced unconsciousness in volunteers but did not obliterate movement in response to painful stimuli. Anesthetic doses of thiopental in man were associated with a 52 per cent decrease in CMR$_{O_2}$ and a 48 per cent decrease in CBF. The decrease in CMR$_{O_2}$ during barbiturate anesthesia seems to be related to the cerebral functional effects of the drug. Michenfelder found that CMR$_{O_2}$ decreased progressively in dogs given a continuous thiopental infusion. When the EEG became isoelectric, indicating cessation of cortical function, additional thiopental had no further effect on CMR$_{O_2}$.

Focal Ischemia

One would expect some of these effects to be protective in focal cerebral ischemia. The decreased oxygen demand should ameliorate tissue hypoxia and the vasoconstriction in normal brain might induce an “inverse steal.” Protection was demonstrated by Smith et al. in a series of dogs subjected to unilateral ligations of the internal carotid artery and the middle cerebral artery (fig. 1, table 1). Control animals, whose vessels were clipped during light halothane anesthesia and who were allowed to awaken immediately, suffered infarctions averaging 10 per cent of the affected hemispheres. Similar infarction sizes were observed when five hours of light (8 per cent) halothane anesthesia followed vessel ligation. Deep (1.9 per cent) halothane anesthesia increased infarction size to about 30 per cent even when arterial blood pressure was supported. When deep pentobarbital anesthesia (56 mg/kg, isoelectric EEG) was induced before vessel

<table>
<thead>
<tr>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP</td>
</tr>
<tr>
<td>ATP</td>
</tr>
<tr>
<td>CBF</td>
</tr>
<tr>
<td>CMR$_{O_2}$</td>
</tr>
<tr>
<td>CSF</td>
</tr>
<tr>
<td>EEG</td>
</tr>
<tr>
<td>ICP</td>
</tr>
<tr>
<td>MCA</td>
</tr>
<tr>
<td>$\sim P$</td>
</tr>
<tr>
<td>PCr</td>
</tr>
</tbody>
</table>

