Amelioration of Post-ischemic Brain Damage with Barbiturates

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Perhaps there is no major pathological state so profound in its damaging effects on the sufferer, on his family, and on society as the brain injury produced by cardiac arrest, ischemic stroke, or other anoxic states. Thus, there is great interest among physicians and the lay public in experimental results which suggest a protective effect against brain damage after either focal or global brain ischemia by the use of barbiturate administration, measures to increase blood flow, or subject immobilization with controlled ventilation. These experimental results have also increased interest in what might be called "therapeutic anesthesia" programs expanding cardiopulmonary resuscitation (CPR) and cardiopulmonary-cerebral resuscitation (CPCR) procedures and the possibility of improved brain survival in a variety of injurious processes.

The potential importance of these experimental results is obvious, but confusion and controversy have arisen because of incautious conclusions drawn from comparisons of experimental results with different animal models, treatment regimens, and post-insult management. In this brief overview the present status of barbiturate therapy in anoxic-ischemic brain injury will be described.

When interpreting experiments or analyzing clinical situations, one must keep in mind the sometimes subtle but nonetheless distinct differences between the kinds of injury that may be produced in the brain by ischemia, anoxia, hypoglycemia, anemia, trauma, hemorrhage, metabolic or toxic abnormalities, inflammation, or by different combinations of these processes. Furthermore, with ischemic insults there are important distinctions between global ischemia as in shock states or cardiac arrest and the focal ischemia of transient or permanent embolic occlusion with cerebral infarction. There are also important differences between reduced flow states such as in shock and the total cessation of flow with cardiac arrest. In considering therapeutic measures, there is an obvious but sometimes overlooked distinction between protection, measures instituted before an insult, and resuscitation, measures taken after an insult. Finally, the direct effects of the insult should be distinguished from secondary mechanisms. These mechanisms can be complex and damaging but may offer an opportunity for therapeutic intervention totally separate from the primary stress, for example, combating cerebral edema occurring as a relatively delayed sequel of ischemia. In spite of similarities in mechanisms, treatment which is effective in one condition may not be effective in others.

The pathophysiological changes following focal ischemia are better understood than those following cardiac arrest and CPR. In acute ischemic stroke the patient usually remains conscious with a focal neurological deficit. Only massive infarcts are likely to produce edema leading to intracranial pressure rise, coma, and brain death. The collateral circulation influences the size of the infarct by maintaining viable neurons in the tissue which surrounds the eventually necrotic center.

In global ischemia without reperfusion (as in experimental decapitation), uniform neuronal changes can be detected by microscopy after five to seven minutes of circulatory arrest, with necrosis evident after about 60 minutes arrest. In global ischemia with reperfusion, multifocal necroses develop after shorter periods of arrest. Reperfusion seems to provoke secondary changes which are multifocal and multifactorial and can evolve into "miliary infarcts." The probable causative factors include transient vasoparalysis; nonhomogeneous hypoperfusion from blood cell sludging, tissue edema, and vasospasm; hypermetabolism (perhaps related to catecholamine release); tissue acidosis; release of free chemical radicals which tend to damage membranes; and varying degrees of intra- and extracellular cerebral edema. These secondary changes can be intensified by failure of function in noncerebral organ systems, but some of them may be treated separately with survival benefit to the brain.

Standard Measures of Life-Brain Support

There are several accepted measures based on experimental evidence or extensive clinical trial experience which are useful in the severe ischemic insult. Arterial blood pressure should be controlled to avoid hypotension (defined in terms of the individual patient) or severe hypertension. Tracheal intubation...
and mechanically controlled ventilation maintain arterial \( \text{Paco}_2 \) (25 to 35 Torr), \( \text{PaO}_2 \) (over 100 Torr), and pH (7.2 to 7.6). Partial neuromuscular blockade, utilizing a curare-like agent such as pancuronium, allows prolonged immobilization and, experimentally, appears to reduce the severity of brain injury.\(^2\)

Maintenance of optimal hematocrit, blood sugar, electrolytes, osmolality, hydration, and alimentation must be assured. Treatment or prevention of noxious afferent stimuli — restlessness, straining, and more serious events like seizures — may require a central nervous depressant such as intravenous thiopental or pentobarbital in conventional anesthetic doses, which do not depress the cardiovascular system.

Intracranial pressure monitoring has become increasingly common to guide the use of other measures to control intracranial pressure: ventricular cerebrospinal fluid drainage, osmotic diuretics, loop of Henle active diuretics (e.g., furosemide), forced hyperventilatory hypocapnia, glucocorticoid therapy, and hypothermia. Although these interventions have developed from experience with patients after brain surgery or head injury, the measures are appropriate for some patients with encephalitis, cardiac arrest, or stroke. While short-term (12 to 72 hours) low dose osmo therapy with mannitol or glycerol continues to be utilized, intracranial hypertension is increasingly controlled with anesthetic doses of intravenous thiopental or pentobarbital, particularly when the treatment need extends for more than 24 hours or when large doses of osmotic agents are required for pressure control. In this last circumstance rebound edema may be a major complication of osmo therapy.

