Cerebral Resuscitation with Barbiturates

To the Editor:—In a recent Editorial,[1] Michenfelder discussed a study by Nussmeier *et al.*[2] on the pretreatment of incomplete ischemia. Unfortunately, Michenfelder used the Editorial format to give an unbalanced view of our past studies on resuscitation after complete ischemia in monkeys[3] and patients.[4]

The rhesus monkey study by Bleyaert *et al.*[3] was the first long-term (7-d) study of outcome after complete global brain ischemia with intensive care. Michenfelder initially criticized our model, and then later invited a member of the Pittsburgh group to introduce it into his laboratory. The study by Bleyaert *et al.*,[3] published in ANESTHESIOLOGY after peer review, was based on a rationale that is still valid today: 1) Barbiturates, which had been shown to ameliorate incomplete focal ischemia[5,6] and incomplete global ischemia,[7] might also favorably alter the secondary multifocal, incomplete ischemic mismatching of oxygen supply and demand that we[8,9] and others[10,11] have demonstrated occurs after complete global ischemia and reperfusion. 2) Barbiturates exert many potentially beneficial short-term effects beyond their ability to reduce brain metabolism.[3,4,7,11,12]

The subsequent pigtail monkey study by Gisvold *et al.*[13] with the same model could not duplicate the results of Bleyaert *et al.*[3] This does not necessarily mean that the study by Bleyaert *et al.* was "flawed"; rather, it reveals how difficult it is to achieve consistently effective cerebral resuscitation after complete ischemia. Many factors not appreciated by us or others at the time might have influenced the outcome: the use of different subspecies; reperfusion pressure patterns; duration of controlled ventilation; and details of intensive care. The only valid criticism of the study by Bleyaert *et al.* now is the fact that some of the control experiments were not performed concurrently with the thiopental experiments.

The Brain Resuscitation Clinical Trial[4] was initiated in 1979 as a National Institutes of Health–supported multicenter program. It was not designed to "thrust on the medical community prolonged barbiturate coma with evangelistic zeal,"[1] but rather to establish an ongoing mechanism for clinical study and evaluation of novel treatment potentials for coma after cardiac arrest. The rationale for having chosen thiopental loading as the first novel treatment to be tested was based on more than the results of the Bleyaert *et al.* study; it included many other demonstrated beneficial effects of barbiturates[3–7,14] and the widespread clinical use of thiopental loading after cardiac arrest at the time.

Our clinical study showed that thiopental loading, started in comatose patients 10–50 min after restoration of spontaneous normotension, is safe, *i.e.*, does not increase rearrests or mortality, but also does not significantly improve cerebral or overall outcome.[4] We have concluded, therefore, that this treatment should not be used routinely after cardiac arrest. This does not negate the possibility that some beneficial effects might be achieved with barbiturates after milder insults with earlier or more prolonged administration, or with a barbiturate used as one of a combination of treatments. Until such possibilities are proven in the laboratory, we agree with Yatsu[14] that barbiturates should be used after cardiac arrest only in selected cases for selected indications. These include prevention or control of seizures, sedation, and normalization of elevated intracranial pressure.

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REFERENCES

1. Michenfelder JD: A valid demonstration of barbiturate-induced brain protection in man—At last (editorial). ANESTHESIOLOGY 64:140–141, 1986
2. Nussmeier NA, Arlund C, Slogoff S: Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. ANESTHESIOLOGY 64:165–170, 1986
3. Bleyaert AL, Nemoto EM, Safar P, Stezoski SW, Mickell JJ, Moossy J, Rao GR: Thiopental amelioration of brain damage after global ischemia in monkeys. ANESTHESIOLOGY 49:390–398, 1978
4. Brain Resuscitation Clinical Trial I Study Group: Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med 314, 397–403, 1986
5. Smith AL, Hoff JT, Nielsen SL, Larson P: Barbiturate protection in acute focal cerebral ischemia. Stroke 5:1–7, 1974

6. Michenfelder JD, Milde JH, Sundt TM Jr: Cerebral protection by barbiturate anesthesia: Use after middle cerebral artery occlusions in Java monkeys. Arch Neurol 33:345–350, 1976

7. Yatsu FM, Diamond I, Graziana C, Lindquist P: Experimental brain ischemia: Protection from irreversible damage with a rapid-acting barbiturate (methohexital). Stroke 3:726–732, 1972

8. Snyder JV, Nemoto EM, Carroll RG, Safar P: Global ischemia in dogs: Intracranial pressures, brain blood flow and metabolism. Stroke 6:121–127, 1975

9. Kofke WA, Nemoto EM, Hossmann KA, Taylor F, Kessler PD, Stezoski SW: Brain blood flow and metabolism after global brain ischemia and post-insult thiopental therapy in monkeys. Stroke 10:554–560, 1979

10. Kagstroem E, Smith ML, Siesjo BK: Local cerebral blood flow in the recovery period following complete cerebral ischemia in the rat. J Cereb Blood Flow Metab 3:170–182, 1983

11. Hossmann KA: Treatment of experimental cerebral ischemia. J Cereb Blood Flow Metab 2:275–297, 1982

12. Safar P, Vaagenes P: Systematic search for brain resuscitation potentials after total circulatory arrest, NATO Conference on Mechanisms of Secondary Brain Damage, 1984. Edited by Baethmann A, Go KG, Unterberg A. New York, Plenum Press, 1986 (In press)

13. Gisvold SE, Safar P, Hendrickx HHL, Rao G, Moossy J, Alexander H: Thiopental treatment after global ischemia in pigtailed monkeys. ANESTHESIOLOGY 60:88–96, 1984

14. Yatsu FM: Cardiopulmonary cerebral resuscitation (editorial). N Engl J Med 314:440–441, 1986

In reply:—'Tis true that I initially criticized their primate model (because they failed to demonstrate absence of cerebral blood flow in individual animals during ischemia and because neurologic function was assessed by a nonblinded observer). 'Tis also true that we later invited a then *past* member of the Pittsburgh group (Gisvold) to introduce the basic model into our laboratory. The final truth is that we modified the model in order to demonstrate absence of cerebral blood flow in individual animals during ischemia and to provide for blinded evaluation of the animal's neurologic status postischemia.[1] It is now a good model.

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REFERENCE

1. Steen PA, Gisvold SE, Milde JH, Newberg LA, Scheithauer BW, Lanier WL, Michenfelder JD: Nimodipine improves outcome when given after complete cerebral ischemia in primates. ANESTHESIOLOGY 62:406–414, 1985

Position of Proximal Orifice Determines Electrocardiogram Recorded from Multiorificed Catheter

To the Editor:—Johans[1] reported that the intravascular electrocardiogram (ECG) monitored with a multiorificed catheter depends on the position of the proximal orifice, and that further work is needed to explain this finding. Examination of the electrical principles involved make this finding predictable.

The saline-filled catheter is a conductor with a different voltage source at each orifice provided by the summed electrical activity of the heart at that orifice. The electrocardiograph is electrically connected to the proximal orifice by a column of saline with impedance Z_c. The voltage measured by the electrocardiograph, V_{ECG}, is related to the voltage at the proximal orifice, V_p, by the following equation:

$$V_{EKG} = V_p - I_c Z_c$$

where I_c is the current flowing from the orifice to the electrocardiograph. Because the electrocardiograph has a high-input impedance compared with Z_c, I_c approaches 0, and V_{EKG} must nearly equal V_p. Johans' observation that this relationship is true confirms the expectation that the summed electrical activity of the heart at the proximal orifice provides an independent voltage source unaffected by voltages at more distal orifices.