CON: The Toxic Effects of Anesthetics in the Developing Brain: The Clinical Perspective

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“All models are wrong, some models are useful”¹

This quote by the statistician George E. P. Box seems to have relevance for the current preeminent controversy in pediatric anesthesiology, namely, developmental neuroapoptotic cell death after an anesthetic exposure in the immature brain.

Worldwide, general anesthetics and sedatives are used in hundreds of thousands of neonates and infants every year during surgical operations, invasive procedures, and imaging studies. The possibility of anesthesia-induced neuronal cell loss, as suggested by animal models, during an otherwise uneventful procedure has sparked vigorous discussions among anesthesiologists about the safety of anesthesia in human newborns and infants.²⁻⁶ These concerns were recently addressed at the March 29, 2007, public hearing of the Anesthesia and Life Support Drugs Advisory Committee of the Food and Drug Administration (transcript available at http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4285t1.pdf).

Although the exact mechanism of general anesthesia is not entirely understood, alterations of synaptic transmission involving γ-aminobutyric acid type A (GABAₐ) and N-methyl-D-aspartate (NMDA) glutamate receptors, to varying degrees, seem to play an important role.⁷ Because GABA and NMDA-mediated neuronal activity is essential for normal mammalian brain development, exposure to anesthetics could potentially interfere with brain maturation, learning, and neurocognitive function.⁸,⁹

Concerns about the effects of general anesthetics on neuronal structure and neurocognitive function were first raised more than two decades ago.¹⁰,¹¹ In a series of studies, chronic subanesthetic exposure of pregnant rats to halothane led to delayed synaptogenesis and behavioral abnormalities in their pups. More recently, the potential for ketamine to cause increased neuronal cell death was documented in rat pups.¹²,¹³ However, although ketamine is rarely used for pediatric anesthesia, general anesthetics routinely used in pediatric practice have subsequently also been implicated not only in producing widespread neuronal cell death, but also in leading to long-term cognitive impairment in adult animals exposed to neonatal anesthesia.¹⁴ A 6-h exposure to a combination of isoflurane, nitrous oxide, and midazolam led to widespread apoptotic brain cell death in 7-day-old rats. When animals were examined in adulthood, many tests of behavior and attention remained normal. However, several tests of spatial learning and memory demonstrated impairment in adult animals that were exposed to the anesthetic cocktail as neonates, compared with their unanesthetized littermates. Several groups of investigators have now confirmed the neurotoxic effects of various anesthetics in a variety of in vivo and in vitro developing animal models.
Although the documented neurotoxic effects of anesthetics in developing animal models are certainly alarming to pediatric anesthesiologists, the implications of these findings for clinical practice remain uncertain. To evaluate the immediate applicability of data obtained in animal models to humans, it is critical to examine the similarities and differences between the experimental models and clinical pediatric anesthesia practice. First, how does the anesthetic exposure in preclinical studies compare with pediatric anesthesia practice? Second, is the maturational state of the brain in experimental models comparable to that of patients undergoing pediatric anesthesia? Third, are there any detectable clinical markers of neurodegeneration in children after exposure to anesthetics?

Previous discussions have elucidated the differences between anesthetic management in small rodent studies and clinical anesthesia practice, related to airway management, continuous monitoring of physiological data, duration of anesthesia, and anesthetic doses. Pediatric patients are commonly tracheally intubated, mechanically ventilated, and vital signs are continuously monitored, whereas small animals are anesthetized without control of airway or vital signs. Attempts have been made to more closely monitor vital signs and even use orotracheal intubation and mechanical ventilation in a neonatal mouse model, but serious limitations, such as acid-base and glucose imbalances, remain in this model.

Importantly, anesthesia in rodent studies is usually administered without noxious stimulation, whereas during pediatric surgical anesthesia the central nervous system is stimulated by surgical interventions and painful stimulation. Accordingly, a recent study in a newborn rat model documented neurodegenerative effects and behavioral impairment after repetitive painful stimulation, which were ameliorated by a low dose of ketamine (5 mg/kg). It therefore seems conceivable that painful stimulation during surgical anesthesia protects the brain from anesthesia-induced neurodegeneration, whereas anesthetics administered during the noxious surgical stimulation protect the brain from the deleterious effects of unopposed painful insults.

Moreover, studies of injectable anesthetics in animals indicate that the neurodegenerative effect is highly dependent on anesthetic dose and exposure time. This finding is consistent with the pharmacological tenant of “area under the curve,” where the bioavailability of a drug is the product of both the plasma concentration of the drug and the exposure time. Anesthetic requirements for injectable anesthetics are much higher in small animals compared with humans, by a factor of 10 for ketamine and a factor of 100 for propofol. Although pharmacokinetic differences might account for some of these discrepancies, the pharmacodynamic consequences of higher effect site doses, compared with clinical practice, of potential neurotoxicants might limit the conclusions reached from experimental species. Experiments in small rodents as well as non-human primate models reveal neurodegenerative effects after injections of high or repeated doses of ketamine (i.e., a single injection of 40 mg/kg or 4 injections of 20 mg/kg), which led to higher plasma levels than those measured in clinical practice. Similarly, long-term neurocognitive dysfunction has thus far been demonstrated only in animals after administration of ketamine doses that led to higher plasma levels than used in clinical practice. In contrast, lower doses of ketamine, closer to pediatric anesthesia practice, resulting in lower plasma concentrations, did not increase neuronal cell death. It is important to point out that, because of the higher anesthetic dose requirements in animal models, inferences from animal studies regarding the neurotoxic effects of injectable anesthetics for pediatric practice can only be made if anesthesia and neurotoxicity act by the same mechanism, which has yet to be established.

