

Positive Experimental Demonstration of the Negative Brain “Protective” Effects of Anesthetics following Cardiac Arrest

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The cerebral metabolic effects of a massive dose of thiopental (177 mg/kg) were investigated in seven dogs. The systemic circulation was supported with an extracorporeal circuit. At an infusion rate of 2 mg/kg/min, cerebral oxygen consumption (CMR_{O_2}) decreased progressively until cerebral electrical silence was produced. This occurred after a mean dose of 72 mg/kg, which caused a mean decrease in CMR_{O_2} to 58% of the control value (measured at 1.5% halothane inspired). Thereafter, despite continued at 4 mg/kg/min, CMR_{O_2} did not decrease further. The oxygen-glucose index never changed during the infusion period and, at the termination of the infusion, brain assays for ATP, phosphocreatine, lactate, and pyruvate revealed normal concentrations. It is concluded that there was no alteration in normal cerebral metabolic pathways, that cerebral metabolic effects of thiopental are secondary to functional effects, that thiopental would provide no cerebral protection during hypoxia sufficient to abolish cerebral function, and that thiopental does not uncouple oxidative phosphorylation *in vivo*. (Key words: Anesthetics, intravenous: thiopental; Brain: metabolism; Metabolism: brain.)

WHEN I was informed that this article¹ was selected for inclusion in the Classic Papers Revisited section of ANESTHESIOLOGY I was, of course, pleased. One dictionary definition of “classic” is “of lasting significance.” I certainly hope this applies to the work selected. Although not consulted in the selection process, I can only say that I consider this study to be my single most important contribution to the massive literature encompassed by the topic “Pharmacologic Brain Protection.” A photograph is available on the ANESTHESIOLOGY Web site at <http://www.anesthesiology.org>.



Additional material related to this article can be found on the Anesthesiology Web site. Go to the following address, click on the Enhancements Index, and then scroll down to find the appropriate article and link. <http://www.anesthesiology.org>

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Received from the Department of Anesthesia, Mayo Clinic, Rochester, Minnesota. Submitted for publication August 20, 2000. Accepted for publication September 26, 2001. Support was provided solely by institutional and/or departmental sources.

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The stimuli for pursuing this study were twofold. 1) Scientifically, there was at the time of this study in the early 70's a “chicken or egg” question: whether anesthetics primarily altered brain metabolism with resulting functional effects, or alternatively, primarily suppressed function with resulting metabolic effects; and 2) Clinically, barbiturates were being used to “protect” the brain during and after anoxic events (*i.e.*, cardiac arrest) based upon an assumed metabolic suppressive effect that would reduce cerebral oxygen requirements. In a previous canine study² we had reported compelling (in our opinion), but indirect, evidence that thiopental (and other anesthetics) appeared to impact on brain function primarily and that cerebral metabolic suppression was entirely secondary. If so, this would negate possible brain “protective” effects in a clinical setting of hypoxia/anoxia sufficient to abolish brain function (*i.e.*, an isoelectric EEG). This study was specifically designed to determine by direct approach the interrelationships between brain functional and metabolic effects.

The hypothesis and the approach to test it were conceptually simple and straightforward. We used a canine model for the direct measurement of cerebral blood flow and metabolism, which we had previously described and validated³; we in addition utilized extracorporeal circulation to support and maintain satisfactory systemic hemodynamics. The latter permitted the administration of massive doses of anesthetics (in this study, thiopental) which would otherwise overwhelm normal cardiac function. This in turn made possible the measurement of cerebral metabolic parameters in the presence and absence of cerebral function (as reflected by EEG activity) and as impacted upon by even massive doses of thiopental.