Downloaded From: http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931504/ on 10/29/2018
<table>
<thead>
<tr>
<th>Species</th>
<th>Type of Occlusion (MCA = middle cerebral artery; ICA = internal carotid artery)</th>
<th>Timing of Barbiturate Therapy</th>
<th>Barbiturate Dose</th>
<th>Duration of Therapy or Monitoring</th>
<th>Barbiturate Ketamine Background</th>
<th>Infarction Size Per Cent of Hemispheric Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>Permanent MCA + ICA</td>
<td>Before vessel occlusion</td>
<td>Pentobarbital</td>
<td>56 mg/kg 7 1/2 hr</td>
<td></td>
<td>10.8 + 1.4 NS</td>
</tr>
<tr>
<td>Dog</td>
<td>Permanent MCA + ICA</td>
<td>Before vessel occlusion</td>
<td>Thiopental, halothane background</td>
<td>40 mg/kg 6 hr</td>
<td></td>
<td>10.8 2.7 NS</td>
</tr>
<tr>
<td>Dog</td>
<td>Permanent MCA + ICA</td>
<td>15 min after vessel occlusion</td>
<td>Thiopental, halothane background</td>
<td>40 mg/kg 6 hr</td>
<td></td>
<td>10.8 0.1 NS</td>
</tr>
<tr>
<td>Baboon</td>
<td>Permanent MCA</td>
<td>Before vessel occlusion</td>
<td>Pentobarbital</td>
<td>60 mg/kg 7 1/2 hr</td>
<td></td>
<td>14.7 8.6 NS</td>
</tr>
<tr>
<td>Baboon</td>
<td>Permanent MCA</td>
<td>Before vessel occlusion</td>
<td>Thiopental, halothane background</td>
<td>60 mg/kg 7 1/2 hr</td>
<td></td>
<td>14.7 1.3 NS</td>
</tr>
<tr>
<td>Baboon</td>
<td>Permanent MCA</td>
<td>Before vessel occlusion</td>
<td>Thiopental</td>
<td>120 mg/kg 7 1/2 hr</td>
<td></td>
<td>14.7 1.9 NS</td>
</tr>
<tr>
<td>Dog</td>
<td>Permanent MCA + ICA</td>
<td>Before vessel occlusion</td>
<td>Pentobarbital</td>
<td>40 mg/kg 3 hr</td>
<td></td>
<td>9.6 6.8 NS</td>
</tr>
<tr>
<td>Cat</td>
<td>Permanent MCA + ICA</td>
<td>Before vessel occlusion</td>
<td>Pentobarbital</td>
<td>40 mg/kg 3 hr</td>
<td></td>
<td>6.3 5.3 NS</td>
</tr>
<tr>
<td>Squirrel monkey</td>
<td>Permanent MCA + ICA</td>
<td>Before vessel occlusion</td>
<td>Pentobarbital</td>
<td>40 mg/kg 2 hr</td>
<td></td>
<td>17.7 8.0 NS</td>
</tr>
<tr>
<td>Java monkey</td>
<td>Permanent MCA</td>
<td>30 min after vessel occlusion</td>
<td>Pentobarbital</td>
<td>14 mg/kg 48 hr</td>
<td></td>
<td>18.7 2.0 NS</td>
</tr>
<tr>
<td>Rhesus monkey</td>
<td>Embolization</td>
<td>30 min after vessel occlusion</td>
<td>Pentobarbital, ketamine background</td>
<td>4 mg/kg/hr 17 hr</td>
<td></td>
<td>42-53% 15-28%</td>
</tr>
<tr>
<td>Dog</td>
<td>Permanent MCA</td>
<td>1 hr after vessel occlusion</td>
<td>Pentobarbital</td>
<td>40 mg/kg 21</td>
<td></td>
<td>5.0* 11.0 NS</td>
</tr>
<tr>
<td>Dog</td>
<td>Permanent MCA</td>
<td>3 hr after vessel occlusion</td>
<td>Pentobarbital</td>
<td>40 mg/kg 21</td>
<td></td>
<td>15.0 NS</td>
</tr>
<tr>
<td>Dog</td>
<td>Permanent MCA</td>
<td>6 hr after vessel occlusion</td>
<td>Pentobarbital</td>
<td>40 mg/kg 21</td>
<td></td>
<td>15.0 NS</td>
</tr>
</tbody>
</table>

* Change considered statistically significant by the author.  † Estimated values; means not reported. NS = not significant.

In a study in the baboon model of Hoff et al., the protective effect of a 48-hour course of pentobarbital given after the middle cerebral artery occlusion was 40 mg/kg. In a subsequent study, the authors found that the protective effect of pentobarbital was unequivocal, with a statistically significant difference in infarction size compared to controls. However, the authors noted that the administration of pentobarbital was associated with cardiorespiratory depression and required close monitoring. The use of newer anesthetic techniques, such as ketamine, may offer additional benefits.

anesthesia (14 mg/kg for induction and 3.5 mg/kg/hr maintenance) and the control group received only light diazepam sedation. Animals given pentobarbital had infarctions averaging 2 per cent of the affected hemisphere, compared with 19 per cent in the control group.

Barbiturate protection was also observed in rhesus monkeys subjected to embolization of one internal carotid artery during ketamine anesthesia. Control animals were allowed to recover without further intervention. In the second group, a pentobarbital infusion (4 mg/kg/hr) was begun about 30 minutes after segmental occlusion and was continued for 12 hours. Monkeys given pentobarbital had smaller infarctions (no statistics given) and smaller neurologic deficits. The size of infarction following embolization was more than double that resulting from proximal occlusion of the middle cerebral artery and usually included both deep structures and cerebral cortex. Pentobarbital anesthesia was effective mainly in ameliorating cortical damage.

