Anesthetic Neuroprotection? It's Complicated

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ANESTHETICS possess numerous pharmacologic properties that could increase tolerance of brain to an ischemic insult. Despite investigation for over half a century,[1] and robust demonstration of such benefit in laboratory animals,[2] there is no solid evidence that anesthetic neuroprotection is present in humans.[3] The article by Archer *et al.*[4] in this issue of ANESTHESIOLOGY provides considerable insight into this apparent paradox.

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It once seemed so straight forward. The brain consumes adenosine triphosphate at an incredible rate and holds little stores of this critical metabolite. Hence, continuous delivery of oxygen and glucose is essential to maintain adenosine triphosphate synthesis, neural function, and cellular integrity. Most anesthetics can markedly suppress metabolic rate. Thus, the duration the brain can survive in low-flow or no-flow states should be increased substantially. Neuroprotection investigation was focused on the perioperative environment for several decades. Anesthesiologists and surgeons were at the forefront of therapeutic stroke research.

In the late 1980s, problems arose for the metabolic suppression hypothesis. Nonanesthetic drugs that had little or no effect on metabolic rate were found highly neuroprotective in the laboratory. Evidence rapidly grew in support of protective benefits from mild hypothermia, which again induced little change in metabolic rate. It was becoming clear that other neuroprotective mechanisms were important. And later, it became evident that exposure of brain to a mild stressor stimulus, either before (preconditioning) or after (postconditioning) a severe ischemic insult, set in play a biomolecular cascade that improved ischemic outcome. It is now known that anesthetics can also serve as effective conditioning stimuli, again independent of effects on metabolic rate during the ischemic insult. At the same time, a series of failures in detecting anesthetic neuroprotection in clinical trials accumulated, dashing almost all hope for such intervention. This caused a pivot of investigation away from neuroprotection in the perioperative environment toward development of nonanesthetic drugs relevant to the large number of patients who sustain out-of-hospital stroke.

While the above logic sequence seems reasonable, is it all correct? The fact remains that after trials of scores of drugs in human stroke, other than tissue plasminogen activator, there is no pharmacologic intervention proven efficacious for any form of stroke in humans. This body of failure has led to serious questions regarding the pathway from bench to bedside for stroke drugs. Most such criticism has focused on the preclinical side of efficacy analysis. While major flaws in clinical trial designs must also be considered, lessons from the preclinical stroke research community are highly relevant to the study of anesthetics in the perioperative environment. Our method of translating from bench to operating table should also be reconsidered.

This is where the study of Archer *et al.*[4] becomes important. Using a robust search strategy, 80 laboratory investigations were identified that employed the intraluminal filament middle cerebral artery occlusion model[5] to investigate anesthetic neuroprotection in rodents. Although this focal ischemia model has been criticized for near-instantaneous flow restoration compared to gradual restoration of flow occurring with endogenous or pharmacologic thrombolysis,[6] the model may be particularly relevant to anesthetic neuroprotection. Rapid flow restoration occurs with numerous

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perioperative events (*e.g.*, temporary arterial occlusion during cerebral aneurysm or carotid surgery). Further, the model is widely employed allowing this search strategy to capture a large body of research. The model has been the workhorse for study of nonanesthetic neuroprotective drugs. Hence, parallels from that body of literature can be also drawn. The results of the Archer *et al.*[4] analysis were surprising.

An important feature of this study was use of an established systematic scoring system to grade strengths and weaknesses of the studies. Strengths of the body of research were use of physiologic monitoring, randomization, blinded outcome assessment, and publication in peer-reviewed literature. A major weakness was lack of pilot data and sample size calculation. This is important because the number of animals studied can define the robustness of the experiment to capture the treatment effect size. If an insufficient number of animals is studied, the experiment could either over- or underestimate how effective the drug is. Clinical investigators need to know the true effect size to decide whether to do a trial, and if so, how many patients should be enrolled to detect it. Archer *et al.*[4] found that across anesthetics the *reported* effect size (*i.e.*, improvement in histologic and neurologic outcomes) averaged 30% in the higher quality studies. But, the potential range of *true* effect sizes was calculated to be 3 to 58%. In other words, use of small sample sizes in controlled laboratory investigations could erroneously produce evidence of an effect size that had no chance of being detected in a heterogeneous human surgical population. Only with the study of a large number of animals can the true effect size be defined. This likely exceeds the capacity of any single laboratory. Archer *et al.*[4] point out that this same problem is paralleled in the study of nonanesthetic stroke drugs. Recognition of this limitation has led the stroke community to advocate use of multiinstitutional preclinical trials that allow investigation with large sample sizes before any drug is advanced to human study.[7] Indeed, such an effort has now been achieved[8] and can serve as a model for how anesthetics should be vetted before human study is initiated.

Another interesting finding was lack of anesthetic neuroprotection in females. This is not novel in the world of neuroprotection research investigating nonanesthetic drugs. Based on lines of evidence from the study of neuroprotective interventions, stroke drug development advisory panels have long advocated preclinical testing in females and males before advancing a compound to clinical trials.[9–11] The National Institutes of Health (Bethesda Maryland) now requires sex to be accounted for as a biologic variable in all preclinical studies conducted in animals and even cell lines.[12] It is noteworthy, however, that Archer *et al.*[4] conclude sex to be an important determinant of anesthetic neuroprotection on the basis of the only study designed to specifically investigate this.[13] That study was markedly limited in experimental design and clinical relevance, most notably use of only a 24-h poststroke recovery interval, which is now widely accepted to be insufficient to measure final stroke outcome.[14] Regardless, the fact that 78 of 80 studies reviewed by Archer *et al.*[4] were conducted on adult male rodents is sufficient evidence to conclude that effort must be made to determine the role of sex in the question of anesthetic neuroprotection.

A final highlight from the review was the finding that anesthetic neuroprotection was absent in aged animals and those with comorbidities (*e.g.*, hypertension, diabetes). Again, the number of such studies was few, preventing a meaningful conclusion to this consideration. But, what was enticing was that Archer *et al.*[4] also compiled mechanisms of action for anesthetic neuroprotection among the studies evaluated. When studies investigating aged animals and those with comorbidities were considered, a pattern of anesthetic-mediated suppression of prosurvival pathways was present. Notably, all such studies were conducted in postconditioning experiments. This finding could have implications for aged patients subjected to anesthesia *after* ischemic stroke. If the aged brain recovering from ischemia is vulnerable to anesthesia, the at-risk interval should be mechanistically determined and relevance defined by outcome analysis. Few, if any, clinical trials of anesthetic neuroprotection have considered sex, age, or comorbidities as potential confounds to efficacy analysis.

The study by Archer *et al.*[4] is a report card on the research community's efforts to understand anesthetic neuroprotection, and the finding is that such work remains insufficient. To a large extent, study of anesthetic neuroprotection has become a dormant field, given the litany of failed human studies investigating this potential. But, patients still require anesthesia and still suffer ischemic insults in that context. This has become even more poignant with convergent recent evidence that endovascular thrombectomy is efficacious for out-of-hospital acute ischemic stroke[15]; many patients receive anesthetics for this procedure. Archer *et al.*[4] have defined weak links in our knowledge and offer potentially fruitful areas of investigation to better understand which patients under which conditions might be suitable for further investigation of anesthetic efficacy or adverse effects.

Competing Interests

Dr. Warner is the principal investigator of National Institutes of Health (Bethesda, Maryland; grant no. 1R21NS087157), designed to optimize preclinical efficacy for xenon in intracerebral hemorrhage. He holds no proprietary interest in this effort. The other author declares no competing interests.

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