### Controversial Measures For Brain Resuscitation

Although some applications of the “acceptable” methods outlined in the prior paragraphs could be disputed, depending on the specific clinical states to which they are applied, the most controversial measures are hypothermia, certain attempts to promote reperfusion, and use of a variety of drugs, particularly barbiturates, in large doses.

Therapeutic hypothermia after ischemic brain insult reduces the rate of brain metabolism, cerebral edema, and the extent of ischemic infarction. Its resuscitative effect after global ischemia remains to be documented, however. Hypothermia has not gained wide acceptance because of difficult management problems, especially after 24 hours, and a variety of undesirable, injurious side-effects.

A combination of measures to promote reperfusion immediately after cardiac arrest reduced mortality and brain damage in dogs subjected to 12 minutes of ventricular fibrillation.\(^3,4\) These measures included sustained, moderate hypertension, heparinization, and normovolemic intracarotid hemodilution with dextran 40. Each of these measures is now being studied separately in primate models.\(^5,6\) Preliminary results suggest the value of sustained, moderate hypertension but do not demonstrate benefit from hemodilution to hematocrit of 25% nor from heparinization. Severe, intermittent hypertension is clearly detrimental and brain damaging.

Because of a lack of reliable animal models, the Pittsburgh group developed a reasonably reproducible primate model of global brain ischemia, utilizing a high pressure neck tourniquet combined with induced hypotension to diminish vertebral artery flow further. Long-term postischemic intensive care nursing was provided the animal. The outcome is measured not by mortality, which is often largely influenced by extracerebral organ system failure, but rather by neurological deficit (100% = brain death, 50% = vegetative state; 0% = normal) and histopathological damage.

In 1975, Bleyaert and associates\(^1\) initiated monkey studies with thiopental loading, using the above model. They were inspired by the promising results of Yatsu\(^6\) with concurrent use of methohexital in experimental global anoxia and of Smith and Hoff\(^7\) with thiopental loading after experimental focal ischemia. Amelioration of focal ischemia was later confirmed by Levy,\(^8\) Michenfelder,\(^9\) and others. In experimental animals with middle cerebral artery occlusion,\(^6,9\) pre- and post-treatment with large doses of thiopental or pentobarbital reduced infarct size.

Using the above monkey model with 16 minutes of global ischemia, Bleyaert tested thiopental loading with intravenous administration of 90 mg/kg between 5 and 60 minutes after start of reflow, the dose which Smith had found effective in focal ischemia. Because thiopental reduces blood pressure, norepinephrine was used to maintain normal values. Thiopental significantly reduced neurological deficit scores after 7 days from about 50% deficit in controls to 0 deficit in five treated monkeys. Histopathological damage scores were also lower. Less impressive, but still significant, was the reduction in neurological deficit when thiopental was given 15 minutes after the ischemic stress; no significant reduction was noted when the delay was 30 or 60 minutes. Delayed administration of a larger dose was partially effective. Immobilization for 48 hours with pancuronium (without barbiturate) resulted in a seven-day neurological deficit of 20% which is significantly lower than that of the control group but significantly higher than in the best thiopental group.

Barbiturates are known to reduce neuronal metabolic rate and edema formation and to suppress seizure activity, implying a protective influence on survival. There is also evidence to suggest benefit from anesthetic block of noxious effects and from prolonged immobilization. There are other possible mechanisms not yet fully documented such as “scavenging” of free chemical radicals evolved during ischemia,\(^8,9\) alteration in metabolic pathways, and suppression of catecholamine-induced hypermetabolism.

### Clinical Studies With Barbiturates

In spite of clear-cut reduction in infarct size in animal models by post-insult barbiturate loading,
Another clinical study with a different protocol after cardiac arrest utilizing a randomized protocol. A study under NIH sponsorship of thiopental loading in 1979-1982 international multicenter clinical trials. In 1975, a patient trial protocol with thiopental loading was developed. Control and treatment groups were to receive comparable intensive care measures to improve brain survival. The treatment group was to receive thiopental, up to 30 mg/kg, as rapidly as tolerated and as early as possible. Hypotension was to be prevented or treated by plasma volume expansion and a vasopressor. Thiopental-induced hypotension, due to vasodilation and myocardial depression, is common and can be severe in patients with cardiovascular disease, although it is uncommon or mild in patients with a normal cardiovascular system.