The effect on infarction size of time delay between cerebral vessel occlusion and initiation of barbiturate therapy was studied in dogs. The middle cerebral and internal carotid arteries were clipped during nitrous oxide—halothane anesthesia and pentobarbital, 40 mg/kg, was given intramuscularly one, three, or six hours later. The control group received no barbiturate. Infarction size was decreased significantly only when pentobarbital was begun one hour after occlusion.

In summary, in three separate studies barbiturates have been found to reduce cerebral infarction following focal cerebral-artery occlusion in primates. Two laboratories also reported protection in dogs, but one group failed to observe the phenomenon in non-primate species. The reason for the latter finding may be that non-primates have considerable variability in collateral circulation to the brain. Thus, arterial occlusion results in variable infarctions and drug effects on infarction size could be obscured. In contrast, primates with ligation of the middle cerebral artery seem to develop infarctions similar in size and distribution to those seen in man.

Severe Hypotension

Barbiturates are protective in global as well as in focal cerebral ischemia. Nilsson subjected rats to severe hypotension (mean arterial blood pressure 25–35 torr) for 5 minutes. Animals anesthetized with phenobarbital (150 mg/kg ip) had less accumulation of lactate in the brain and higher ATP levels than those anesthetized with nitrous oxide.

Severely hypotensive (mean arterial blood pressure 25–35 torr) and hypoxic (4 per cent inspired O2) rab-

bits developed EEG flattening within 1–4 minutes. Five minutes after the EEG became isoelectric, control animals were resuscitated with oxygen and catecholamines, but all had suffered irreversible neurologic damage. However, when methohexitol, 5 mg/kg, was given just after the appearance of EEG isoelectricity, all animals recovered completely.

Michenfelder maintained dogs at mean arterial blood pressures of 25–35 torr for nine minutes; EEG's were all active. Animals pretreated with 15 mg/kg thiopental sustained higher cerebral ATP levels for the initial 5–7 minutes of hypotension than did controls, but ATP levels of the two groups did not differ after nine minutes of hypotension.

Cerebral Circulatory Arrest

The use of barbiturates in circulatory arrest was first suggested by Goldstein et al. They reported that pentobarbital anesthesia extended the duration of total cerebral ischemia tolerated by the dog without the occurrence of neurologic deficit.

Nemoto produced cerebral circulatory arrest in monkeys by combining severe systemic hypotension with a high-pressure neck tourniquet. After 16 minutes of global cerebral ischemia, the animals were resuscitated and given a standard intensive care regimen for seven days. Neurologic deficit was computed using a 100-point scale that included evaluation of consciousness, motor function, and respiration. Un-
treatment was delayed until 30 minutes after resuscitation, marked improvement over control monkeys was still evident. These data strongly suggest that thiopental might ameliorate clinical encephalopathy following cardiac arrest.

HYPOXEMIA AND ASPHYXIA

A protective effect of barbiturates on the oxygen-deprived brain has not been demonstrated as clearly in arterial hypoxemia and asphyxia as in cerebral ischemia. Thiopental, like a variety of other barbiturates, was found to increase survival time of mice as much as 180 per cent during breathing of 5 per cent \( \text{O}_2 \). By contrast, inhalational anesthetics had little or no protective effect. However, whole-body hypoxia is produced with this model, and the mechanism of “protection” might relate at least in part to cardiorespiratory actions of barbiturates rather than to a specific cerebral effect.

In rats subjected to 3 minutes of asphyxia (\( \text{P}_{\text{aO}_2} \) 9–14 torr, \( \text{P}_{\text{aCO}_2} \) 74–80 torr), cerebral ATP decreased by 50 per cent and lactate increased tenfold. Neither pentobarbital nor thiopental ameliorated these biochemical abnormalities. In dogs suddenly ventilated with 100 per cent \( \text{N}_2 \), pretreatment with 15 mg/kg thiopental prolonged the persistence of EEG activity. However, the rates of cerebral ATP depletion and lactate accumulation were not affected. Failure to demonstrate a salutary effect of barbiturates on cerebral energy state in these studies could mean that hypoxia of this severity is not amenable to barbiturate therapy. However, biochemical recovery was not studied, and it is conceivable that it would have been improved by barbiturates.

