BARBITURATES ameliorate brain damage after a variety of cerebral ischemic anoxic insult in animals\textsuperscript{15-18} and, apparently, in man.\textsuperscript{14} In an earlier study in monkeys,\textsuperscript{8} we reported that thiopental 90 mg/kg improved neurologic recovery when administered at 5 and 15 min, but not at 30 or 60 min after 16 min global brain ischemia. These findings suggest that after global brain ischemia, substantial brain damage occurs within the first 30 to 60 min after restoration of circulation.

Proposed hypotheses on the mechanism of barbiturate amelioration of ischemic brain damage are: a) reduction of cerebral metabolic rate (CMR) of oxygen (O\textsubscript{2}), thereby improving brain oxygenation;\textsuperscript{10, 11} b) activation of the hexose monophosphate shunt and increased glucose utilization via biosynthetic processes;\textsuperscript{12} and c) "quenching" of free radicals thus preventing membrane lipid peroxidation.\textsuperscript{13} In this study, we evaluated changes in cerebral blood flow and metabolism with post-insult thiopental therapy at a time and dose proven effective in ameliorating ischemic brain damage.

Methods and Materials

Eleven prequarantined and fasted female rhesus monkeys weighing 4–5 kg (Primate Imports, Inc.) were anesthetized with halothane, 4 percent pure oxygen, injected intramuscularly with 0.4 mg atropine and 0.08 mg/kg pancuronium bromide and their tracheas intubated with cuffed endotracheal tubes. Their lungs were mechanically ventilated by a fixed volume time-cycled piston respirator (Harvard Apparatus, Inc.) on 1 percent halothane, 66 percent nitrous oxide and 33 percent oxygen plus CO\textsubscript{2}. Endtidal CO\textsubscript{2} was continuously monitored (Beckman LB-1 infrared analyzer) and maintained between 5 and 6 percent by manipulation of inspired CO\textsubscript{2}.

Sodium chloride 0.9 percent, was infused at 3–5 ml/kg/h via peripheral venous catheters. EKG leads were attached and transurethral bladder catheters and rectal thermistors were used for continuous monitoring of urine output and rectal temperature. Femoral artery and vein catheters were inserted for arterial blood sampling, drug infusions and monitoring of mean arterial pressure (MAP). Catheters inserted in the right brachial artery (catheter tip in the innominate artery) were used for \textsuperscript{133}Xe in saline injection for CBF and rCBF measurements (fig. 1). The external carotid arteries were bilaterally ligated to minimize extracranial contamination of CBF measurements.

Supradural electroencephalogram (EEG) screw electrodes were inserted over the parietal-occipital cortex and subdural, supracortical catheters inserted...
over the parietal cortex for intracranial pressure (ICP) monitoring. Angiocaths (18 ga), inserted into the torcular were connected to an extracorporeal circulation system (fig. 1) for continuous sampling of cerebral venous blood. A focused collimated scintillation probe was fixed over the parietal-occipital cortex for rCBF measurements. A 30 min stabilization period was allowed before measurements were begun.

Pre-ischemic measurements of CBF and rCBF with arterial and cerebral venous blood sampling for oxygen content, glucose, lactate, pH, \( \text{PO}_2 \), \( \text{PCO}_2 \) and hematocrit were made during 1 percent halothane, 66 percent nitrous oxide, and 33 percent oxygen anesthesia. Arterial and cerebral venous blood samples were simultaneously withdrawn immediately before isotope injection, changed to 1 sec for 1 min after peak activity, then changed to 5 sec for the remaining 9 min or longer of monitoring. The clearance curves were recorded on a dual pen chart recorder (Linear Instruments, Inc.) for at least 10 min after isotope injection.

