Preoperative Corticosteroids for Reactive Airway?

IN this issue of the Journal, Silvanus *et al.* studied the effects of preoperative interventions in patients with reversible airway obstruction (RAO).[1] This article raises the question of when corticosteroids may be useful to prevent an adverse perioperative outcome for the patient with RAO.

The low frequency of adverse outcomes in anesthesia practice limits the ability of researchers to conduct prospective randomized controlled trials to identify best practices. This is certainly the case for adverse outcomes linked to reactive airways disease and anesthesia. Warner *et al.* looked at the population of patients with asthma who underwent surgery in Olmstead County, Minnesota, and found the incidence of adverse outcomes to be very low.[2] On the other hand, we know from the American Society of Anesthesiologists Closed Claims study that severe bronchospasm occasionally leads to brain damage or death.[3] Furthermore, the present author has repeatedly informally surveyed the audience at his American Society of Anesthesiologists refresher course on bronchospasm as to whether they had ever cared for a patient with what they believed was life-threatening bronchospasm under anesthesia. Although the results are certainly biased (because clinicians probably tend to go to a lecture on the topic after such an event), many audience members raise a hand in response to the question. Hence, severe bronchospasm seems to be a serious complication of low but finite incidence.

Because of this low incidence of severe adverse outcomes, researchers interested in bronchospasm have tended to study the more common but less serious surrogate outcomes of increased respiratory resistance or audible wheezing.[4,5] Audible wheezing occurred in 4% of patients intubated following an induction dose of thiopental, and reversible bronchoconstriction following intubation is probably the rule rather than the exception when assessed by respiratory resistance.[4,6] Bronchospasm severe enough to require treatment probably occurs in the range of 1 in 250 patients anesthetized but is probably more prevalent in some populations with a high frequency of lung disease. We do not know, however, whether these phenomena can be linked to the rare severe outcome attributed to bronchospasm. Despite the absence of that link, it does seem reasonable to assume that reducing the incidence of mild bronchospasm is a useful goal.

Silvanus *et al.* studied patients who were scheduled for surgery and who were found to have RAO during preoperative assessment. Only patients who had RAO and were not currently receiving treatment were studied. The patients tended to fit the criteria for chronic obstructive pulmonary disease to a greater extent than for asthma, as they had some evidence of limited vital capacity and their forced expiratory volume in 1 s appeared to reverse only moderately with treatment. The patients were divided into three groups: those who received no treatment other than albuterol just before induction and intubation, those who received 5 days of albuterol prior to intubation, and those who received 5 days of corticosteroid plus albuterol prior to intubation. The group receiving steroids had a much lower incidence of wheezing than did the other two groups.

Should we be surprised that albuterol alone, while improving the forced expiratory volume in 1 s, did not prevent intubation-induced bronchoconstriction? Probably not. Patients may show marked improvement following albuterol when their airways are not provoked. However, the mechanical stimulus of intubation is a powerful provocation for bronchoconstriction that may unmask ongoing disease. This is probably analogous to a methacholine provocation test: a patient may have a normal forced expiratory volume in 1 s but still react to a stimulus.

Does this study differ from previous studies documenting that albuterol alone markedly limits intubation-induced bronchoconstriction? Not really, because those studies were in unselected patients, whereas these patients had significant preexisting disease. Rather, this article suggests that in patients with documented reversible disease, it may be best to provide therapy beyond a beta agonist alone.

How should this article affect our practice? We probably don't see many patients with untreated disease as severe as these patients had. The mean forced expiratory volume in 1 s/forced vital capacity ratio of 55% seen in this study would generally be enough to bring someone to medical attention and treatment. Given a reversible component of airway obstruction, the National Heart Lung and Blood Institute Expert Panel on Asthma supports the use of antiinflammatory therapy.[7] Hence, most patients with this degree of illness will likely already be receiving inhaled steroids. If they are not, this article certainly supports the benefits of adding a short course of oral corticosteroids preoperatively. Even if they are

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receiving inhaled steroids but have ongoing symptoms, a brief trial of steroids may be warranted.

