Barbiturate Protection From Cerebral Infarction in Primates

BY JULIAN T. HOFF, M.D.,* ALLAN L. SMITH, M.D.,† HAL L. HANKINSON, M.D., AND SURL L. NIELSEN, M.D.

Abstract: Baboons were anesthetized with halothane or pentobarbital prior to middle cerebral artery (MCA) occlusion to test the protective effect of barbiturates against stroke in primates. Significantly less infarction was found in animals that received 90 mg per kilogram pentobarbital or more than occurred in control animals. Because of cardiovascular and ventilatory complications at high doses of barbiturate, however, therapeutic trials to suppress stroke in the human must await further identification of an effective regimen which includes a safe barbiturate dose.

Additional Key Words: pentobarbital, cardiovascular complications

Introduction

Several methods have been tested to control cerebral ischemia: hypothermia, hyperventilation, inhalation anesthesia, hemodilution, cerebral dehydration, alpha adrenergic blockade, and steroids. All have suppressed infarction in the laboratory, but few have been of value in managing patients with acute cerebral artery occlusion.

Recently barbiturates were shown to protect a variety of animals from acute cerebral ischemia and hypoxia. Whether barbiturates can protect man from stroke remains the central question. To establish the effect of barbiturates on focal cerebral ischemia in primates, we studied the effect of anesthesia on the pathological sequelae of middle cerebral artery (MCA) occlusion in baboons. This paper reports our findings.

Methods

Adult baboons, weighing between 11 and 15 kg, were tranquilized with phencyclidine (1 mg per kilogram IM), their tracheas were intubated, and controlled ventilation was instituted with 70% N2-30% O2. An intravenous catheter was placed to administer fluids and drugs. Systemic arterial pressure was recorded continuously from a femoral artery. Mean arterial pressure was maintained constant (103 ± 7 mm Hg) with an infusion of phenylephrine as necessary. End-tidal Pco2 was monitored continuously by infrared analysis and kept at 40 mm Hg. Arterial blood gases, measured hourly, were controlled to maintain a steady state (Pao2 172 mm Hg ± 13, Paco2 38.3 mm Hg ± 12, pH 7.41 ± 0.02, occasionally by correction of base deficits with NaHCO3. The electroencephalogram, obtained from two left fronto-occipital leads, was recorded at 10-minute to 30-minute intervals. Normal saline (1,000 cc) was administered intravenously throughout each experiment and hematocrits remained physiological (37% ± 4). Body temperature was controlled (37.3 ± 0.4°C).

ANESTHETIC DRUGS

Animals were divided into four groups according to anesthetic management. Group 1 consisted of five baboons maintained with halothane (1.16% ± 0.07). Inspired and end-tidal halothane concentrations were determined at least hourly by infrared analysis. Group 2 included five animals anesthetized with pentobarbital intravenously in increments over one hour before MCA occlusion to a total dose of 60 mg per kilogram (59 ± 3). Group 3 consisted of three animals, anesthetized with pentobarbital 90 mg per kilogram (90 ± 1) given over one hour, and Group 4, three animals, received 120 mg per kilogram (122 ± 8) during the hour before occlusion. Arterial barbiturate levels, determined by ultraviolet assay, were drawn 30 minutes after MCA occlusion, again at the resumption of EEG activity, and finally at extubation. Heart blood for barbiturates was sampled from two animals who died prematurely.

MIDDLE CEREBRAL ARTERY (MCA) OCCLUSION

The right MCA was occluded permanently in all animals, during steady state halothane anesthesia in Group 1, and within five minutes after the total barbiturate dose had been given in Groups 2 to 4. The artery was exposed with the aid of the surgical microscope after removal of a portion of the lateral orbital wall and medial sphenoid wing. After the dura was opened, a Scoville clip was placed across the MCA at its origin. Brain retraction was minimal and the globe was not removed.

Animals were extubated no sooner than six hours after occlusion and only if spontaneous respirations were...
sufficient to maintain \( P_{aco} < 46 \) mm Hg and \( P_{ao} > 80 \) mm Hg while breathing air.

Neurological examinations were conducted daily for seven days, and grades of neurological function were assigned according to the cumulative postoperative course (table 1). Parenteral fluids were given when animals could not drink and prophylactic antibiotics were administered routinely.

**PATHOLOGY**

The animals were killed by an overdose of intravenous pentobarbital on the seventh day after operation; their brains were removed and fixed in 10% formalin. Animals that died prematurely were autopsied immediately after death or within four hours. Gross and histological examinations of the brains were conducted by one of the authors (SLN) without knowledge of the anesthetic drugs used. MCA occlusion was verified (fig. 1). Infarction size was quantified in percent of cerebral hemisphere by a grid system previously reported. Representative areas of normal and abnormal tissue were stained with hematoxylin and eosin and the abnormalities confirmed microscopically. Criteria for infarction included loss of normal cellular elements, infiltration with macrophages, and early vessel proliferation. The infarction size data were analyzed by the Dunnett procedure for comparison of several treatments with a control group.