Calculations of CBF and rCBF from the clearance curves were done by the height/area method using a Graf-Pen-3 (Scientific Research Corp.) in line with model 600-14 Wang computer using the formula shown below.

\[
\text{CBF or rCBF} = \frac{\text{peak height}}{\text{peak area}} \times \frac{100}{\text{hematocrit}} \text{ ml/100 g/min}
\]

where: \( \chi \) = brain/blood xenon partition coefficient weighted for gray and white matter and corrected for hematocrit according to the equation.

\[
\chi = \frac{(1.04)}{C + 0.787(1-C)}
\]

where:

\[
C = \frac{(0.3)}{\text{hematocrit}}
\]
1.04 = Xe brain/blood partition coefficient for 60 percent gray matter and 40 percent white matter at a hemoglobin concentration of 17 g/100 ml or a hematocrit of 57 percent.

Average blood values for rhesus monkeys are: hemoglobin, 12.6 grams/100 ml; hematocrit; 42 percent; and mean corpuscular hemoglobin concentration, 30.18

Arterial and cerebral venous pH, PCO2 and PO2 were measured with a Corning model 175 trielectrode blood gas unit. Blood glucose and lactate were analyzed by enzymatic methods19, 20 and oxygen content by the Lexicon Oxygen Content Meter.

Calculated physiologic variables were as follows: Cerebral perfusion pressure (CPP) = mean arterial pressure (MAP) minus intracranial pressure (ICP); cerebrovascular resistance (CVR) = CPP/CBF; and cerebral metabolic rate (CMR) for oxygen (O2), and glucose (G) = A-V difference X CBF; and oxygen utilization coefficient (O2UC) = CMRO2/CBF X arterial O2 content.

In some cases, statistical analyses where done using log or square root transformations to stabilize the variance for analysis of variance. Significance among groups of means were tested with the Student-Newman-Keuls test at the 0.05 level.22

Results

Mean arterial pressure in control and thiopental treated monkeys was maintained at about 100 torr throughout the study (except during ischemia) with a range of mean values between 87 ± 7 (SEM) and 113 ± 6 torr. Mean ICP at 6 min post-ischemia in thiopental monkeys (27 ± 7 torr) was higher (p < 0.05) than in controls (17 ± 2 torr), but was otherwise similar in both groups. In the first 15 min post-ischemia, arterial pH in controls was 7.28 ± 0.03 and lower (p < 0.05) than in thiopental treated monkeys (7.41 ± 0.02). PaO2 was about 100 torr pre-ischemia and greater than 400 torr post-ischemia while mean Paco2 ranged between 32 ± 1 and 45 ± 4 torr in both groups. Hematocrit ranged between 33 ± 3 and 40 ± 2 percent and rectal temperature was maintained within a range of 37.9 ± 0.1 to 38.2 ± 0.3°C.

Pre-ischemic CBF and rCBF (fig. 2) in both groups was about 70 to 80 ml/100 g • min1. Total CBF at 6 min post-ischemia (i.e., 60 secs after the start of thiopental infusion) in thiopental monkeys increased

![Figure 2. Cerebrovascular variables before and after 16 min global brain ischemia in seven untreated control monkeys (●...●) and 4 monkeys treated with thiopental 90 mg/kg infused intravenously over 60 min beginning at 5 min post-ischemia (○...○). Global ischemia was induced by trimethaphan hypotension (mean arterial pressure = 50 torr) and a high pressure (1500 torr) neck tourniquet. Total cerebral blood flow (CBF) and regional cerebral blood flow (rCBF) were measured simultaneously after intra-arterial injection of 133Xe in saline (500 μCi) by continuous monitoring of cerebral 133Xe activity, and external scintillation detection of parietal-occipital activity by a focused collimated scintillation probe. Post-ischemia, mean arterial pressure was restored by titrated intravenous norepinephrine infusion.* = p < 0.05 compared to pre-ischemic value.](http://stroke.ahajournals.org/doi/abs/10.1161/01.STR.10.5.948?journalCode=stroke)
to 133 ml/100 g \cdot min^{-1} compared to 70 ml/100 g \cdot min^{-1} in controls. By 30 min total CBF in the thiopental group fell to 47 ml/100 g \cdot min^{-1} and was maintained at about that level for up to 240 min. Total CBF hyperemia observed in thiopental monkeys at 6 min post-ischemia was not seen in control monkeys. Cerebrovascular resistance in thiopental monkeys fell at 6 min post-ischemia \((p < 0.05)\) while not significantly altered in control monkeys.