Should every patient with a history of reactive airways receive such treatment? Not even close. The incidence of wheezing at some point in life is very high. A recent study from New Zealand (admittedly a country with one of the highest rates of wheezing) found that over 50% of individuals followed from birth to 26 yr of age complained of wheezing at some point, and 14.5% continued to have occasional symptoms.[8] An 8% incidence for asthma is often cited in the U.S. population. To test all of those individuals preoperatively and to give them a steroid bolus would be a large and unnecessary undertaking.

Which patients should we consider for steroid treatment? As always, the highest-risk patients: those about to undergo abdominal or thoracic surgery, who will be at greatest risk for postoperative pulmonary complications, and those with the worst pulmonary function preoperatively. To some extent, the assessment of preoperative pulmonary function must be based on clinical assessment, because we are unlikely to routinely perform preoperative pulmonary function tests in all patients.

In being realistic, we must recognize that the scheduled procedure may drive how aggressive we are with preoperative steroid treatment. A patient scheduled for an upper abdominal procedure with a high risk of pulmonary complications must be treated with the utmost caution. On the other hand, a patient scheduled for a knee arthroscopy or a foot procedure who has evidence of mild-to-moderate disease and is not under absolutely optimal treatment for RAO may still safely undergo the procedure, given our access to local and regional anesthetics and laryngeal masks. A real-life example: the Alaskan bush resident who arrives at the Puget Sound Veterans Hospital 2,000 miles from home for a foot reconstruction and has wheezing on preoperative examination will probably receive albuterol and a spinal or regional anesthetic rather than preoperative steroids. On the other hand, if this patient were scheduled for a thoracotomy, the case would probably be postponed pending steroid treatment.

We should also recognize that this study probably overstates the risks of postintubation wheezing in that the trachea was intubated following thiopental induction. There is ample evidence that propofol prevents postintubation wheezing and bronchoconstriction,[4,5] and few of us currently would use thiopental as our induction agent for these patients. Also, if appropriate for the planned procedure, we would probably opt for a laryngeal mask airway, which does not provoke bronchoconstriction.[9]

Are there any reasons not to treat patients aggressively with corticosteroids? Brief courses of corticosteroids do not seem to be associated with significant effects on wound healing or infection.[10] However, a preoperative course can delay surgery, and many patients find high doses of steroids somewhat unpleasant. Thus, for most patients with RAO, a steroid course is unnecessary.

Where does that leave us? This article provides data to support an already existing recommendation, that of the National Heart Lung and Blood Institute Expert Panel, which recommended that before surgery, the clinician review symptoms, medication use, and measurements of pulmonary function and that attempts should be made to improve lung function to a personal best. The monograph goes on to note that this may occasionally require a short course of steroids. Silvanus *et al.* have provided us with data to support the beneficial effects of steroids on wheezing during the perioperative period. Whether this truly affects adverse outcomes may require a study that would be logistically very difficult to perform.

Michael J. Bishop, M.D. Anesthesiology/Operating Room Services, Puget Sound Health Care System, Seattle, Washington; Central Office Anesthesia Service, Department of Veterans Affairs, Seattle, Washington; and University of Washington School of Medicine, Seattle, Washington. bish@u.washington.edu

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No Magic Bullets: The Ephemeral Nature of Anesthetic-mediated Neuroprotection