The complexity of mammalian central nervous system development complicates the extrapolation of data derived from experimental species to humans. Brain development involves many intricate processes, including cellular proliferation, differentiation, cellular migration, synaptogenesis, myelination, and neurodegeneration, which vary in their timing relative to gestational age and their rate among mammalian species. Moreover, different parts of the central nervous system mature at different rates. Although the most vulnerable period for anesthesia-induced neurodegeneration appears to be very brief in animals, occurring during the first postnatal week in small rodents, the corresponding developmental stage of the human brain remains unclear. Previously, simple estimations of brain cell numbers and degree of myelination were used to define a phase of rapid brain growth, or period of synaptogenesis, in small rodents during the first 2 wk of life. Using the same criteria of rapid brain growth, this period was then equated to human brain development spanning from the last trimester of pregnancy all the way to the third year of life. Because peak anesthesia-induced neurodegeneration in rodents occurs on postnatal day 7, coinciding with this period of rapid synaptogenesis in small rodents, it was asserted that human susceptibility to this phenomenon spanned the last trimester of pregnancy and the first three years of life. However, using a more contemporary neuroinformatics approach, combining neuroscience, evolutionary science, statistical modeling, and computer science to compare brain development among different species, the brain developmental state of a newborn, postnatal day 7 rat more closely corresponds to the human fetus between 17 and 22 wk of gestation (calculator available at http://www.translatingtime.net). Although some have argued that this finding renders the most commonly used animal models of anesthesia-induced neurodegeneration irrelevant for routine pediatric anesthesia.
practice, it would at least point towards potential susceptibility in premature neonates and not routine pediatric anesthesia. However, it may also heighten concerns about the risks of abnormal neuronal cell death in the fetal brain after maternal anesthetic exposure during pregnancy.

It is important to understand that widespread apoptotic cell death is not uncommon in developing human or rodent brains but, rather, an integral part of normal brain development. Neurons are produced in excess during regular fetal and neonatal brain maturation and substantial numbers of neurons die by an energy-consuming cell suicide program. This autodigesting program, termed “apoptosis,” which is built into every cell, can be triggered by physiological and pathological stimuli. The number of supernumerary neurons removed by physiological apoptosis during normal brain development has widely been estimated, both in humans and in rodents, to be 50% to 70% of the entire neuronal cell population. Conversely, disruption of this physiological apoptotic cell death during development leads to brain malformations and premature lethality in rodent models. Because the mechanism of anesthesia-induced neuronal cell death in not entirely understood, it remains unclear whether anesthesia induces apoptosis of cells otherwise not destined to die (i.e., pathological apoptosis), or whether it accelerates apoptosis of cells destined to die at a later time (i.e., premature physiological apoptosis).

The clinical phenotype of anesthesia-induced neurocognitive impairment remains elusive. This lack of evidence for a clinical marker of neurocognitive impairment after anesthetic exposure has led to comparisons with fetal alcohol syndrome, when neurobehavioral abnormalities were only discovered after clinicians were alerted to examine affected children due to their concomitant craniofacial malformations. However, anesthetic exposure in childhood is relatively brief compared with the duration of brain development and maturation, and it occurs in later phases of brain development compared with the chronic exposure to alcohol during earlier phases of brain development leading to fetal alcohol syndrome.

There are no published, randomized, controlled studies comparing neurocognitive outcome in children after painful procedures with or without anesthesia. Anecdotal data of prolonged anesthetic exposure, accidental overdoses, and postanesthetic negative behavioral changes, after surgical anesthesia, have therefore been cited as evidence for neuroapoptosis in children (for details see Ref. 37). However, simple neurological examinations after prolonged anesthetic exposure or accidental overdoses did not demonstrate prolonged neurocognitive dysfunction in any of the reports. In the study by Arnold et al., half of the patients who had received in excess of 70 MAC-hours of isoflurane, benzodiazepines, and opioids experienced transient agitation and nonpurposeful movements, which responded to treatment of opioid withdrawal. These behaviors have been interpreted as a manifestation of an acute withdrawal or abstinence syndrome. In a study by Kelsall et al., children exhibited transient ataxia, agitation, and hallucinations after isoflurane administration in excess of 24 h, but no symptoms were observed in patients who had received isoflurane for <15 h. Follow-up examinations 4–6 wk after discharge were reported as normal in all patients.