The sequelae of asphyxiation immediately after delivery by cesarean section were studied in newborn monkeys. The mothers received either local anesthesia or 16–43 mg/kg pentobarbital. The newborn animals were resuscitated after 12 minutes of total asphyxia. Monkeys whose mothers had been given pentobarbital suffered less systemic acidosis, resumed rhythmic breathing earlier, and had less brain damage than controls. These data are consistent with the finding that fetal distress in monkeys often can be ameliorated by pentobarbital administration to the mother.

CEREBRAL EDEMA AND HEAD INJURY

Anesthetic effects on cerebral edema were studied in dogs subjected to a cold injury of the cerebral cortex. The resulting “vasogenic” cerebral edema appears in white matter and is similar to that occurring in head trauma, around brain tumors, and in white matter adjacent to some infarctions. Moderate cerebral edema (water content 78 per cent) was found in white matter beneath the cold-induced lesion in animals given either no anesthetic or 1 MAC halothane, enflurane, or isoflurane. Deep halothane anesthesia worsened the edema (water content 80 per cent), while 60 mg/kg pentobarbital significantly lessened it (water content 73 per cent). Innovar was also salutary. As would be expected from the decreased cerebral edema, pentobarbital and Innovar were associated with lower intracranial pressures than were the volatile anesthetics. Clasen also found that pentobarbital decreased cerebral edema, although comparisons with other anesthetics were not reported.

The neurologic outcomes of patients operated upon for evacuation of traumatic subdural or epidural hematomas depend in part on control of ICP and cerebral edema. Since barbiturates reduce both ICP and cerebral edema, their use as anesthetics for emergency neurosurgery might improve the neurologic outcome. In a pilot study of 46 patients performed by the author, thiamyl–nitrous oxide and halothane–nitrous oxide were compared in alternate patients with head injuries. Mean dosages were 17 mg/kg thiamyl and 0.39 per cent inspired halothane. Patients were treated similarly except for the anesthetic, and preoperative clinical states of the two groups were comparable. All patients who were conscious preoperatively survived. Of the unconscious patients, 8/16 barbiturate patients and 4/16 halothane patients survived. Among survivors, anesthesia did not appear to affect severity of
neurologic deficits. These results should be considered very preliminary, and need to be supplemented by the addition of many more patients.

Mechanism

There are several possible mechanisms by which barbiturates could protect the brain against hypoxia. Barbiturate anesthesia decreases CMRO$_2$ by as much as 50 per cent$^{29}$ and slows the rate of P depletion during cerebral circulatory arrest.$^{47}$ Since P is required for sodium pumping, the decreased metabolism might allow for longer survival of oxygen-deprived brain tissue. However, it is probable that the decreased CMRO$_2$ reflects decreased cerebral function, not a decrease in oxygen required to maintain cellular integrity.$^{21,32}$ Also, against a major role for decreased oxygen consumption as a mechanism is the fact that deep halothane anesthesia, which also decreases CMRO$_2$, has deleterious effects in the presence of focal cerebral ischemia and vasogenic cerebral edema. In addition, the major depressive effect of barbiturates on CMRO$_2$ occurs at clinically used doses. If metabolic reduction is the major mechanism of protection, then the very large dose of barbiturates reported by both Hoff$^{78}$ and Nemoto$^{27}$ to be necessary for producing protection cannot be explained.

Cerebral vasodilating agents (e.g., halothane) worsen infarction in focal cerebral ischemia. On the other hand, cerebral vasoconstrictors (barbiturates, Innovar) are beneficial. Vasoconstriction of normal areas of brain might shunt blood to the ischemic regions (inverse steal) and thus reduce infarction. However, in the monkey middle-cerebral-artery-ligation preparation, Hansen et al. found that flows to the ischemic area were the same with halothane and pentobarbital anesthesia.$^{17}$ Thus, there is little evidence for "inverse steal" as the mechanism of barbiturate protection.

