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Neurotoxic Properties of Propofol Sedation Following Traumatic Brain Injury*

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Traumatic brain injury (TBI) is one of the leading causes of neurologic disability worldwide. It is estimated that there are 10 million cases severe enough to warrant hospitalization annually and that TBI survivors, many of whom have long-lasting or permanent neurologic sequelae, presently number about 57 million (1). Numerous patients with TBI receive anesthetic drugs for sedation in the ICU in order to alleviate increased intracranial pressure by reducing cerebral metabolic demand. Additionally, sedation may be used following TBI to control hemodynamics and to improve ventilator synchrony in intubated patients. Currently, no strong evidence exists to guide this intervention. Recent findings point to potentially neurotoxic effects of commonly used anesthetics that are either used as sedatives in the ICU or share mechanisms of action with common ICU sedatives, principally via agonist activity at γ -aminobutyric acid (GABA) receptors. Both retrospective clinical studies and preclinical investigations in animal models ranging from rodents to primates demonstrate that anesthetic drugs cause substantial neurotoxic effects when given in early postnatal life (2). Exposure to anesthetics during brain development leads to lasting deficits in learning and memory, and the first mechanism of injury to be described was an increase in neuronal apoptosis seen throughout the brain (3). Subsequent research has revealed a number of additional mechanisms by which transient exposures to anesthetic drugs can cause lasting disruptions in brain circuit formation via effects on neurite growth, axon guidance, and synapse formation (4). Collectively these data may be of tremendous relevance to the question of how to sedate TBI patients of any age, as the process of recovery from brain injury in the adult involves a recapitulation of many features of neuronal development (5). Thus, the use of sedative agents known to have toxic effects in the developing brain may be counterproductive for recovery following TBI.

In the accompanying article in this issue of *Critical Care Medicine*, Sebastiani et al (6) employed a controlled cortical impact (CCI) mouse model to investigate the effects of propofol on injury and recovery from TBI. Propofol is considered a first-line agent for ICU

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sedation following TBI because its short duration of action allows intermittent neurologic assessment (7). Previously, the same group found that propofol administration following the same TBI model increased mortality, worsened neurobehavioral outcomes, and reduced hippocampal neurogenesis (8). The current study shows that even a single bolus dose of propofol administered 24 hours after CCI results in increased lesion volume, increased apoptotic neuronal cell death, and worsened chronic motor function when compared with unsedated controls. Intriguingly, the authors provide strong evidence of a mechanism of injury involving the p75 neurotrophin receptor (p75NTR) and its ligand, the precursor of brain-derived neurotrophic factor (Pro-BDNF). Propofol administration after CCI increases expression of Pro-BDNF relative to cleaved brain-derived neurotrophic factor, and outcomes, including measures of apoptosis neuronal cell death, are markedly improved with pharmacologic or genetic attenuation of the Pro-BDNF-driven p75NTR signaling (6). These data are strikingly consistent with the findings of investigations of anesthetic toxicity induced by propofol in the developing brain. Using similar methods in primary cultures of developing neurons, Pearn et al (9) found that propofol induced p75NTR-dependent neuronal apoptosis. Signaling through the Pro-BDNF-p75NTR pathway during brain development leads to apoptotic cell death that is critically important in neuronal pruning during normal development. This pathway is relatively quiescent in the adult brain, but expression of p75NTR is up-regulated in numerous types of brain injury (10). Thus, up-regulation of Pro-BDNF by propofol in the setting of increased expression of p75NTR due to TBI likely enhances neuronal apoptosis and impairs neurogenesis, which would be expected to substantially impair recovery.

Although Sebastiani et al (6) provide strong evidence of the neurotoxicity of propofol in the context of TBI, numerous questions remain to be answered before any change in clinical practice can be justified. Absent from this study is any investigation of alternative agents for sedation which would potentially replace propofol for this application. It is quite likely that other agents with action at GABA receptors would share similarly neurotoxic properties, given that isoflurane, an anesthetic drug that has little else in common with propofol beyond its agonist activity at GABA receptors, causes a similar p75NTR-mediated neurotoxicity in the developmental model (11). However, the hypothesis that non-GABAergic alternatives such as dexmedetomidine are free of neurotoxic effects has yet to be tested. Additionally, as with all studies conducted in the rodent model, testing in large animal models or primates is critical for establishing whether propofol neurotoxicity in rodent TBI is likely to translate to more complex nervous systems. This hypothesis is certainly plausible, as propofol administration in an anesthetic model in nonhuman primates leads to enhanced neuronal apoptosis (12). Furthermore, the relevance of the study by Sebastiani et al (6) to sedation as practiced in the ICU is limited by the use of a single bolus dose, rather than a continuous infusion, and by the absence of tight control of physiologic parameters, such as blood pressure, oxygenation, and temperature that is standard in the ICU. This issue could also be easily addressed in large animal or primate model studies. In conclusion, there is good reason to suspect that administration of propofol, and likely other drugs with similar mechanisms of action, may be counterproductive for recovery when employed as sedatives in the setting of TBI. Considerable work remains both in the clinical and preclinical arenas

to elucidate the potential neurotoxicity of propofol, and related drugs, as sedatives for patients with TBI, and also to identify and test alternative sedation strategies.

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