U.S. Food and Drug Administration
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Drug Safety Communications

FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women

Safety Announcement

[12-14-2016] The U.S. Food and Drug Administration (FDA) is warning 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.

Consistent with animal studies, recent human studies suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. However, further research is needed to fully characterize how early life anesthetic exposure affects children's brain development.

To better inform the public about this potential risk, we are requiring warnings to be added to the labels of general anesthetic and sedation drugs (see List of General Anesthetic and Sedation Drugs Affected by this Label Change). We will continue to monitor the use of these drugs in children and pregnant women and will update the public if additional information becomes available.

Anesthetic and sedation drugs are necessary for infants, children, and pregnant women who require surgery or other painful and stressful procedures, especially when they face life-threatening conditions requiring surgery that should not be delayed. In addition, untreated pain can be harmful to children and their developing nervous systems.

Health care professionals should balance the benefits of appropriate anesthesia in young children and pregnant women against the potential risks, especially for procedures that may last longer than 3 hours or if multiple procedures are required in children under 3 years. Discuss with parents, caregivers, and pregnant women the benefits, risks, and appropriate timing of surgery or procedures requiring anesthetic and sedation drugs.

Parents and caregivers should discuss with their child's health care professional the potential adverse effects of anesthesia on brain development, as well as the appropriate timing of procedures that can be delayed without jeopardizing their child's health. **Pregnant women** should have similar conversations with their health care professionals. Also talk with them about any questions or concerns.

Published studies in pregnant animals and young animals have shown the use of general anesthetic and sedation drugs for more than 3 hours caused widespread loss of nerve cells in the brain. Studies in young animals suggest these changes result in long-term effects on the animals' behavior or learning (see Data Summary).[1-20] Studies have also been conducted in children,[21-43] some of which support findings from previous animal studies, particularly after repeated or prolonged exposure to these drugs early in life. All the studies in children had limitations, and it is unclear whether any negative effects seen in children's learning or behavior were due to the drugs or to other factors, such as the underlying medical condition that led to the need for the surgery or procedure.

FDA has been investigating the potential adverse effects of general anesthetic and sedation drugs on children's brain development since the first animal study on this topic was published in 1999.[9] We held advisory committee meetings in 2007, 2011, and 2014. To coordinate and fund research in this area, we also formed a partnership with the International Anesthesia Research Society (IARS) called SmartTots (Strategies for Mitigating Anesthesia-Related neuroToxicity in Tots). More research is still needed to provide additional information about the safe use of these drugs in young children and pregnant women.

We urge health care professionals, patients, parents, and caregivers to report side effects involving anesthetic and sedation drugs or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

List of General Anesthetic and Sedation Drugs Affected by this Label Change*

Generic Name	Brand Name
desflurane	Suprane
etomidate	Amidate
halothane	Only generic is available
isoflurane	Forane
ketamine	Ketalar
lorazepam injection	Ativan
methohexital	Brevital
midazolam injection, syrup	Only generic is available
pentobarbital	Nembutal
propofol	Diprivan
sevoflurane	Ultane, Sojourn

*This list includes anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity. No specific medications have been shown to be safer than any other.

Facts about General Anesthetics and Sedation Drugs

- General anesthetic and sedation drugs are used to put people into a deep sleep so they do not feel pain during surgery or procedures.
- These drugs are usually injected into a vein or breathed in through a mask.

- General anesthetic and sedation drugs are widely used to ensure the health, safety, and comfort of children and adults undergoing surgery or other procedures.

Additional Information for Parents, Caregivers, and Patients

- Studies conducted in pregnant animals, young animals, and children exposed early in life suggest repeated or prolonged use of general anesthetic and sedation drugs may have negative effects on the developing brain (see List of General Anesthetic and Sedation Drugs Affected by this Label Change).
- Based on FDA's understanding of brain development, the data suggest that the fetuses of women in their third trimester of pregnancy and children younger than 3 years are most likely vulnerable to this effect.
- Recent studies in children suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. More research is still needed to fully understand how anesthetics might affect brain development, especially longer or repeated exposures and in more vulnerable children.
- Most anesthetic drugs have been shown to cause these negative effects on brain development in different species of animals, and no specific medications have been shown to be safer than any other.
- Anesthetic and sedation drugs are necessary for infants, children, and pregnant women who require surgery or other painful and stressful procedures. Moreover, untreated pain can be harmful in children and to their developing nervous systems.
- Parents and caregivers should ask for information about the planned surgery or procedure, including the likely duration of surgery and the need, if any, for repeated procedures. Parents should also discuss with their child's health care professional the potential adverse effects of anesthesia on brain development and appropriate timing of procedures that can be delayed without jeopardizing their child's health. Pregnant women should have similar conversations with their health care professionals.
- Examples of life-threatening conditions in newborns and other children younger than 3 years that require surgery that should not be delayed include, but are not limited to:
    - Serious congenital heart defects
    - Esophageal atresia, a disorder in which the esophagus does not develop properly
    - Intestinal blockage or twisting of the intestines
    - Gastroschisis and omphalocele, which are birth defects of the abdominal wall
    - Diaphragmatic hernia, which is a birth defect in which there is an abnormal opening in the diaphragm
    - Congenital lung lesions
    - Pyloric stenosis, which is a narrowing of the opening from the stomach into the small intestine
- Examples of other common procedures for non-life-threatening conditions in children younger than 3 years that are necessary and should not be delayed are cleft lip or palate repair and surgery to repair undescended testicles in boys.