The results of clinical feasibility trials with this protocol (without randomized controls) during 1977-1978 suggested a favorable effect. Fifteen of the 25 patients with arrests of over five minutes' duration recovered consciousness. The proportion of severely damaged survivors was no higher than in other series using standard therapy. Patients with healthy hearts tolerated thiopental loading without the need for vasopressor support of blood pressure. Those with myocardial ischemia required dopamine, and three of them developed recurrent cardiac arrest.

Recently, the Pittsburgh group initiated a three-year (1979-1982) international multicenter clinical study under NIH sponsorship of thiopental loading after cardiac arrest utilizing a randomized protocol. Another clinical study with a different protocol (thiopental for 2 to 3 days) is being planned by a group at Stanford University in California.

The optimal type, dosage, blood level, and timing of barbiturate administration remain to be determined on the basis of the margin of safety between what reduces brain damage and what depresses the heart. The doses needed for maximal depression of cerebral metabolism and EEG "silence" are smaller than those found to reduce brain damage in monkeys and have not yet been studied for their protective effect (table).

### Negative Results With Barbiturates

Failure of barbiturates to show a beneficial effect in some instances may be the result of failure to provide other life support measures. Steen, Milde, and Michenfelder could not repeat the results of Goldstein, Wells, and Keats with barbiturate protection against total circulatory arrest, perhaps because of differences in life support. Michenfelder has postulated that barbiturates reduce ischemic brain damage only by depression of cellular activity and metabolic rate. In a mouse model of alveolar anoxia, he showed that an anesthetically inactive isomer of a barbiturate failed to prolong breathing time. This model does not measure post-ischemic changes or their treatment in terms of viability of neurons. He concluded that barbiturates provide protection against incomplete focal ischemia but not in cardiac arrest. Michenfelder's hypothesis does not take into consideration the results of several studies already mentioned nor the fact that resuscitation cannot change the initial insult but can ameliorate secondary post-insult changes. Michenfelder's hypothesis can explain the beneficial effect of barbiturate when given after complete global brain ischemia because these secondary changes are multifocal incomplete ischemia.

Some have argued that barbiturates benefit the brain only by reducing intracranial pressure. In Bleyaer's experiments with global ischemia, intracranial pressure was not increased. Moreover, in Réye's syndrome conventional anesthetic doses (1 to 5 mg/kg IV repeated as necessary) of thiopental or pentobarbital which do not depress the circulation may be clinically beneficial in certain situations.

### Table: Summary of Present Knowledge of Measures in Brain Resuscitation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Acute ICP rise</th>
<th>Cardiac arrest</th>
<th>Brain infarct</th>
<th>Trauma, edema</th>
<th>Toxic, metabolic, inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodilution</td>
<td>?</td>
<td>?</td>
<td>0</td>
<td></td>
<td>(+)</td>
</tr>
<tr>
<td>Heparinization</td>
<td>—</td>
<td>—</td>
<td>(+)</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Thiopental—high dose</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Immobilization</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Osmotherapy</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td>+</td>
</tr>
</tbody>
</table>

Key: ? = not known; 0 = no effect shown; — = increases brain damage; (+) = possibly reduces brain damage; + = reduces brain damage; ICP = intracranial pressure.
treatment very early after severe brain injury will suppress seizures, facilitate mechanical respiratory control, contribute toward reduction of edema, and protect against possible secondary ischemic or anoxic events regardless of what the first brain insult was. However, since the treatment suppresses neurological function, careful diagnostic evaluation is necessary because the usual clinical signs are removed. After head injury or encephalitis, administration of prophylactic barbiturate without intracranial pressure monitoring is controversial and may be dangerous. In shock states with coma, since barbiturate may precipitate cardiac arrest, cardiovascular stabilization has therapeutic priority.

Brain resuscitation measures must continue to be accompanied by critical care triage. Brain death and the presence of a persistent vegetative state must be meticulously determined to allow withdrawal of extraordinary support measures from the patient. In making these determinations, however, premature action must be avoided. Recovery of consciousness has occurred as long as two weeks after cardiac arrest treated with brain resuscitation measures.

Physicians and the public should be made aware of the fact that at present benefit can be expected from barbiturate therapy only if it is started soon after the insult.

Conclusions

In the near future, treatment for brain insult will probably not consist primarily of barbiturates but rather will include some anesthetic as part of a combined pharmacological and physiological scheme of therapy. Brain resuscitation studies with barbiturates have triggered the search for other therapeutic approaches with fewer cardiovascular and central nervous system depressant effects. Clinicians should remain informed about current developments in cerebral resuscitation so as to provide the most effective therapy to the greatest number of patients.

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