The resulting observations relating the EEG reflected functional effects and the cerebral metabolic effects were remarkably consistent in a series of seven individual canine preparations. A constant intravenous infusion of thiopental initially produced the expected progressive decrease in cerebral oxygen consumption (CMR_{O_2}) while the EEG reflected increasing functional suppression. With the onset of an isoelectric EEG there was a simultaneous plateau effect on CMR_{O_2} . This occurred at widely different total thiopental doses in dogs, but at

quite similar levels of CMR_{O_2} , while the EEG remained isoelectric. Thereafter, despite continued administration of thiopental, no further effect on CMR_{O_2} was observed. At the termination of these studies the cerebral energy state in each of the dogs was determined and found to be normal as reflected by normal cerebral tissue levels of adenosine triphosphate (ATP), phosphocreatine (PCr), lactate, and pyruvate.

The conclusions seemed obvious: 1) There were no measurable *in vivo* cerebral metabolic toxic effects of thiopental, no matter the dose administered; 2) Cerebral metabolic suppression by thiopental was entirely secondary to functional suppression (as reflected by EEG) such that with complete functional suppression no further metabolic effects were demonstrable; and 3) any relevant "protective" effects of thiopental (based on metabolic suppression) were only possible in hypoxic events insufficient to abolish cerebral function (*i.e.*, EEG activity). Accordingly, such clinical emergencies as cardiac arrest which abruptly induces an isoelectric EEG could not be favorably impacted upon by thiopental (and presumably other anesthetics).

The impact of this study along with supporting evidence from other studies was twofold: 1) The question as to the primacy of the "chicken or egg" was answered to the satisfaction of most: thiopental (and presumably other anesthetics) by acting primarily "in a physical-chemical, or physical, or electrical way on membranes"⁴ altered function and only secondarily altered metabolism; and 2) Clinically, although barbiturates continued to be used for a time by some in the hopes of providing a degree of brain "protection" during and following cardiac arrest, enthusiasm waned and the practice was ultimately abandoned when clinical studies confirmed the lack of efficacy of such therapeutic interventions.⁵ That this study explained (and predicted) such a lack of efficacy was scientifically rewarding even if the clinical implications in the management of cardiac arrest patients were disappointing.

In subsequent studies the same methodologies were utilized to examine the effects of increasing concentrations of both halothane⁶ and isoflurane.⁷ In the case of halothane EEG silence ensued at 4.5% (end-expired); however, CMR_{O_2} did not plateau, but rather continued to decrease up to concentrations of 9.0%. In these dogs terminal measurements of the brain energy state revealed severe depletions in ATP and PCr with large accumulations of lactate. The conclusion was that, un-

like thiopental, halothane produced toxic metabolic effects at high concentrations.

In striking contrast, isoflurane at concentrations sufficient to abolish EEG activity (3.0% end-expired) was associated with onset of a stable CMR_{O_2} which remained unaffected up to concentrations of 6.0%. Similar to thiopental, the brain energy state at the termination of these studies was normal. These results encouraged speculation that isoflurane might provide a limited degree of brain protection similar to that assumed for barbiturates (*i.e.*, in circumstances wherein the brain hypoxia is not sufficient to abolish EEG activity). Such speculation remains controversial to this day.

As a result of these experiments we were encouraged to pursue, often at the behest of interested pharmaceutical houses, a large number of outcome studies in laboratory animal models of stroke, hypoxia, shock or cardiac arrest in an effort to uncover possible brain protective effects for a variety of pharmacological interventions, as well as, hypothermia. The pharmacological agents examined included, in addition to barbiturates, the following: isoflurane, naloxone, physostigmine, phenytoin, pentoxifylline, midazolam, cyclocreatine phosphate, nimodipine, flunarizine, deferoxamine, lidoflazine, superoxide dismutase, catalase, and dizocilipine maleate. Most of these studies yielded largely negative results. There were, however, some modest positive effects identified for barbiturates, isoflurane, nimodipine and, of course, hypothermia. In retrospect, the hope of discovering a pharmacological "magic bullet" that might provide major protective effects for the brain in event of clinical hypoxia is probably akin to seeking the Holy Grail. Still it was stimulating and instructive to look for such.

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