Prevention or reduction of cerebral edema may be related to barbiturate protection in ischemia. Pericapillary edema, presumably caused by damage to capillaries, appears within minutes after a severe hypoxic insult.$^{5,7}$ Neuronal swelling shortly follows. The role of both pericapillary and neuronal edema in the irreversibility of ischemic damage has been stressed by Meyer$^{28}$ and Sundt.$^{53}$ Since pericapillary edema impedes flow, a vicious circle could ensure whereby ischemia and edema worsen each other. Thus, barbiturates might protect against infarction by preventing cerebral edema.

The concentration of free radicals in neurons is increased after a severe hypoxic insult and may cause destruction of nucleic acids and eventual cell death. An intriguing but untested hypothesis suggests that barbiturates are free-radical scavengers and prevent build-up of these lethal moieties (B. Siesjö, personal communication).

Clinical Applications

All of the published studies demonstrating a protective effect of barbiturates in cerebral hypoxia have been done in animals. The usefulness of barbiturates in clinical stroke has not been evaluated. A clinical study of barbiturate therapy for prevention of encephalopathy following cardiac arrest is in the planning stage (P. Safrar, personal communication). This author prefers to be conservative and would not recommend general use of barbiturates in cardiac arrest or stroke patients until well-controlled studies establish the risk/benefit ratio.

Patients having carotid endarterectomy are subjected to a period of cerebral ischemia during carotid clamping and also may suffer embolization when the clamps are removed. Unlike the stroke and cardiac-arrest victims, these patients need anesthesia anyway. Thiopental could be given either just before or immediately following the period of carotid clamping to reduce the chance of postoperative neurologic deficit. This would seem to be rational therapy, but it must be emphasized that there are no clinical data to support it. Many anesthetists will recall that hypercarbia, hypocarbia, and normocarbia all have been "rational" adjuncts to anesthesia for carotid endarterectomy at some time within the past ten years.$^{48}$

It has been well established that thiopental decreases abnormally elevated intracranial pressure in neurosurgical patients and that the volatile anesthetics increase ICP.$^{44}$ The salutary effect of barbiturates in traumatic cerebral edema and the deleterious effect of the inhalation agents have been mentioned above. Even in the absence of a completed clinical study, it is difficult to advocate the use of halothane or enflurane in patients with head injury, except perhaps to control hypertension. Nitrous oxide, supplemented by thiopental and perhaps a narcotic, would seem clearly preferable.

References


Downloaded From: http://anesthesiology.pubs.asahq.org/pdfsaccess.ashx?url=data/journals/jasa/931504/ on 10/29/2018
Neurol Scand suppl 52, 1973

cerebral blood flow in man with particular reference to

effects of hyperventilation on CBF during the acute phase of
the total proximal occlusion of a main cerebral artery.
Cerebral Blood Flow. Edited by Brock M, Fischio C, Ingvar D,

7. Brown AW, Brieyly JB: Anoxic-ischemic cell change in
rat brain. Light microscopic and fine-structural observations.
J Neurol Sci 16:59–84, 1972

in cerebral oxygen deficiency caused by arterial
hypoxia. Anesthesiology 44:27–35, 1976

(stroke) treated with or without prolonged artificial
hyperventilation: 2 CSF acid base balance and intracranial

in cryogenic cerebral injury and edema. Neurology 24:642–
648, 1974

obarbital anesthesia on resuscitation and brain damage in
fetal rhesus monkeys asphyxiated on delivery. J Pediatr
75:281–291, 1969

and normocarbia on cerebral blood flow and metabolism

obarbital administration for brain protection in experimental

bral circulation during deliberate hypotension and head-up

15. Farhat SM, Schneider RC: Observations on the effect of sys-
temic blood pressure on intracranial circulation in patients
with cerebrovascular insufficiency. J Neurosurg 27:441–445,
1967

