Chapter

12 ANESTHETIC NEUROTOXICITY

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INTRODUCTION

1. Is anesthetic neurotoxicity limited to pediatric patients?
2. Is the issue of anesthetic neurotoxicity a recent finding?
3. Has any regulatory agency commented on the issue of anesthetic neurotoxicity?

ANESTHETIC DRUGS AS A CAUSE FOR NEURODEGENERATION AND LONG-TERM NEUROCOGNITIVE DEFICITS

4. What are the primary receptors that are the targets of anesthetic drugs and the purported cellular intermediaries for the reported toxicity in preclinical reports?
5. What are the neurodevelopmental processes that are impaired with exposure to anesthetic drugs?
6. How does the developmental stage of the GABAergic neuron affect its excitatory state?
7. Does neuronal apoptosis always impair neurodevelopment?
8. Is there an age-dependent impact on dendritic development after exposure to anesthetic drugs?
9. What is the preclinical link between anesthesia and Alzheimer disease in older animal models?
10. Neonatal rat pups exposed to volatile anesthetics have been shown to develop learning deficits. Which interventions mitigate this adverse outcome?
11. What are the three factors that increase the development of neuronal cell death in neonatal laboratory animals exposed to anesthetic drugs?

CLINICAL EVIDENCE FOR NEUROTOXICITY

12. Recent retrospective reports detected neurocognitive deficits after exposure to surgery and anesthesia. What are the drawbacks of these investigations?
13. Are there any prospective reports that examine the impact of surgery and anesthetic at an early age on subsequent neurocognitive function?

INTRAOPERATIVE COURSE AND NEUROCOGNITIVE OUTCOMES

14. Are there any other perioperative factors that can impair subsequent neurocognitive function?
15. Parents are in your office for surgery and want to know the long-term risks of general anesthesia for their 6-month-old infant. They have concerns about the possible neurocognitive effects of general anesthesia and are contemplating a regional anesthetic rather than a general anesthetic. What is your advice to them?

ANSWERS*

INTRODUCTION

1. Preclinical reports clearly demonstrate a neurotoxic effect of anesthetic drugs at all stages of neurodevelopment. This effect spans from the fetus to the aged. (176)
2. Abnormal behavior has been reported in the 1950s in both children and the elderly after general anesthesia. Halothane was initially reported to be toxic to rodents in the 1960s. (176)
3. The Food and Drug Administration (FDA) held several open hearings and on December 14, 2016, published a cautionary perspective on the use of anesthetic drugs in patients under 3 years of age. The FDA warned that "repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains." (176)

ANESTHETIC DRUGS AS A CAUSE FOR NEURODEGENERATION AND LONG-TERM NEUROCOGNITIVE DEFICITS

4. Most anesthetic and sedative drugs are either γ-aminobutyric acid (GABA) receptor agonists, *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonists, or a combination of the two. General anesthesia and sedation can be achieved by inhalation or intravenous administration of specific drugs. Both GABA agonists and NMDA antagonists have been implicated in causing anesthetic-induced developmental neurotoxicity. (177)
5. Neurodevelopment progresses through several steps that include neurogenesis, neuronal morphogenesis, migration, synaptogenesis, and remodeling. Exposure to anesthetic drugs impaired these processes and has been implicated in the subsequent neurobehavioral deficits observed in laboratory animals. (177)
6. GABAergic general anesthetics act on the GABA receptor. Although GABA is inhibitory in the mature brain, it has been found in many preclinical studies to be an excitatory agent during early stages of brain development. The immature Na/K/2Cl transporter protein NKCCl produces a chloride influx leading to neuron depolarization. Therefore, GABA remains excitatory until the GABA neurons switch to the normal inhibitory mode when the mature chloride transporter, KCC2, is expressed and which actively transports chloride out of the neural cell. This switch begins around 15th postnatal week in term human infants but is not complete until about 1 year of age. (177)
7. The proliferative stage of neurogenesis produces an overabundance of progenitor cells that develop into neural and glial cells. Neural development is regulated by early elimination during embryonal and programmed cell death during postnatal modification of the central nervous system. Redundant neural progenitor cells and neurons that do not migrate properly or make synapses are physiologically pruned by apoptosis. (178)
8. Dendrites and axons extend from the cell body to form functional synapses with other neurons. Exposure to ketamine and isoflurane decreases synapse and spine density in very young infant rats. However, in slightly older rats, exposure to anesthetic drugs leads to an increase in dendritic spine formation. The implications of both the decrease in dendritic spine formation at a very young age and an increase in slightly older animals are unclear, but these different effects highlight the impact of specific developmental stages. (178-179)
9. Preclinical reports demonstrate expression of biological precursors of Alzheimer disease. Experimental surgery on mice increased β-amyloid accumulation in the hippocampus. Furthermore, exposure to isoflurane leads to increased tau and β-amyloid levels in cell culture and rodent brains. (179)

*Numbers in parentheses refer to pages, figures, boxes, or tables in Pardo MC, Miller RD, eds. *Basics of Anesthesia*. 7th ed. Philadelphia: Elsevier; 2018.

10. Anesthetic-induced cell death and neurobehavioral deficits in neonatal pups exposed to volatile anesthetics can be mitigated by concurrent exposure to an enriched environment, exercise, lithium, estrogen, erythropoietin, melatonin, and dexmedetomidine. (179–180)
11. The combination of high doses and prolonged exposure to anesthetic drugs and vulnerable age is directly related to neuronal cell death. (180)

CLINICAL EVIDENCE FOR NEUROTOXICITY

12. Most published reports implicating that general anesthesia is harmful to children are limited to retrospective epidemiologic analyses. This evidence may be confounded by the effects of surgery and the effects of the underlying comorbid conditions. Most of the studies have attempted to control for obvious confounders, but the retrospective nature of these investigations makes it impossible to control for all the known and unknown confounders. Large database clinical investigations from Canada and Sweden reveal that exposure to surgery and anesthesia at age greater than 2 to 4 years of age increased the odds ratio of cognitive deficits but not to the extent of previously published retrospective reports from smaller populations. Scrutiny of these large data sets reveals a lower percentage in academic achievement scores for toddlers undergoing ear, nose, and throat surgery. This finding suggests that early derangements in hearing and speech may have an impact on subsequent cognitive domains assessed by school performance. (180)
13. Two clinical reports that prospectively examined children receiving surgery and anesthesia (GAS and PANDA studies) did not demonstrate a decrement in cognitive function. The GAS study was an interim report of neurocognitive assessment after 2 years. A 5-year assessment is under way. A report on a smaller group of children exposed to anesthetic before 1 year showed deficits in measures of long-term recognition memory but no differences in familiarity, intelligence quotient, and Child Behavior Checklist scores. (181)

INTRAOPERATIVE COURSE AND NEUROCOGNITIVE OUTCOMES

14. The developing central nervous system is exquisitely sensitive to its internal milieu. Because critical periods of plasticity during brain development are modulated by the environmental milieu, perioperative conditions have the potential to influence brain development. Maternal deprivation, hypoglycemia, hypoxia, and hypotension and hypocarbia leading to cerebral ischemia during these critical periods of development may lead to neuronal injury and altered neurodevelopment. (181)
15. You advise them that they are correct to be concerned based on the animal and epidemiologic data, but the only published prospective randomized trial (GAS study) in children thus far did not show a neurocognitive difference between general and regional anesthesia. (181)