Pre-ischemia, rCBF was about 80 ml/100 g \cdot min^{-1} and immediately after recirculation fell to about 60 ml/100 g \cdot min^{-1} in both groups then increased at 6 min post-ischemia to 113 and 135 ml/100 g \cdot min^{-1} in control and thiopental groups, respectively. Thereafter, rCBF in both groups fell to 40 ml/100 g \cdot min^{-1} (approximately 50 percent of the preischemic value) and fluctuated between 30 and 40 ml/100 g \cdot min^{-1}. Pre-ischemic and post-ischemic cerebral perfusion pressures were similar at about 90 torr in both groups.

In the first 60 min post-ischemia, CMRO\(_2\) increased by about 200 percent in control monkeys whereas in the therapy group, it fell by 40 percent \((p < 0.02)\) then returned to control values by 60 min (fig. 3). After 60 min, CMRO\(_2\) remained at 160 percent of pre-ischemia in controls compared to 80 and 90 percent in thiopental monkeys. Mean CMRG in therapy monkeys at 6 min post-ischemia, rose sharply by 950 percent, fell to about 150 percent, then fluctuated between 75 and 225 percent. In contrast, mean CMRG in the untreated control group was only 175 percent of control at 6 min post-ischemia then ranged between 50 and 150 percent. Because of data variability, however, significant differences between the 2 groups were not observed.

Changes in lactate a-v differences (fig. 3) were not observed between the 2 groups and the data were combined for statistical analyses. At 6 min post-ischemia, lactate a-v differences increased \((p < 0.05)\) to 320 percent of pre-ischemia, fell sharply to pre-ischemic levels by 60 min post-ischemia and thereafter ranged between about 50 and 100 percent. Changes in \(O_2UC\) were similar in both groups, but appeared to be lower in the thiopental group after 120 min post-ischemia.

In the thiopental monkeys, arterial glucose increased from 5.65 \(\mu\)moles/ml at 6 min post-ischemia to a peak value of 8.55 \(\mu\)moles/ml at 60 min (fig. 4). In controls it gradually increased from 4.78 \(\mu\) moles/ml at 6 min to 7.69 \(\mu\) moles at 240 min. At 30 and 60 min post-ischemia, arterial glucose was higher in the thiopental compared to the control group. In general, cerebral venous glucose followed the pattern observed for arterial glucose. The norepinephrine required to maintain MAP from 5 to 120 min post-ischemia in thiopental monkeys was between 0.34 and 0.63 mg/h and higher \((p < 0.05)\) than for controls which required

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3.** Cerebral metabolic variables in rhesus monkeys before and after 16 min global brain ischemia. Global brain ischemia induced by trimethaphan hypotension (MAP = 50 torr) and high pressure (1500 torr) neck tourniquet. \(\bullet\) and \(\circ\) were treated with thiopental (90 mg/kg) infused intravenously over one h beginning at 5 min postischemia \((\circ---\circ)\). Mean arterial pressure restored by titrated intravenous norepinephrine infusion. Cerebral metabolic rate (CMR) for oxygen \((O_2)\) glucose \((G)\) and lactate \((L)\) = total CBF \(\times\) A-V difference. Total CBF measured by continuous monitoring of the cerebral \(^{133}\text{Xe}\) activity after intra-arterial bolus injection. \(\ast\) = \(p < 0.05\) compared to controls at the corresponding time period. \(+\) = \(p < 0.05\) compared to preischemia.
between 0.06 and 0.29 mg/h. Between 150 and 240 min post-ischemia, both groups required similar amounts of norepinephrine.