16. Goldstein A, Wells BA, Keats AS: Effects of anesthetia on the
tolerance of dog brain to anoxia (abstr). Anesthesiology
25:98, 1964

vasoconstricting and vasodilating agents on blood flow in
regions of cerebral ischemia. Stroke 6:642–648, 1975

18. Hoff JT, Smith AL, Hankinson HL, et al: Barbiturate pro-
tection from cerebral infarction in primates. Stroke 6:28–33,
1975

19. Hossman KA, Kleinhans P: Reversibility of ischemic brain dam-

20. Kaasik AE, Nilsson L, Siesjö BK: Effect of arterial hypo-
tension upon CSF, lactate, pyruvate, and bicarbonate con-
centrations of brain tissue and cisternal CSF, and upon the tissue
concentrations of phosphocreatine and adenosine nucleotides

21. Katzman R, Pappius HM: Brain Electrolyte and Fluid Metabol-

flow and metabolism in schizophrenia. The effects of barbi-
trates semi-narcosis, insulin coma, and electroshock. Am J
Psychiat 104:765–770, 1948

content during circulatory arrest. J Thorac Cardiovase

24. Larsen CP, Ehrenfeld WK, Wade JG, et al: Jugular venous oxygen saturation as an index of adequacy of cerebral oxygena-

25. Lassen NA: Cerebral blood flow and oxygen consump-

26. Lassen NA, Palvigvi R: Cerebral steal during hypcapnia and
the inverse reaction during hypcapnia observed by the
133 xenon technique in man. Scand J Lab Clin Invest suppl
70:457, 1958

27. Levy D, Briery J, Plum F: Ischemic brain damage in the
gerbil in the absence of "no-reflow." J Neurol Neurosurg
Psychiat 38:1197–1205, 1975

experimental cerebral infarction. Brain 95:833–852,
1972

29. Meyers R: Material psychological stress and fetal asphyxia: A

30. Michenfelder JD, Theye RA: The effects of anesthesia and
hypothermia on canine cerebral ATP and lactate during
anoxia produced by decapitation. Anesthesiology 33:430–
439, 1970

31. Michenfelder JD, Theye RA: Cerebral protection by thiopental

32. Michenfelder JD: The interdependency of cerebral func-
tional and metabolic effects following massive doses of
thiopental in the dog. Anesthesiology 41:291–296, 1974

33. Michenfelder JD, Milde JH: Influence of anesthetics on met-
abolic, functional, and pathological responses to regional
cerebral ischemia. Stroke 6:405–410, 1975

34. Michenfelder JD, Milde J, Sundt T: Cerebral protection by bar-

35. Michenfelder JD: Failure of prolonged hypcapnia, hypother-
mia, or hypotension to favorably alter acute stroke in

36. Moseley JI, Laurent JP, Molinari GF: Barbiturate attenuation
of the clinical course and pathologic lesions in a primate

37. Nemoto E: Amelioration of ischemic brain damage by
thiopental. Crit Care Med (in press)

38. Nilsson L: The influence of barbiturate anesthesia upon the
energy state and upon acid-base parameters of the brain in
arterial hypotension and in asphyxia. Acta Neurosurg Scand
47:233–253, 1971

circulation and metabolism during thiopental anesthesia and
hyperventilation in man. J Clin Invest 41:1064–1071,
1962

40. Rosomoff HL: Protective effects of hypothermia against patho-
logical processes of the nervous system. Ann NY Acad Sci
80:475–486, 1959

41. Salford L, Plum F, Siesjo B: Graded hypoxia–oligemia in rat
brain. I. Biochemical alterations and their implications. Arch
Neurol 29:227–233, 1973

42. Salford L, Plum F, Briery J: Graded hypoxia–oligemia in rat
brain. II. Neuropathological alterations and their implica-

43. Secher O, Willhjem B: The protective action of anesthetics

44. Shapiro H: Intracranial hypertension: Therapeutic and anes-
thetic considerations. Anesthesiology 43:445–471, 1975

45. Siesjo B, Nilsson L: The influence of arterial hypoxemia upon
lable phosphates and upon extracellular and intracellular