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Cerebral Protection: Are all Barbiturates Created Equal?

To the Editor—We enjoyed the recent article by Warner et al.1 They have had the audacity to challenge a verse of the neuroanesthesia catechism that has been chanted faithfully for years. They are to be congratulated (or burned at the stake) for demonstrating that, in the setting of focal ischemia, a maximal cerebral protective effect can be achieved with only one third of the dose of pentobarbital required to achieve electroencephalographic burst-suppression. Their observations refute the notion that a maximal cerebral protective effect requires a dose sufficient to achieve complete electroencephalographic suppression. But their observations lead to another heretical question.

It has been tacitly accepted, with respect to cerebral protection, that one barbiturate is equivalent to another. In the many studies of cerebral protection, several barbiturates (thiopental, methohexital, pentobarbital) have been used, invariably, without any attempt to justify the choice on a pharmacodynamic basis. However, the data of Warner et al. should force us to reexamine that assumption of protective equivalence. That assumption seemed reasonable when it was accepted that cerebral metabolic rate suppression was the important protective mechanism because the barbiturates appear very homogenous in their capacity to suppress cerebral metabolic rate. However, if, as suggested by Warner et al., we must begin to suspect some other pharmacologic effect, then is it reasonable to assume that all barbiturates share that effect (whatever it is) equally? Is it possible that one barbiturate is a more effective protector than others or that some barbiturates are no more protective than other general anesthetics?

These questions are highlighted by material in the very thorough discussion section of the current paper. Warner et al. candidly point out that the protective effect they observed (expressed as a percentage reduction in infarct volume) was smaller in their current investigation of pentobarbital than was the case in an earlier, though methodologically similar, study that included a group anesthetized with halothane.2 Both studies used an awake control state. Infarct volume was reduced by approximately 25% in the pentobarbital groups in the current study and by 40% in the investigation involving halothane. In an even earlier investigation by Warner and his colleagues, it was demonstrated that methohexital provided greater protection (again expressed as percentage reduction at infarct volume) than did 1 MAC halothane anesthetic.3 From the three investigations, one might be tempted to construct a "protective hierarchy" as follows: methohexital > halothane > pentobarbital (another heresy!). On the basis of nonconcurrency alone, such a conclusion would be unreasonable. However, we think that, in the uncertainty, there is justification for a concurrent investigation of the effects of volatile agents and several barbiturates on reduction of infarct size. It no longer appears reasonable to assume that all barbiturates are equal in their cerebral protective potential or, for that matter, to rest assured that they are all superior to anesthesia with a volatile agent.

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Optimal Dose for Barbiturate Protection of the Ischemic Brain

To the Editor: — The report by Warner et al.1 showed no difference between the degree of cerebral ischemic protection provided by an electroencephalographic-isoelectric burst dose of pentobarbital compared with a dose barely suppressing electroencephalographic activity. Their results on the effects of barbiturate suppression of electroencephalographic activity on severity of ischemic brain damage confirm, histologically, what we found biochemically in 1983, when we determined the dose of thiopental, pentobarbital, and phenytoin associated with maximal attenuation of all free fatty acid release during decapitation ischemia in rats.2 In the rat, the intraperitoneal anesthetic dose for pentobarbital and thiopental is 60 mg/kg, and maximal attenuation of free fatty acid release was achieved at a dose of 30 mg/kg intraperitoneally. Maximal attenuation was achieved at the anticonvulsant dose of 150 mg/kg for phenytoin. We concluded that maximal therapeutic effects are already achieved at subanesthetic doses of barbiturates and at anticonvulsant doses of phenytoin. In support of this, an intraperitoneal dose of 30 mg/kg pentobarbital, glucose utilization is almost maximally inhibited.3 These observations could explain the difficulty in demonstrating the efficacy of barbiturates in clinical trials of complete global brain ischemia.4 In these clinical studies, other drugs, such as sedatives, somatic agents, and opioids, were used in the controls, which may be as protective as the barbiturates. The conclusion of these studies should not be that barbiturates are not protective, but rather, that they are no more protective than the other therapies combined.

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