<table>
<thead>
<tr>
<th>Neurological Evaluation Scores</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neurological deficit</td>
<td>0</td>
</tr>
<tr>
<td>Awake, mild hemiparesis, progressive improvement</td>
<td>1</td>
</tr>
<tr>
<td>Awake, marked hemiparesis, progressive improvement</td>
<td>2</td>
</tr>
<tr>
<td>Stupor-coma, no improvement, death in less than one week</td>
<td>3</td>
</tr>
</tbody>
</table>

**FIGURE 1**

The right temporal lobe has been partly removed to show the Scoville clip occluding the middle cerebral artery. Baboon brain (819), ventral surface, formalin fixation.
Results

Blood gases, arterial blood pressure and body temperature were similar in all experimental groups, but anesthesia time, from MCA occlusion to extubation, differed. Halothane animals were anesthetized for 297 ± 13 minutes, while barbiturate animals were anesthetized for 442 ± 181 minutes. Blood barbiturate levels varied from group to group (table 2). Thirty minutes after MCA occlusion blood barbiturate levels in all animals were sufficiently high to have produced coma in man. Moreover, EEG activity usually became isoelectric when the barbiturate dose exceeded 50 mg per kilogram. Activity resumed within two hours in animals that received 60 mg per kilogram and within five hours in animals that received larger doses when blood barbiturate levels had fallen to 4 mg %.

HALOTHANE ANESTHESIA

The mean cerebral hemisphere infarction sustained after MCA occlusion in animals anesthetized with halothane was 14.9% ± 11.1 (fig. 2). Individual varia-

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>20 min. after occlusion</th>
<th>EEG activity resumed</th>
<th>Adequate spontaneous ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>4.3 ± 1.7</td>
<td>3.6 ± 0.9</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>90</td>
<td>10.0 ± 1.7</td>
<td>5.5 ± 1.8</td>
<td>3.6 ± 0.8</td>
</tr>
<tr>
<td>120</td>
<td>7.1 ± 1.3</td>
<td>4.2 ± 0.0</td>
<td>3.7 ± 1.0</td>
</tr>
<tr>
<td>Mean</td>
<td>4.3 ± 1.2</td>
<td>2.9 ± 1.2</td>
<td></td>
</tr>
</tbody>
</table>

CEREBRAL HEMISPHERE INFARCTION AFTER MIDDLE CEREBRAL ARTERY OCCLUSION DURING HALOTHANE OR BARBITURATE ANESTHESIA

(16 Baboons)

Cerebral hemisphere infarction after middle cerebral artery occlusion during halothane or barbiturate anesthesia. Sixteen baboons. The animals receiving 90 mg per kilogram barbiturate or more before occlusion had significantly less infarction than the control group anesthetized with halothane (P < 0.05).
BARBITURATE PROTECTION FROM CEREBRAL INFARCTION IN PBIMATIS

TA-LI

Sequela of MCA Occlusion During Halothane Anesthesia

<table>
<thead>
<tr>
<th>Baboon</th>
<th>H(Urban) concentration (%)</th>
<th>Neurological deficit</th>
<th>Time after injection</th>
<th>Infarction size</th>
</tr>
</thead>
<tbody>
<tr>
<td>817</td>
<td>1.21</td>
<td>2</td>
<td>1 week</td>
<td>27.0</td>
</tr>
<tr>
<td>824</td>
<td>1.07</td>
<td>1</td>
<td>1 week</td>
<td>47</td>
</tr>
<tr>
<td>845</td>
<td>1.10</td>
<td>3</td>
<td>22 hours</td>
<td>17.9</td>
</tr>
<tr>
<td>846</td>
<td>1.26</td>
<td>2</td>
<td>1 week</td>
<td>23.0</td>
</tr>
<tr>
<td>848</td>
<td>1.17</td>
<td>1</td>
<td>1 week</td>
<td>2.0</td>
</tr>
</tbody>
</table>

- AKBITURATI ANISTHIJA (TABU 4)

The mean cerebral infarction that followed MCA occlusion in the 60 mg per kilogram group was 8.7% ± 14.3 (fig. 2). With one exception (818), consciousness was unimpaired, hemiparesis improved progressively, and infarcts were small. Figure 4 shows the infarction present in one of the barbiturate animals. Baboon 818 recovered from anesthesia, but its hemiparesis was profound, the infarct large, and death unexpected.

With 90 or 120 mg per kilogram of pentobarbital, neurological deficits varied from none, to hemiparesis followed by improvement, to premature death. Mean infarction size was less (P < 0.05) for the combined high dose barbiturate animals (2.9% ± 3.5) than for the halothane group (14.9% ± 11.1).

