

These methods are well-summarized in common statistical texts. They include techniques for normally distributed data (Bonferroni's method, Tukey's method, Dunnett's method and Scheffe's method, for example) and nonparametric techniques as well (the Kruskal-Wallis method). The reader who seeks more information on these methods is referred to a recent review of several possible approaches to these and other common problems in biostatistics.⁵ An introductory text, which was stimulated by an awareness of these problems, was published recently and it explains many of these principles in a simple and understandable manner, even for those with limited mathematical skills.⁶

Over the past years we have seen the development of more rigorous scientific approaches to biomedical research. Studies which formerly involved only a single dose of a drug now commonly include dose-response data. Blood levels of drugs are reported with increasing frequency. Randomized allocation to various treatment groups, blind or double-blind experimental protocols, and the administration of a placebo in a control group are common examples of the more rigorous approaches which are employed in biomedical research. Despite these advances in the scientific method, biomedical scientists have been slow to adopt sensitive, reliable, and appropriate statistical techniques which allow proper interpretation of results. A product is no better than its weakest link. If valid data are analyzed improperly, then the results become invalid and the conclusions may well be inappropriate. At best, the net effect is to waste time, effort, and money for the project. At worst, therapeutic decisions may be based upon invalid conclusions and patient's wellbeing may be jeopardized.

While the journal cannot and will not endorse any single method or approach for statistical analysis, the readers will note an increasing level of sophistication in the techniques used to analyze the data which appear in *Anesthesiology*. We owe that to our patients, whose medical care is based on the statistical analysis of experimental data. We owe it to our readers, who expect valid results to be presented in the journal. Finally, we owe it to the authors, many of whom are competing for research support in an environment which requires that all aspects of the research, including the statistical methods, receive proper attention in order to ensure valid conclusions.

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Barbiturates for Brain Resuscitation: Yes and No

PREVIOUS STUDIES concerned with the question of whether barbiturates can favorably alter brain outcome following a period of complete global ischemia have yielded either a yes or no answer and have created controversy and confusion. Dr. Shapiro's group in San Diego has now addressed that question and reports in this issue that the answer is neither yes nor no; rather it is *yes and no*.¹ It is hoped that this study represents the first step toward clarifying what has been a near-hopeless muddle of contradictory reports.

The study was done in cats. Complete ischemia was induced by electrically fibrillating the heart. The periods of circulatory arrest ranged from 12 to 16 min. Resus-

citation was always accomplished within four minutes. The barbiturate was thiopental; the dose was 60 mg/kg initiated five minutes after resuscitation. And no, among the survivors there were no differences in the neurologic deficits of treated animals compared to controls. But yes, there *were* significantly fewer deaths due to neurologic dysfunction in the treated group. And yes, there was a significantly lesser incidence of a seizure-like pattern appearing in the EEG of treated animals following resuscitation.

The design of this study and the close control that was achieved of the many difficult variables encountered in this type of protocol should stand as a model for future investigators interested in studying the chronic effects of a period of complete global ischemia. Todd *et al.*¹ should

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also be congratulated for their careful analysis and conservative interpretation of the data. There is little of substance to criticize. Does the use of cats invalidate the results? Intuitively one might prefer a primate model, but this should not be a critical consideration. Presumably differences in collateral circulation and other anatomic differences should not be important when the insult is one of complete global ischemia. In this situation re-perfusion is primarily dependent on cardiac function and should not be influenced by differences in vascular anatomy. Should different doses of thiopental have been examined? Ideally, yes. But it would appear that Todd *et al.* used a near maximum dose from the standpoint of hemodynamic tolerance. Since cardiac function is the key to re-perfusion, this is a critical consideration. Furthermore, the dose used was sufficient to totally suppress the EEG for 64–91 min post-resuscitation (compared to 27 to 36 min in controls) and to cause persistent burst-suppression in the EEG for approximately six hours.

Most refreshing, not only is there a convincing positive result reported in this study but there is also a reasonable hypothesis, supported by data, to explain this result. The absence of neurologic deaths in the treated animals appears to correlate with the lesser incidence of “abnormal” EEGs observed in the post-resuscitation period. All ten of the animals in the control group that were classified as neurologic deaths demonstrated an “abnormal” EEG at some point early in the post-resuscitation period. Furthermore, of the three treated animals that had an “abnormal” EEG, all sustained a severe neurologic deficit. Whether or not this “abnormal” EEG represented a true seizure pattern could not be answered in this study but, no matter, it almost certainly reflects increased cerebral energy expenditure in the same way that a true seizure does. And in the early post-resuscitation period (for at least six hours) there is known to be a persistent hypoperfusion state² (despite adequate blood pressure). Likely, any sudden increase in energy demands during this period could not be matched by increased delivery of oxygen (as normally occurs with seizures) and the net result is further ischemic brain damage.

If this interpretation is correct then there are potentially important clinical applications, one or more of which could be adopted at this time and none of which should add significant risk. One would be to monitor patients for seizure-like activity in the post-arrest period, and another would be to suppress such activity with available drugs. As Todd *et al.* suggest, the use of barbiturates may be totally unnecessary. Rather, such drugs as phenytoin, or possibly diazepam could be used either prophylactically or therapeutically. Reports of phenytoin protection in various animal models are already in the literature.^{3–5} Unlike barbiturates, relatively large doses of phenytoin are well-tolerated hemodynamically; neither will phenytoin obscure the neurologic status of the

patient. Perhaps as Todd *et al.* speculate, “Something can be done to aid a patient’s resuscitation from a severe ischemic insult.”

In addition, if the basis for any barbiturate “protection” in the post-arrest period is as simple and direct as the one suggested, perhaps some of the past contradictions can be resolved. It is to be hoped that Dr. Shapiro’s laboratory and others will pursue some of the obvious studies suggested by the current study. Will phenytoin (or other antiseizure therapy) yield results as good as or better than those reported with thiopental? What are the determinants of the “abnormal” EEG pattern and can a reproducible model be developed which will reliably yield such an EEG pattern? If the latter can be developed, then it should be possible to examine the cerebral metabolic and vascular events which accompany the EEG changes. And thereby begin to uncover mechanisms.

Must the clinician await the results of such studies? Is it perhaps analogous to the status of steroids in head trauma—unproven, but with an acceptably low risk-benefit ratio? In fact, there are those now who do administer phenytoin to post cardiac-arrest patients.^{6,7} It does seem to have a very low risk-benefit ratio. Possibly, unlike the case with barbiturates, clinical application may be appropriate even though definitive results are still lacking. Certainly it would seem inappropriate to condemn such an application.

In any case there is a suggestion in the Todd *et al.* study that a logical “plot” is developing in the barbiturate “story.” Perhaps it is not all chaos after all.

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