CEREBRAL ischemia, although infrequent, is a potentially devastating complication of anesthesia and surgery. The exquisite vulnerability of the brain to cessation of blood flow has fostered a substantial investigative effort to identify pharmacologic agents that might reduce ischemic cerebral injury. Among these, anesthetics have long been considered logical candidates, given their ability to suppress cerebral metabolic rate, to antagonize glutamate-mediated excitotoxicity, and to enhance inhibitory synaptic transmission. Indeed, a large number of studies have shown that anesthetics can reduce ischemic injury in models of global,[1,2] focal,[3–5] and hemispheric ischemia.[6] In fact, the magnitude of the neuroprotective efficacy of anesthetic agents is similar to that of antiglutamatergic agents. In most of these investigations, the recovery period after the initiation of ischemia has been relatively short, on the order of 1 to 5 days. Recent data have shown that postischemic neuronal injury is a dynamic process in which neurons continue to die for a long time after ischemia (at least several weeks).[7] This begs the question of whether anesthetic neuroprotection, evident early after ischemia, is sustained after a much longer recovery period. This question is addressed by two meticulously conducted investigations by Bayona et al.[8] and Elsersy et al.[9] in this issue of the Journal.

Bayona et al.[8] show that propofol infusion decreased infarction volume 3 days after insult in an endothelin-induced striatal ischemia model. When the animals were evaluated 3 weeks after ischemia, no difference between propofol-treated or control animals could be detected histologically. In the study of Elsersy et al.,[9] isoflurane reduced neuronal injury within the hippocampus of rats subjected to global cerebral ischemia when the injury was evaluated 5 days later. However, when injury was evaluated 3 weeks or 3 months after insult, no difference in injury, either morphologically or neurologically, could be detected. The results of these studies are consistent

◆ This Editorial View accompanies the following articles: Bayona NA, Gelb AW, Jiang Z, Wilson JX, Urquhart BL, Cechetto DF: Propofol neuroprotection in cerebral ischemia and its effects on low-molecular-weight antioxidants and skilled motor tasks. ANESTHESIOLOGY 2004; 100:1151–9; Elsersy H, Sheng H, Lynch JR, Moldovan M, Pearlstein RD, Warner DS: Effects of isoflurane *versus* fentanyl/nitrous oxide anesthesia on long-term outcome from severe forebrain ischemia in the rat. ANESTHESIOLOGY 2004;100:1160–6.

with those published by Kawaguchi et al.,[10] who demonstrated that isoflurane-mediated neuroprotection, apparent 2 days after ischemia, was not sustained 2 weeks later. This transient neuroprotection is by no means limited to anesthetic agents; sustained protection has not been achieved with the administration of the *N*-methyl-D-aspartate antagonist dizocilpine,[11,12] alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline (NBQX),[13] and postischemic hypothermia.[14] Common to these investigations is the slow progression of injury such that neurons that were initially protected nonetheless underwent delayed death.

These studies highlight the importance of long-term neuronal viability as an endpoint in experimental studies of cerebral ischemia and pharmacologic neuroprotection. The aforementioned glutamate antagonists (*N*-methyl-D-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor antagonists) entered clinical trials in stroke patients, in part based on very strong preclinical studies that demonstrated robust *short-term* neuroprotection; *long-term* neuroprotection was not systematically evaluated. Subsequent studies that used a recovery interval of greater than 2 weeks demonstrated no neuroprotective efficacy that could be attributed to glutamate antagonists. Although a number of factors contributed to the failure of the glutamate antagonists in the clinical setting, the lack of long-term neuroprotection by these agents was undeniably a major contributor. This inevitably leads to the question of what constitutes an appropriate postischemic time interval for the evaluation of neurologic outcome in studies of cerebral ischemia and neuroprotection. Clearly, the requisite recovery period is dependent on the experimental model of cerebral ischemia that is used. Nonetheless, the bulk of the available data indicate that, in studies in which *neuroprotection* is the primary outcome measure, a postischemic recovery interval of 2 weeks at a minimum, and preferably 4 weeks or longer, is needed to ensure that short-term neuroprotection is sustained. In fact, a cogent argument can be made that such a long-term recovery period should now be considered to be a standard for such studies. Of course, this standard should not apply to *mechanistic* studies in which considerably shorter postischemic intervals are essential.

