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# Editorial Views

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## *Barbiturates Following Cardiac Arrest:*

### *Possible Benefit or Pandora's Box?*

WIDESPREAD successful application of cardiopulmonary resuscitative techniques increases the necessity to develop more effective therapy aimed at decreasing the neuropathologic impact of this insult. Following cardiac arrest the rate of persistent coma remains 40–50 per cent, despite standard post-arrest therapy. This variably includes the use of steroids, mannitol, hyperventilation, hypothermia, and measures to maintain adequate cerebral oxygenation and perfusion. In this issue, Bleyaert and his colleagues report that massive doses of thiopental given to primates after a period of global ischemia of the brain can decrease the incidence and severity of neuropathologic abnormalities and improve neurologic function.[1] This may represent a significant forward step in neuroresuscitation, or it could open a Pandora's box consisting of dangerous, expensive and emotionally draining exercises in therapeutic futility. In view of the implications of this study, our commentary is directed toward establishing a scientific and clinical perspective of this work.

Barbituric acid was first synthesized in 1864, and over the next hundred years derivatives have had important uses for production of sedation, hypnosis, anesthesia, and seizure control. Since 1940, numerous studies have demonstrated that pharmacologically induced central nervous system depression results in prolongation of survival times (last gasp or cardiac arrest) in hypoxic or asphyxiated animals.[2] Barbiturates appear to offer the greatest protection in this circumstance. Recently, Steen and Michenfelder confirmed this work and found that only the isomer of mephobarbital with anesthetic activity conferred protection in mice breathing 5 per cent oxygen.[3]

In 1937, barbiturates were reported to decrease intracranial pressure (ICP),[4] and in the last five years this property has been of value in the care of patients with abnormally high ICP in the operating room,[5] or as a result of trauma to the head[6] or encephalitis.[7] These agents appear to decrease ICP by increasing cerebral vascular resistance, thereby decreasing intracranial blood volume.[8]

A *direct* effect of barbiturates in protecting ischemic brain is much less clear. Barbiturate protection following *focal* ischemia was first demonstrated in 1974 in dogs following ligation of the middle cerebral artery,[9] and has since been confirmed in primates.[10–12] Treatment with large doses of pentobarbital or thiopental before or as long as 30 min after ischemia has been effective in decreasing neurologic and neuropathologic deficits. Despite these reports, human studies demonstrating effectiveness in strokes are lacking. The protective action of barbiturates in experimental focal ischemia may be due to decreased cerebral metabolic demand and vasoconstriction of normal cerebral vessels, resulting in shunting of blood flow from healthy brain to ischemic areas.

The case for barbiturate protection following *global* ischemia of the brain is an entirely different issue. When the blood flow of the brain is decreased by hemorrhagic hypotension, pretreatment with barbiturates decreases lactic acid formation and high-energy phosphate depletion.[13,14] One group of rabbits subjected to hypotension and hypoxia survived longer than controls when given methohexital, 5 mg/kg, immediately after the EEG became flat.[15] However, *complete* global ischemia, as following cardiac arrest, is very difficult to produce experimentally.

Studies have used many species and models, and they are often not comparable. Interruption of the carotid and vertebral circulation is an unreliable method for producing complete global ischemia because of markedly variable collaterals.[16] Increase of ICP to levels exceeding blood pressure may produce global ischemia but frequently is incompatible with long-term survival.[17] Total circulatory arrest, such as that produced by ventricular fibrillation, sufficient to produce neurologic impairment, results in many animals which cannot be resuscitated.[18] Aortic and vena caval occlusion improves cardiopulmonary outcome; experiments with this technique have indicated the critical period of total ischemia for severe neurologic dysfunction in dogs and monkeys is 10–20 min when post-clamping hypotension is prevented.[19,20] One study using this model found that anesthesia with pentobarbital, 30 mg/kg, improved the survival rate when compared with local anesthesia,[21] but other general anesthetics were not evaluated. In dogs, high pressure applied to the neck with a tourniquet after cervical laminectomy produces deficits only after similar periods of ischemia.[22] To date, therefore, there has not been any definitive study clearly proving a specific protective action of barbiturates in global ischemia.

