the science is remarkably consistent over the past 10 years, and suggests the answer is yes. Should one continue working in an environment with powdered, high-
antigen latex gloves capable of sensitizing those exposed with a prevalence of 12.5% and a clinically allergic prevalence of 2.5%? Don’t bet your life on it.

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Anesthetic Agents and Hypothermia in Ischemic Brain Protection

ANESTHETICS can affect ischemic injury by numerous mechanisms,1 and their potential for cerebroprotection is clinically relevant. The effects of anesthetics have been widely studied for the past three decades in various animal models of cerebral ischemia. The magnitude of their neuroprotective effects has been variable depending on the experimental animal model, severity of the ischemic insult, and the choice of anesthetic.

In this issue of Anesthesiology, Miura et al.,2 have demonstrated the differential effects of anesthetics on outcome from near-complete but not incomplete global ischemia in the rat. The logical and dramatic conclusion from this study is that metabolic suppression is not the major mechanism by which anesthetics provide neuroprotection. This is an important finding that needs to be incorporated into our current rationale for care in the clinical arena. Reducing cerebral metabolic rate

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(CMR) has been the major operative principle of pharmacologic brain protection. However, anesthetics that equivalently reduce CMR do not provide equivalent or consistent protection from focal ischemia. Perhaps the most widely studied anesthetics are the barbiturates, long known to be neuroprotective in focal cerebral ischemia in numerous animal models and the only such intervention that has proven useful in humans.\(^5\) Anesthetics that have markedly different effects on CMR all produce neuroprotection in models of hemispheric global ischemia. Thus the potential mechanisms for neuroprotection with these agents are not limited to depression of CMR during ischemia. Concomitant to reducing CMR, barbiturates reduce \(\text{Ca}^{2+}\) influx, inhibit free radical formation, potentiate GABAergic activity, enhance cyclic AMP production, and delay the loss of inotropic glutamate receptor-mediated transmembrane electrical gradients. Among the other potentially protective effects of barbiturates is their ability to reduce glucose transport into cells, block \(\text{Na}^+\) channels, reduce glutamate, aspartate, lactate, and catecholamines. Although the ability of barbiturates to protect the brain from global ischemia is controversial, the one large, randomized, human study done to date found only statistically insignificant trends in favor of barbiturate protection as a resuscitative measure subsequent to cardiac arrest.\(^1\)

Vascular effects of anesthetics also may play a significant role in ischemic neuroprotection.\(^1\) Experiments in the cat model of focal cerebral ischemia indicate that some of the protective effect of barbiturates can be attributed to postischemic hyperemia.\(^5\) Inhalational anesthetics cause an increase in CBF in vitro and vasodilatation of cerebral vessels in vitro.\(^9\) Isoflurane, the most widely studied inhalational anesthetic, does not affect CBF but causes a 10% increase in cerebral blood volume possibly by causing dilation of the cerebral capacitance vessels.\(^7\) Consistent with its neuroprotective role, the ischemic threshold with isoflurane is greater than that of methohexital but not different from halothane.\(^8\)

A particular strength of the study reported by Miura et al.\(^7\) is the use of controlled experimental conditions, particularly temperature, which is a critical determinant of outcome in cerebral ischemia. Small differences in intraischemic brain temperature critically determine the extent of neuronal injury in experimental global cerebral ischemia.\(^7\) When ischemia reduces supply, hypothermia remains the \textit{sine qua non} for reducing demand. Estimates of reduction in CMR (range, 50–80%)\(^10\) as temperature is varied from 37\(^\circ\)C to 27\(^\circ\)C. However, like the anesthetics, the major mechanism for neuroprotection during hypothermia probably does not result from its direct effects on CMR.

Hypothermia also decreases the primary synergists of the ischemic cascade by the reduction of glutamate, glycine, and dopamine release, inhibition of protein kinase C, reduction of free radical-triggered lipid peroxidation, and recovery of ubiquitin synthesis. Although hypothermia may be the most potent technique at our disposal for prophylactic cerebral protection, hypothermia does have some adverse effects. With regard to neuronal membrane integrity and ionic gradients of \(\text{Na}^+\), \(\text{K}^+\), and \(\text{Ca}^{2+}\), the deleterious effects of hypothermia develop more slowly but are quantitatively similar to the effects of hypoxia.\(^11\) Laboratory results have demonstrated that the beneficial effects of mild hypothermia are likely to outweigh its real, but clinically manageable, untoward effects.

The importance of diligent monitoring and control of brain temperature in experimental paradigms of cerebral ischemia and reperfusion cannot be overemphasized. Miura et al.\(^7\) report an important study that not only has measured, but controlled, pericranial temperature during ischemia and reperfusion.\(^2\) Previous experimental studies evaluating the effects of neuroprotective agents have been lacking in strict and rigid control of brain temperature, resulting in large experimental variability. Future research in prophylactic and post-insult pharmacologic brain protection would do well to pursue drugs that act synergistically with moderate hypothermia. Perhaps in future studies a standard control against which to test the effectiveness of new experimental neuroprotective therapies should include a hypothermic group.

The neuroprotective potential of anesthetics has to be carefully evaluated in appropriate animal models that simulate clinical scenarios, and the complex neuroprotective mechanisms, involving biochemical and vascular as well as metabolic pathways, need to be delineated.

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