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 (CMRO₂) decreased progressively until cerebral electrical silence was produced. This occurred after a mean dose of 72 mg/kg, which caused a mean decrease in CMRO₂ to 58% of the control value (measured at 1.5% halothane inspired). Thereafter, despite continued at 4 mg/kg/min, CMRO₂ 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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quite similar levels of CMR_{O2}, while the EEG remained isoelectric. Thereafter, despite continued administration of thiopental, no further effect on CMR_{O2} 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 demostratable; 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_{O2} 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, unlike 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_{O2} 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, pentoxifylline, midazolam, cyclocreatine phosphate, nimodipine, flunarazine, deferoxamine, lidoflazine, superoxide dismutase, catalase, and dizocilpine maleate. Most of these studies yielded largely negative results. There were, however, some modest positive 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.

References

1. Michenfelder, JD: The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. Anesthesiology 1974; 41:251–6