In the model of Bleyaert and associates, whole-brain ischemia was obtained in monkeys by rapid inflation of a neck tourniquet to 1,500 torr and induction of systemic hypotension. The latter was accomplished by a combination of deep halothane anesthesia (4–5 per cent), PEEP (to 20 cm $H_2O$), and intermittent infusions of trimethaphan in order to obtain a mean blood pressure of about 50 torr. These extreme measures are necessary because cerebral blood flow will persist through the vertebral arteries, which are protected from compression by the intact cervical spine. This results in surviving control animals with neurologic deficit scores (NDS) of about 50 per cent. Treated animals also received thiopental, 90 mg/kg or 120 mg/kg, 5 to 60 min after 16 min of strangulation had been maintained.

Unfortunately, various problems make interpretation of this study difficult. First, there are differences in postarrest supportive care that can alter neurologic outcome. For example, their data indicate that controlled ventilation *alone* following global ischemia of the brain can decrease NDS from 50 to 20 per cent. The lungs of the control-group monkeys were ventilated for only 2–6 hours postischemia and then the monkeys were allowed to hyperventilate spontaneously, while mechanical ventilation was maintained for as long as 24 hours in the thiopental-treated group. Thus, $Pa_{CO_2}$ differences occurred early. Other minor discrepancies in supportive care between the treated and control groups existed.

Second, in addition to the protocol differences, the results raise several questions. Of the four groups receiving thiopental, 90 mg/kg, only the 5-min group had statistically significant improvement in NDS by six days, although the 15-min group, after evidencing stable adverse NDS for the last three days, suddenly showed significant improvement for unknown reasons immediately before sacrifice. It is also unclear why those animals given thiopental, 120 mg/kg, at 60 min were improved while those given the same dose at 30 min were not. Furthermore, the group treated at 5 min was reported to have a zero NDS, yet some monkeys were found to have occasional ataxia. In their original paper describing this monkey model for global ischemia,[23] ataxia was given 15 points of a possible 500 (or 3 per cent). If the NDS in the most successfully treated group was 3 per cent and ventilation alone decreased the NDS to 20 per cent, the difference attributable to thiopental is much less impressive. Finally, the pathologic assessment of the brain revealed definite abnormalities even in those animals found to be functionally normal, leaving doubt as to the applicability of the improvement to man. In view of these difficulties, and, especially since the experimental groups were small (n = 5), the improved NDS should be interpreted with caution.

Many mechanisms have been postulated to explain a protective action of barbiturates in global ischemia of the brain. These include suppression of subclinical epileptic activity, membrane stabilization, and free-radical scavenging, which prevents lipid peroxidation.[24] In contrast to regional or incomplete ischemia, when used in total global ischemia barbiturates do not augment cerebral blood flow and further anesthetic depression of cerebral metabolism in the presence of an isoelectric EEG cannot occur.[25]

It is also important to note that large-dose barbiturate therapy is not without risk. In addition to prolongation of the need for mechanical ventilation (with its attendant hazards), treated animals needed more cardiovascular support than controls. Laboratory evidence does not yet exist to determine the effects of this type of therapy on the function of other organs, especially the heart with coronary insufficiency. Hoff found frequent cardiopulmonary problems in primates given large doses of pentobarbital.[10] In addition, patients surviving cardiac arrest will often have myocardial dysfunction and infarction. Anyone who has treated patients with massive barbiturate overdose does not need to have the dangers emphasized further.

Assuming that enormous doses of barbiturates may help a recently ischemic brain, how do we reasonably approach clinical trials? The foremost problem in application is deciding who shall be treated. This is especially difficult as prognostic indices for the patient who is comatose immediately following a cardiac arrest are notoriously unreliable. On initial examination of patients who made a functional neurologic recovery, 57 per cent were comatose and had no reflex movements in response to pain.[26] Seventy-six per cent of these patients did not regain consciousness for more than an hour (range 1–48 hr). Without clear-cut, rapid methods of accurately predicting which patients will not spontaneously recover neurologic function after resuscitation from cardiac arrest, are we justified in embarking upon aggressive therapy that must begin immediately after cardiopulmonary resuscitation? Will we be doing more harm than good?

We clearly need additional laboratory studies to support this fascinating initial report.[1] Confirmation of an effective postarrest neuroresuscitative action of barbiturates will then necessitate controlled human studies to establish guidelines for dose, timing and duration of barbiturate administration. Until this information becomes available, clinical applications of high-dose barbiturate therapy for ischemia of the brain should be tempered with caution.

MARK A. ROCKOFF, M.D.
*Research Fellow*
HARVEY M. SHAPIRO, M.D.
*Associate Professor of Anesthesiology and Neurosurgery*
*Research Service*
*Veteran's Administration Hospital and*
*Department of Anesthesia*
*University of California*
*San Diego, California 92093*

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