Does Isoflurane Aggravate Regional Cerebral Ischemia?

Nehls et al.¹ address an important and clinically relevant question in their article which is published in this issue: does isoflurane offer protection similar to that provided by thiopental in the event of regional cerebral ischemia? Their data provide a reasonably definitive negative answer. However, the question is a generic one, while their answer, because of problems they encountered, is highly specific to the circumstances of their study. Lacking additional data, we have little choice other than to assume that their answer is broadly applicable. Certainly, there is no justification at this time to use isoflurane in preference to thiopental in those clinical circumstances wherein pharmacologic brain protection might be indicated.

The authors squarely confront the problems encountered in their study and present an evenly balanced evaluation of the limitations imposed by those problems. To begin with, any who have undertaken an intensive care primate study such as this one can empathize fully with the authors regarding the inherent difficulties imposed by such a study. One of the immediate limitations is on the number of studies that are reasonably possible. The limitations are imposed by both the cost of the studies and the wear and tear on the personnel who must provide the intensive care. Thus, the goal of achieving a definitive answer is constantly threatened by marginal statistics secondary to small group size. Technically, one might point to the P value > 0.05 which they report for the differences in neurologic deficit between the isoflurane and thiopental groups as a failure to "prove" a difference, and thereby deny the authors the use of those magical words "statistically significant." In fact, the authors do not use those words in describing these data, but correctly report the fact that the difference is significant at a 0.055 level. For most, this should be good enough, particularly when supported by the infarct data, which are statistically significant at a P < 0.025 level.

Having reasonably dodged the statistical bullet, the investigators encountered a totally unexpected difficulty. The baboon, chosen for clinical relevancy, consistently developed hypertension when exposed to high-dose thiopental during and following ischemia produced by middle cerebral artery occlusion. The dilemma imposed by this difficulty cannot really be satisfactorily resolved: if the hypertension is allowed during regional cerebral ischemia, the outcome might be strikingly altered; if the hypertension is treated pharmacologically, an interaction with regional cerebral ischemia is a distinct possibility. The investigators did the best they could under the circumstances, but their data can only be interpreted in the light (and shadow) of the resulting problems:

1) All of the thiopental treated animals were given near maximal sub-toxic doses of nitroprusside (about 8 μg · kg⁻¹ · min⁻¹), a known cerebrovasodilator, for more than 6 hours.
2) Many of the thiopental treated animals also were given hydralazine, possibly a cerebrovasodilator.
3) All of the isoflurane-treated animals were given phenylephrine, which does not normally affect the cerebral vasculature.
4) However, in those animals that sustained an infarction, the cerebral vasculature is obviously not normal, nor is the blood–brain barrier; drug effects on the brain under these circumstances are simply unknown.
5) Despite these efforts, the thiopental-treated animals had a significantly higher blood pressure than the isoflurane-treated animals throughout the 6-hour period of ischemia.

Thus, as stated at the outset, the answer provided by these data may be definitive, but it may not be generic. It seems probable that these difficulties could be largely circumvented by either selecting a different primate spe-
cies or by providing a common anesthetic background so as to avoid unwanted hypertension (and drugs). Whether any investigators will prove brave enough to undertake such a follow-up study in order to eliminate the variables introduced by the blood pressure and drug differences in the current study is questionable at best. Without such, we have no choice but to accept as is the results reported by Nehls et al.\(^1\) Certainly, one possible explanation offered for the apparent negative effects of isoflurane is a reasonable one: as a mild cerebral vasodilator, isoflurane may cause an unfavorable redistribution of blood flow during regional ischemia, as contrasted to the effects secondary to the vasoconstrictor properties of thiopental.

In possible contradiction to the results reported by Nehls et al.\(^1\) are those reported by Messick et al.\(^2\) concerning the critical regional CBF in patients undergoing carotid endarterectomy during isoflurane anesthesia. They found that the critical CBF (i.e., the CBF at which EEG ischemic changes appear) during isoflurane was approximately one-half that previously reported for halothane (10 vs. 20 ml·100 g\(^{-1}\)·min\(^{-1}\)). Of itself, this is not evidence of a protective effect for isoflurane, nor was a critical CBF during thiopental anesthesia determined. However, in a recent retrospective survey of over 2000 patients operated at the Mayo Clinic (unpublished data), the incidence of EEG changes during carotid endarterectomy with isoflurane anesthesia was significantly less than that with either enflurane or halothane anesthesia (18% vs. 26 and 25% respectively, \(P < .001\)). These data do imply a relative protective effect for isoflurane, but, again, offer no comparison to thiopental. Thus, although specific pharmacologic intervention to provide brain protection still favors the use of barbiturates, among the volatile anesthetics, isoflurane does appear to offer protective effects in regional ischemia. What remains unknown is whether isoflurane and thiopental, during strictly comparable circumstances, offer the same degree of protection.

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