Discussion

The reactive hyperemia in rCBF in control monkeys followed by a decrease to one-half of normal agrees with earlier findings in dogs and cats using the same method for rCBF measurements. The absence of hyperemia in terms of total CBF in control monkeys also agrees with our findings in cats subjected to 16 min global brain ischemia using the same techniques for total CBF as in this study. If rCBF increases without an increase in total CBF observed in control monkeys, perfusion to other regions must fall. The increase in both total CBF and rCBF in thiopental treated monkeys indicates that the post-ischemic imbalance of blood flow in controls was prevented or corrected by thiopental and that while cortical flow increased, perfusion of other regions was at least maintained. These differences in thiopental and control monkeys were not attributable to differences in CPP, PaO₂ or PaCO₂.

The heterogeneity of regional brain perfusion after ischemic anoxia has been demonstrated using colloid carbon revealing areas of low perfusion after global ischemia and 1C-antipyrine rCBF measurements after focal ischemia in cats. In an earlier study, we obtained indirect evidence of regional differences in reperfusion after 16 min global ischemia in monkeys. After recirculation, local brain tissue Po₂ measurements indicated that reoxygenation occurred at different "apparent" cerebral perfusion pressures; thus, some areas were reperfused more easily than others. The reasons for the variations in regional perfusion after cerebral ischemic anoxia are unclear. However, there are several likely explanations. First, during ischemia, regional edema may develop causing an increase in local tissue pressure thereby reducing local perfusion pressure and blood flow. In support of this concept, we found that during global ischemia, osmolality in different regions increases at different rates and magnitudes and may lead to varying degrees of local brain edema during the insult. Second, if vasospasm is involved, it may occur to varying degrees in different regions. An increase in extracellular potassium to levels in excess of 30-40 mEq/l induces vasospasm and has been implicated as a factor in failure of reperfusion after global ischemia. Our results suggest that the efficacy of thiopental may occur through the reduction of brain edema and redistribution of blood flow in different brain regions.

CMRO₂ changes in thiopental treated monkeys appeared to parallel the changes observed in control monkeys, but were generally lower. It is important to note that pre-ischemia the monkeys are anesthetized with halothane which depresses CMRO₂ by about 30 percent. Halothane was discontinued within 5 to 10 min during ischemia and the monkeys were unanesthetized post-ischemia. Therefore, the degree of reduction in CMRO₂ within the first 30 min post-ischemia is probably greater than our data show, whereas the magnitude of the increase in CMRO₂ in controls may be overestimated by 30 percent. These findings corroborate the observations of Nordstrom, et al who reported CMRO₂ reduced within the first 30 min post-ischemia in rats subjected to 15 min global ischemia. The lower CMRO₂ in thiopental treated monkeys compared to controls suggests that the efficacy of thiopental may be related to local improvement of brain oxygenation secondary to a reduction in CRMO₂. However, oxygen utilization coefficient was unaltered in thiopental treated monkeys compared to controls except at 120 min post-ischemia.

The marked increase in CMRG in the first 15 min post-ischemia in thiopental treated monkeys was not accompanied by a proportional increase in CMRO₂ as one would expect if the glucose was being oxidized. Indeed, CMRO₂ was subnormal indicating either an
increase in non-oxidative metabolism of glucose or greater glucose re-saturation of the thiovalent treated brain. These data support the findings of Hakim, et al. who showed that barbiturates increase the activity of the hexose monophosphate shunt and glucose utilization for synthetic rather than energy-producing (i.e., mitochondrial oxidation) reactions. The marked increase in glucose uptake in thiovalent monkeys was also not attributable to an increase in glycolytic activity since changes in a-v lactate differences in both groups appeared to follow identical patterns. Barbiturate therapy had no effect on a-v lactate differences which were well below normal by 2 and 3 h post-ischemia in control and thiovalent groups.

