



# Perspective

## Anesthesia and Developing Brains — Implications of the FDA Warning

Dean B. Andropoulos, M.D., M.H.C.M., and Michael F. Greene, M.D.

**F**or more than 15 years, the potential for lasting neurotoxic effects of agents used to induce general anesthesia and sedation when administered to young children — and indirectly

through pregnant women to fetuses with developing brains — has been a subject of concern and considerable research interest. The topic has been the focus of three public hearings by the Food and Drug Administration (FDA) since 2007, including an FDA Science Board meeting in November 2014, to better inform the public and practitioners about this potential problem and to foster a discussion between parents and physicians about potential risks posed by using anesthesia in young children.

At the 2014 meeting, the publicly available preclinical and clinical data were presented by representatives of the FDA. The data from studies in animals and in vitro research demonstrate that under experimental conditions, all

general anesthetics tested, including both *N*-methyl-*D*-aspartate (NMDA) antagonists and gamma-aminobutyric acid (GABA) agonists, have immediate neuroanatomical consequences and associated long-lasting, if not permanent, functional effects in species ranging from roundworms to nonhuman primates.<sup>1</sup>

The clinical data were considerably more difficult to interpret. Studies of brief, single exposures for relatively minor procedures have been reassuring. The long-term adverse neurodevelopmental effects that have been observed after prolonged or repeated anesthesia administration are difficult to interpret because of confounding by indication.<sup>2</sup> Otherwise healthy young children do not undergo

lengthy (longer than 3 hours) or repeated procedures under general anesthesia. And the brains of children born prematurely or with cyanotic congenital heart disease may have been injured by inflammation or chronic hypoxia before the children underwent the surgery that required general anesthesia.

Most recently, the interim analysis of the General Anesthesia vs. Spinal Anesthesia (GAS) study and the Pediatric Anesthesia and Neurodevelopment Assessment (PANDA) study, both of which involved formal neurodevelopmental testing, revealed that a brief, single exposure to general anesthesia was not associated with poorer neurodevelopmental outcomes.<sup>3,4</sup> The Mayo Anesthesia Safety in Kids (MASK) study comparing unexposed children, those with a single anesthetic exposure, and those with multiple anesthetic exposures as young children in terms of later neurodevelopmental outcomes is well under way,

with results expected in 2017.<sup>5</sup> Investigators conducting another major study, the Recognition Memory Study, that also specifically addresses prolonged anesthesia in young children, are expected to report data in the next few years.<sup>5</sup> There are no data specifically assessing any association of anesthetic exposure in utero in human fetuses with postnatal neurodevelopmental outcomes.

On December 14, 2016, the FDA issued a “Drug Safety Communication” ([www.fda.gov/Drugs/DrugSafety/ucm532356.htm](http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm)) warning that general anesthesia and sedation drugs used in children less than 3 years of age or in pregnant women in their third trimester who were undergoing anesthesia for more than 3 hours or repeated use of anesthetics “may affect the development of children’s brains.” This warning will result in a labeling change for 11 common general anesthetics and sedative agents that bind to GABA or NMDA receptors, including all anesthetic gases such as sevoflurane, and the intravenous agents propofol, ketamine, barbiturates, and benzodiazepines.

At the November 2014 FDA meeting, recommendations for several possible label changes, including a boxed warning, were considered. Ultimately, no recommendation was made at that time. In light of this conclusion, the reassurance about a single anesthetic exposure, the imminent reporting of additional data regarding multiple exposures in young children, the lack of any data regarding adverse consequences of human fetal exposure to anesthesia, and the lack of new troublesome data, the FDA warning and its timing took clinicians and investigators in the field by surprise.

The warning will raise concerns and questions among practitioners, pregnant women, and parents of young children — questions for which there are currently no clear answers. It will also change medical practice for many of the estimated 1.5 million to 2 million children under 3 years of age who undergo anesthesia annually in the United States.

At Texas Children’s Hospital, where anesthesia is administered in more than 43,000 cases each year, approximately 13,000 of these cases involve patients under 3 years of age, and about 1300 of these patients undergo anesthesia for more than 3 hours; two thirds of these cases of prolonged anesthesia are for procedures related to congenital heart disease. Essentially all these prolonged procedures are for serious or life-threatening congenital conditions for which there are no alternative treatments and for which treatment cannot be delayed until the patient reaches 3 years of age. Approximately 1400 patients at Texas Children’s Hospital who are less than 3 years of age undergo two or more procedures requiring general anesthesia in any year, and 2000 undergo sedation or anesthesia for magnetic resonance imaging examinations. After deliberation among its leaders in anesthesiology, surgery, and hospital risk management, the hospital has changed its practice in response to the FDA warning. The FDA warning itself will now be discussed before surgery with parents of all children younger than 3 years of age who would be receiving an anesthetic. And the hospital has adopted the warning’s recommendation that a discussion occur among parents, surgeons and other physicians, and anesthe-

siologists about the duration of anesthesia, any plan for multiple general anesthetics for multiple procedures, and the possibility that the procedure could be delayed until after 3 years of age; parent-education materials will also cover these topics.

There are no alternatives to these general anesthetic drugs for children younger than 3 years of age, though in rare cases, a lower-abdominal or lower-extremity procedure can be performed under spinal anesthesia in young infants. The only other drugs in clinical use for sedation and anesthesia that do not cause neurodegeneration in animal models are dexmedetomidine and opioids, but these agents are not sufficient for general anesthesia and do not represent a feasible option by themselves. Studies involving these agents are under way, but definitive results will not be available for several years.

Indicated procedures in pregnant women and young children that can safely be delayed are rare. Until reassuring new information from well-designed clinical trials is available, we are concerned that the FDA warning will cause delays for necessary surgical and diagnostic procedures that require anesthesia, resulting in adverse outcomes for patients. We would urge parents, patients, and physicians to carefully consider the risks of delaying indicated procedures.

The warning also states that “additional high quality research is needed to investigate the effects of repeated and prolonged anesthesia exposures in children, including vulnerable populations.” We fully support this effort, including outcome studies specifically for fetuses exposed to general anesthetic and sedative agents in utero.

Disclosure forms provided by the authors are available at NEJM.org.

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From the Department of Anesthesiology, Texas Children's Hospital and Baylor College of Medicine, Houston (D.B.A.); and the Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston (M.F.G.).

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