Although the mechanisms that underlie the progression of injury in the ischemic brain have not been clarified, neuronal apoptosis undoubtedly plays a role.[15–18] In models of focal ischemia, apoptotic neurons are localized within the outer boundary of the evolving in-

farct.[16] Administration of agents that inhibit apoptosis, such as the protein synthesis inhibitor cycloheximide, mitigate the propagation of injury.[19] By contrast, isoflurane does not prevent apoptosis.[20] Kawaguchi *et al.* have shown the increase in the size of cerebral infarction in isoflurane-treated animals subjected to focal ischemia parallels the appearance of markers of apoptosis.[20] Indeed, the broad spectrum caspase inhibitor zVAD-fmk (benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone) and the caspase 8 inhibitor IETD-fmk (z-Ile-Glu-Thr-Asp-(IETD)-fluoromethylketone)[21] decrease neuronal apoptosis, prevent infarct extension, and sustain isoflurane-mediated protection. Prevention of apoptosis clearly presents a target for future interventions.

The development of inflammation in the postischemic brain has been well documented and may well be an important initiator of the apoptotic process. Expression of a variety of adhesion receptors leads to the recruitment of platelets and leukocytes within the cerebral circulation.[22] Experimental therapies directed against adhesion molecules have met with some success. Of considerable importance is the activation of microglia by interleukin-1.[23] The use of interleukin-1 antagonists decreases cerebral injury in a variety of stroke models, and clinical trials to evaluate their efficacy in humans are under way. Microglial activation can be demonstrated as late as 2 months after ischemia.[7] This sustained microglial activation has been taken as evidence of a chronic encephalopathic process, initiated by ischemia, that can lead to ongoing neuronal loss.[7] It is therefore not surprising that neuroprotective agents, administered only briefly prior to or after ischemia, do not provide long-term neuroprotection. In this regard, cerebral ischemia may be thought of as a chronic inflammatory disorder, and the achievement of sustained neuroprotection may well require chronic antiinflammatory therapy.

An interesting aspect common to the investigations of both Bayona *et al.*[8] and Elsersy *et al.*[9] is the finding that the size of the lesion decreased with longer recovery periods. Endothelin induced striatal infarction was smaller 3 weeks after insult than 3 days after insult. Similarly, the number of viable neurons within the CA1 sector of the hippocampus increased in both isoflurane and fentanyl-nitrous oxide groups 3 months after ischemia. It is now quite apparent that the brain is a highly plastic organ and that a substantial turnover of neurons in the adult brain occurs. The generation of neurons and glia from progenitor cells, neurogenesis, has been well characterized.[24,25] In fact, a number of investigators have shown that neurons that develop from progenitor cells can be found in injured brain after focal and global ischemia.[26-28] This process is clearly an attempt at regeneration by the injured brain. Although the administration of anesthetics during the ischemic interval does not appear to interfere with neurogenesis, additional experimental work to clarify the time course of neuro-

genesis and its modulation by anesthetics is needed. The reparative processes, however, add an interesting twist to the problem of evaluating the neuroprotective efficacy of therapeutic interventions. The need for long-term survival studies is now clear. However, the gradual improvement in neurologic function in control subjects would tend to reduce the difference between treated and untreated subjects. A plausible result of this is that an agent that does reduce injury may be considered to be ineffective if long-term differences between treated and untreated subjects are obscured by regenerative processes. As noted by Elsersy *et al.*,[9] long-term neuroprotection studies may have to incorporate a means by which the contribution of ongoing neurogenesis is separated from the survival of "protected" neurons.

It is clear that the pathophysiology of cerebral ischemia is complex. A number of diverse processes are initiated by the ischemic insult. Couple this diversity with temporal and spatial differences among these processes, and it rapidly becomes apparent that a single pharmacologic intervention is unlikely to result in sustained neuroprotection in all (and probably not any) cell populations. A combination of different approaches that target specific stages of the evolution of ischemic injury may be required. Simply stated, the magazine of our cerebral protection "gun" is empty. Currently, there are no magic bullets.

Piyush Patel, M.D., F.R.C.P.C. Department of Anesthesiology, University of California-San Diego, San Diego, California, and Veterans Affairs Medical Center, San Diego, California. ppatel@ucsd.edu

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