Our findings of a rapid early peak in arterial blood glucose at 1 hour post-ischemia in thiovalent monkeys compared to the gradual rise in control monkeys with a peak at 4 hours post-ischemia, are consistent with the findings of Oyama, et al. that barbiturate anesthesia with surgical stress results in decreased insulin secretion, increased growth hormone secretion and hyperglycemia. The higher infusion rate of norepinephrine in thiovalent treated monkeys may also account for the post-ischemic increase in serum glucose levels. The rapid increase in arterial glucose in the thiovalent monkeys may be partly responsible for its efficacy in preventing edema. Dimattio and associates observed that a 1 percent increase in serum osmolality secondary to glucose infusion resulted in a 12 percent decrease in CSF production in rats. The degree of hyperglycemia observed in our thiovalent treated monkeys could cause a 4 mOsm/l increase in serum osmolality and if one assumes a linear relationship, this could account for a 30 to 40 percent reduction in CSF formation. This is also supported by our earlier studies showing that pentobarbital anesthesia reduced the rate of rise in brain osmolality during ischemia.

In summary, thiovalent appears to ameliorate ischemic brain damage by preventing maldistribution of regional blood flow in the early post-ischemic recirculation phase, and by improving glucose delivery and utilization via non-oxidative pathways. Although the reduction in CMRO₂ by thiovalent indirectly suggests that thiovalent may improve brain oxygenation secondary to the reduction in CMRO₂, O₂UC was similar in both groups.

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References

11. Michenfelder JD, Milde JH: Cerebral protection by anaesthetics during ischaemia (a review). Resuscitation 4: 219-233, 1975
Body Fluid Oxygen Tension and Prognosis in Patients With Ruptured Aneurysm

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SUMMARY Body fluid gas pressure and electrolytes of patients with ruptured aneurysm were continuously analyzed. Intracranial pressure (ICP) was regulated at a level of 120–100 mm H2O by cerebral ventricular drainage. There was no significant change in the pH, PCO2, HCO3–, Na+, K+, Ca++ in the cerebrospinal fluid (CSF) of patients with slight or moderate disturbance of consciousness (lethargic-drowsy state). The PcritO2 of the patients with marked disturbances of consciousness (semicoma-coma) was significantly low. PcritO2 of the patients with cerebral vasospasm was significantly lower than for those without vasospasms. PcritO2/PaO2 was 0.27 ± 0.01 in the patients with vasospasm and 0.50 ± 0.01 in those with vasospasm. PcritO2 tended to decrease in patients with markedly bloody CSF. When the bloody CSF was cleared by ventricular drainage, PcritO2 increased. PcritO2 did not return to a normal value in the patients with marked disturbances of consciousness despite sufficient arterial oxygen tension. This suggests that PcritO2 and PcritO2/PaO2 should provide a convenient index for the prognosis of patients with ruptured aneurysm.

Methods

Eleven patients with ruptured aneurysm were examined and the clinical findings are shown in table 1. Patients 5 and 7 had multiple aneurysms. All patients were on continuous ventricular drainage and intracranial pressure (ICP) was regulated at a level of 120–100 mm H2O. Cerebral vasospasm was diagnosed by the criteria of Wilkins et al.2 Clinical symptoms were graded by Hunt’s classification3 at admission as: 8 patients grade III, 2 grade IV, and 1 grade V. The operation (neck clipping of the aneurysm) was performed in 9 patients. Four patients died as a result of cerebral vascular and pulmonary disease. In both CSF and femoral arterial blood pH, Pco2, Hco3– and Base Excess (BE) were examined simultaneously. Na+, K+, Cl–, Ca++ and total protein in both CSF and peripheral venous blood were also examined at the same time. The study was continued for a maximum of 70 days consisting of 8 patients with hypertensive intracerebral hemorrhage, 6 patients with brain tumor and 7 patients with miscellaneous neurological diseases were examined using the same procedures.
Brain blood flow and metabolism after global ischemia and post-insult thiopental therapy in monkeys.

W A Kofke, E M Nemoto, K A Hossmann, F Taylor, P D Kessler and S W Stezoski

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