Reports of negative behavioral changes after brief anesthetic exposures have also been quoted as evidence for neuroapoptotic cell death in children. Parent-reported, postoperative “maladaptive” behavior is more commonly observed in children with anxious preoperative behavior and after “stormy” inductions of anesthesia. The reported incidence has been correlated with increased parental anxiety during induction and symptoms diminished after preoperative administration of benzodiazepines, which would point more towards a psychological, rather than a neurodegenerative, etiology. However, the common denominator in all these studies was the lack of formal neurocognitive follow-up with validated testing tools.

Using these validated neurobehavioral testing tools, several case–control studies, as reviewed in Ref. 37, have examined neurocognitive outcome of critically ill neonates after laparotomy or thoracotomy with anesthesia or after conservative treatment for necrotizing enterocolitis or patent ductus arteriosus. Although several studies observed impairment in neurocognitive function in surgically treated survivors, other investigators were unable to find any differences. An obvious inherent problem of these studies is the separation of the effects of anesthesia, coexisting disease, hereditary syndromes, and surgery on neurocognitive outcome. Moreover, several indications, such as longer periods of hypotension, increased use of inotropic support, and longer periods of parental nutrition in postsurgical patients, suggest that patients undergoing anesthesia were sicker than their matched controls. The search for evidence for anesthesia-related effects on neurocognitive outcome in this patient population is further complicated by the lack of information on the anesthetic management or the sedative treatment in the intensive care unit.

Although the exact mechanism of anesthesia-induced neurodegeneration in animals remains unclear, most lines of evidence point toward the involvement of GABA and/or NMDA receptors. All commonly used anesthetics are thought to exploit their effects on GABA and/or NMDA receptors to produce unconsciousness and immobility during painful stimulation. Moreover, all commonly used anesthetics that were investigated for their neurodegenerative properties, such as benzodiazepines, ketamine, propofol, nitrous oxide, and isoflurane, have been shown to exacerbate neuronal cell death. Because virtually all surgical procedures during early childhood are performed to preserve life or quality of life, removal of these drugs
from the therapeutic armamentarium would leave the pediatric anesthesiologist without any pharmacological alternative to the current anesthetic management. Interestingly, in one animal study, the rarely used NMDA-antagonist xenon did not cause neurotoxicity when administered at 0.5 MAC for 6 h. Xenon has also shown potential for mitigating isoflurane-induced neuronal degeneration when administered in combination with isoflurane. However, when combinations of more commonly used anesthetics are used to produce anesthesia, neurodegeneration seems to be more severe compared with single drug administration.

Withholding anesthetics during painful procedures does not solve this conundrum, and is clearly unethical. Structural brain abnormalities and long-term behavioral abnormalities have been extensively documented after painful stimulation in unanesthetized, newborn humans and animals.

In addition to rendering subjects nonresponsive and amnestic to surgical stimulation, anesthetics have also demonstrated neuroprotective properties during brain ischemia in newborn animals. Rodent models of normothermic brain ischemia and piglet models of hypothermic cardiopulmonary bypass have demonstrated protective effects in the developing brain.

Although not yet confirmed in clinical studies, these properties could benefit children undergoing surgical procedures with increased risk for adverse neurological outcome, such as neurosurgical or cardiac operations. Despite the evidence for widespread neuronal cell death in newborn animals and the immense number of anesthetics delivered in neonates and infants every year, a clinical marker of anesthesia-induced neurotoxicity has yet to be identified in children. However, despite the lack of overt clinical evidence for neuronal cell death in children, there is no reason to easily dismiss the animal data. Anesthesia-induced neurodegeneration has been repeatedly confirmed in multiple in vivo and in vitro animal models. Moreover, limited data in clinical studies suggest neurocognitive impairment after anesthesia and surgery early in life or after prolonged exposure to certain anesthetics. Therefore, pediatric anesthesiologists should use the currently available data from animal models to guide their practice. Animal studies have shown the brain to be most susceptible to anesthesia-induced neurodegeneration in a premature state of development. Moreover, animal models suggest neurodegeneration to be dose- and exposure time-dependent, and combinations of anesthetic drugs produced more severe neurodegeneration than single drugs. After reviewing the preclinical data on anesthetic-induced neurotoxicity the Food and Drug Administration Advisory Committee issued the following statement on March 29, 2007: “(although) there are no adequate data to extrapolate the animal findings to humans”,..., (the) well-understood risks of anesthesia (respiratory and hemodynamic morbidity) continue to be the overwhelming considerations in designing an anesthetic, and the understood risks of delaying surgery are the primary reasons to determine the timing. It therefore seems prudent for pediatric anesthesiologists to observe some of these caveats in their practice.

Evidence obtained in developing animal models is certainly compelling and warrants continued studies into the mechanism of anesthesia-induced apoptosis and mitigating strategies. Identification of the underlying mechanism is of paramount importance, given the ongoing questions about susceptibility of human neonates and the uncertainty about the equivalence of vulnerable developmental periods in neonates and developing animals. Although pediatric anesthesia providers do not have any alternatives to current anesthesia practice for premature and term neonates, several arguments, as outlined above, caution against the direct applicability of the available preclinical data to clinical anesthesia management. Therefore, completion of well-designed prospective clinical studies is necessary to assess the implications of anesthesia during early childhood on subsequent neurocognitive function in humans.

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