Anesthesiology 2007; 107:2–4 Copyright © 2007, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

**Anesthetic Neurotoxicity in Newborns**

**Should We Change Clinical Practice?**

PUBLICATION of findings that ketamine or other N-methyl-D-aspartate receptor antagonists accentuate apoptosis in the newborn brain, and that commonly used anesthetic agents (isoflurane, midazolam, and nitrous oxide) not only enhance neuroapoptosis but also promote long-term learning deficits, sparked controversy in the pages of *Anesthesiology*. This editorial aims to update anesthesiologists on further investigations on the neurotoxic effects of anesthetic agents and methods for extrapolating neurodevelopmental data from animal models to humans, in order to reexamine the clinical applicability of these findings.

Anesthetic-induced Neurotoxicity: A Brief Update

Neurodegenerative changes after anesthesia occur at both ends of the life span. Epidemiologic observations suggested that onset of Alzheimer disease was related to cumulative anesthetic exposure before the age of 50 yr. Animal studies confirmed that inhaled anesthetics enhance the production, aggregation, and neurotoxicity of amyloid-β peptides, appearance of brain plaques and learning/memory deficits characterizing Alzheimer disease, and increased apoptosis, probably in hippocampal areas. This report, however, focuses on the anesthetic neurotoxicity after fetal–neonatal exposure, coincident with developmentally occurring apoptosis, which affects 0.5–1% of rodent neurons and more than 50% of human neurons.

The original finding that N-methyl-D-aspartate receptor antagonists such as ketamine enhance apoptosis in immature neurons has been confirmed in different animal models and by multiple authors (reviewed recently by Mellon et al.). Anesthetic neurotoxicity peaks at postnatal day 7 (P7) in rats and mice and requires prolonged exposures in rats and monkeys. Single large doses of ketamine (50 mg/kg) or benzodiazepines activate apoptosis in mice, signaling developmental differences across species. Further, anesthetic neurotoxicity primarily results from apoptosis in rodents, whereas infant monkeys at P5 (but not at P35) exhibit both excitotoxicity and apoptosis. Despite the accumulating data, practicing anesthesiologists must consider important limitations in applying such experimental results to clinical practice. These include developmental differences across mammalian species, the huge doses and prolonged exposures required to produce...
neurotoxic effects, the use of anesthesia unopposed by surgical/painful stimulation, the need for precise physiologic monitoring, and the neuroprotective and antiinflammatory effects of anesthesia. For example, repetitive inflammatory pain accentuated cell death 3.3-fold in cortical areas and 1.6-fold in subcortical areas of newborn rats, whereas ketamine (5 mg/kg) blocked these cellular changes and ameliorated the consequent adult cognitive deficits.\textsuperscript{20} From a developmental perspective, however, rats and mice are altricial species, whereas humans or rhesus monkeys are precocial species, making it difficult to integrate data across experimental species or to derive clinically meaningful conclusions from animal studies.

### Extrapolating Neurodevelopmental Data from Animals to Humans

To characterize the neurotoxic effects of drug exposure on the developing human brain, clinicians and scientists rely on the data collected from various experimental species that develop and mature at varying rates. Although the vulnerability to anesthetic neurotoxicity at P7 in rats is thought to coincide with peak periods of brain growth or synaptogenesis,\textsuperscript{2,10–12} these associations are based on outdated evidence. Morphologic comparisons based on Carnegie somatic stages\textsuperscript{21,22} or neuroanatomical milestones\textsuperscript{23,24} are fraught with inaccuracies because they assume uniform rates of development between somatic and neural structures or between all brains regions during development. Rules of thumb (measuring human life in “dog years”), although popular, were based on accretion of brain synaptogenesis,\textsuperscript{2,10–12} these associations are based on outdated evidence. Morphologic comparisons based on Carnegie somatic stages\textsuperscript{21,22} or neuroanatomical milestones\textsuperscript{23,24} are fraught with inaccuracies because they assume uniform rates of development between somatic and neural structures or between all brains regions during development. Rules of thumb (measuring human life in “dog years”), although popular, were based on accretion of brain weight or water content, gangliosides or cholesterol (to estimate white matter), total DNA (to estimate neuronal number), the vulnerability of brain growth to nutritional deprivation,\textsuperscript{25–27} or no direct evidence.

Across mammalian species, however, a similar sequence of events in early brain development allows scientists to infer the lacunae in human development from animal studies.\textsuperscript{28} Using anchor events in development, integrating data from several mammalian species into a single statistical model, with corrections for differential rates of growth in the primate cortex and limbic system, provides us with a novel neuroinformatics approach to predict the timing of neural events.\textsuperscript{19} This approach is based on evolutionary and developmental principles and also accounts for correspondences and variability in developing brain regions across species to estimate the timing of neural events for which no direct empirical evidence is available.\textsuperscript{19}

Using this Web-based bioinformatics approach,\textsuperscript{*} we find that P7 (or 28.5 days postconception [PC]) in rat neurodevelopment corresponds to human brain development as follows:

- Cortical regions: 156.8 PC days (22.4 weeks’ gestation)
- Limbic regions: 114.2 PC days (16.3 weeks’ gestation)
- Other (noncortical/nonlimbic) regions: 123.2 PC days (17.6 weeks’ gestation)

Therefore, the rat models showing anesthetic neurotoxicity at P7 have limited, if any, clinical relevance to the care of preterm human neonates. As another example, 122 PC days in the macaque monkey correspond to:

- Cortical regions: 197.1 PC days (28.2 weeks’ gestation)
- Limbic regions: 143.2 PC days (20.5 weeks’ gestation)
- Other (noncortical/nonlimbic) regions: 154.6 PC days (22.1 weeks’ gestation) in terms of human neurodevelopment.

Greater accuracy in the extrapolation of vulnerable periods across species will inform the design of animal experiments and human studies (the timing and duration of exposure, or the brain regions likely to be affected) for examining the neurotoxic effects of anesthetic agents, or other brain injuries (such as hypoxia, hypoglycemia, infection, trauma, and inflammation).

Despite the accumulating animal data on anesthetic neurotoxicity, however, the limitations of the aforementioned experimental models preclude their applicability to the clinical care of infants and children. A significant body of literature also demonstrates the neuroprotective and antiinflammatory effects of anesthetic agents in a variety of clinically relevant species and injury models. This, coupled with substantial evidence from clinical studies that demonstrate the acute and long-term effects of unrelied pain or surgical stress, justify the continued clinical use of potent anesthesia for neonates and infants. Until further empirical evidence becomes available, such as from noninvasive neuroimaging of cell death after anesthesia in human infants or identifying a behavioral “phenotype” after anesthetic exposure in infancy, changing clinical practices based on these animal data are premature. At an open public meeting, the Anesthetic and Life Support Drugs Advisory Committee of the US Food and Drug Administration unanimously came to the same decision. Future scientific experiments must be designed using animals at comparable neurodevelopmental stages, using doses and durations of anesthetic exposure that are clinically relevant, in animal models where anesthesia is provided for some type of surgical procedure and supported with continuous physiologic monitoring.

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### References


Accepted for publication March 15, 2007. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.