Premature deaths occurred in three (827, 840, 843) of the six animals anesthetized with barbiturates, 90 mg per kilogram or more. One (840) never regained consciousness and had a significant cerebral infarction. Two (827, 843) failed to recover from anesthesia, but neither had evidence of cerebral infarction. Pathological evidence of infarction may not have yet

Cerebral hemisphere infarction (23%) after MCA occlusion, halothane anesthesia, 1.2%. Baboon 846. coronal section. formalin fixation.

Stroke, Vol. 6, January-February 1975
Sequelae of MCA Occlusion During Barbiturate Anesthesia

| Baboon no | IVMhiratil dose (mg/kg IV) | Neurological score | Survival time after occlusion | Infarction (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>818</td>
<td>54.3</td>
<td>3</td>
<td>2 days</td>
<td>34.0</td>
</tr>
<tr>
<td>820</td>
<td>60.9</td>
<td>2</td>
<td>1 week</td>
<td>6.0</td>
</tr>
<tr>
<td>822</td>
<td>60.0</td>
<td>2</td>
<td>1 week</td>
<td>1.0</td>
</tr>
<tr>
<td>823</td>
<td>58.9</td>
<td>1</td>
<td>1 week</td>
<td>0.5</td>
</tr>
<tr>
<td>826</td>
<td>62.1</td>
<td>1</td>
<td>1 week</td>
<td>1.7</td>
</tr>
<tr>
<td>819</td>
<td>89.7</td>
<td>2</td>
<td>1 week</td>
<td>3.5</td>
</tr>
<tr>
<td>827</td>
<td>91.3</td>
<td>3</td>
<td>24 hours</td>
<td>0</td>
</tr>
<tr>
<td>840</td>
<td>89.8</td>
<td>3</td>
<td>2 days</td>
<td>9.3</td>
</tr>
<tr>
<td>843</td>
<td>128.4</td>
<td>3</td>
<td>10 hours</td>
<td>0</td>
</tr>
<tr>
<td>844</td>
<td>126.3</td>
<td>2</td>
<td>1 week</td>
<td>3.8</td>
</tr>
<tr>
<td>847</td>
<td>113.0</td>
<td>1</td>
<td>1 week</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Discussion

Barbiturates reduced the extent of infarction that followed permanent occlusion of the middle cerebral artery in primates. The dose required to protect the baboon brain from stroke, however, was larger than that shown to protect dogs from MCA occlusion. The dose-response differences observed in our experiments, earlier with dogs and now with baboons, might be attributed to dissimilar cerebrovascular
anatomy to species-specific tolerance to barbiturates or to other unknown factors.

The pentobarbital dose (90 ± mg per kilogram) needed to reduce stroke commonly was accompanied by prolonged ventilatory insufficiency, intermittent cardiac arrhythmias, and systemic hypotension sufficient to require a continuous infusion of phenylephrine. In man similar doses produced similar cardiovascular and pulmonary effects, often with a fatal outcome in the absence of resuscitative measures. Thus, the dose, route, and duration of pentobarbital administration used in our study would likely be accompanied by severe drug-induced complications in man. On the other hand, massive barbiturate intoxication has not been uniformly fatal, provided supportive measures were vigorous and prolonged.

Protection from clinical stroke might conceivably be achieved with smaller doses of barbiturate given over a longer time or when combined with other therapeutic maneuvers including hyperventilation and hypothermia. With one exception (baboon 818) animals anesthetized with 60 mg per kilogram were protected from large infarcts. While the mean infarction size (2.3%) in the remaining four animals of Group 2 was not significantly different from that of control halothane animals, protection was suggested at this more tolerable barbiturate dose.

Other important questions remain unsolved. The effect of barbiturates on stroke given minutes or hours after arterial occlusion has not been determined in primates, though the drug has been effective when given after occlusion in dogs. The mode of protective action of barbiturates, whether by cerebral metabolic depression, by intracranial pressure reduction, or by reduction of cerebral edema, or by a more specific effect, has not been clarified. And, the effects of other barbiturates, perhaps less toxic, and of other barbiturate-like drugs on ischemic brain remain unexplored.

The therapeutic implications of barbiturate protection from focal cerebral ischemia are obvious. At the same time, we believe clinical trials in man must await further experimental work suggesting an effective therapeutic regimen which includes a safe barbiturate dose.

References

Barbiturate Protection From Cerebral Infarction in Primates
JULIAN T. HOFF, ALLAN L. SMITH, HAL L. HANKINSON and SURL L. NIELSEN

Stroke. 1975;6:28-33
doi: 10.1161/01.STR.6.1.28

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/6/1/28

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/