- Examples of surgeries for life-threatening conditions in pregnant women that should not be delayed include, but are not limited to:
    - Removal of the appendix
    - Removal of the gallbladder
    - Repair of traumatic injury (e.g., related to a car accident)
- Talk to your child's health care professional for more information or if you have any questions or concerns.
- Report side effects from anesthetic or sedation drugs to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- In published juvenile animal studies, use of anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity for longer than 3 hours has been demonstrated to increase neuronal apoptosis in the brain resulting in long-term cognitive deficits (see List of General Anesthetic and Sedation Drugs Affected by this Label Change).
- Adverse effects on brain development following use of general anesthetic and sedation drugs have been demonstrated in multiple animal species ranging from flatworm to nonhuman primates.
- Consistent with animal studies, recent human data suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. However, further research is needed to fully characterize how early life anesthetic exposure might affect children's brain development, particularly for more lengthy or repeated exposures and in more vulnerable children.
- No specific anesthetic or sedation drug has been shown to be safer than any other.
- Based on comparisons across species, the window of vulnerability to these changes in the brain is believed to correlate with exposures in the third trimester of pregnancy through the first year of life, but may extend out to approximately 3 years in humans. The clinical significance of these nonclinical findings is not clear.
- Some published studies suggest that similar deficits in cognition and behavior may occur in children, particularly after repeated or prolonged exposures to anesthetic drugs early in life. These studies have limitations, and it is not clear if the effects reported are due to the anesthetic/sedation drugs, or to other factors such as the surgery or underlying illness.
- Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the risks.
- Discuss with parents, caregivers, and pregnant women the benefits, risks, and appropriate timing and duration of surgery or procedures requiring anesthetic and sedation drugs. Also discuss with them the health risks of not treating certain conditions.
- Report adverse events involving anesthetic or sedation drugs to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

FDA reviewed many published research studies, including both nonclinical and clinical data.

Nonclinical Studies

We reviewed published nonclinical studies showing that early exposure to anesthetic drugs can produce adverse neurotoxic effects in different species, including simple nematodes, rats, and nonhuman primates.[1-20] The studies demonstrate that the use of anesthetic drugs during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain, and alterations in synaptic morphology and neurogenesis. Based on comparisons across these nonhuman species, the window of vulnerability to these changes is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years.

In pregnant primates, late in gestation during peak fetal brain development, exposure to 24 hours of ketamine in the third trimester or exposure to 5 hours of isoflurane or 5 hours of propofol increased neuronal cell loss in the fetus. In neonatal primates, exposure to 3 hours of ketamine that produced a light surgical plane of anesthesia did not increase neuronal cell loss; however, neuronal cell loss was seen with treatment regimens of 24 hours of ketamine, or 5 hours or more of isoflurane plus nitrous oxide or propofol. Data in isoflurane-treated rodents and in ketamine-treated primates suggest the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical (animal) findings is not known.

Clinical Studies

We also reviewed the epidemiologic literature investigating the association between childhood anesthesia exposure and adverse neurodevelopmental outcomes.[21-41] The studies were published between 2009 and 2014. Some studies found no association between pediatric exposures and neurodevelopmental outcomes,[21-29] whereas others did.[30-41] In particular, several of the studies have increased concerns that longer or repeated exposures may contribute to various cognitive and behavioral problems, including neurodevelopmental delay-related diagnoses, learning disabilities, and attention deficit hyperactivity disorder.[32, 33, 37, 38, 41] However, it remains unclear whether these associations represent an effect of the anesthesia drugs as opposed to the surgery itself, or are the result of uncontrolled confounding related to the underlying condition or other factors. The observational studies had many limitations, including heterogeneous exposure and outcome definitions and measures, potential for selection and information biases, incomplete control for confounding, and insufficient power. Most studies included children exposed to anesthesia before age 2-3 years, but the studies varied widely in the age groups included. Some focused only on newborns and infants, while

others included children with anesthesia exposures up to 12 years of age. Most of the studies were not able to determine the duration of anesthesia exposure.

More recently, interim findings from the General Anesthesia Compared to Spinal Anesthesia (GAS) trial and results from the Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) Study have been published.[42, 43] The GAS trial is an ongoing international, multicenter, randomized controlled trial comparing neurocognitive outcomes following randomization to either awake-regional anesthesia or to sevoflurane-based general anesthesia in children younger than 60 weeks but born at more than 26 weeks gestation who required inguinal hernia repair. The primary outcome of the trial is Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale Intelligence Quotient (IQ) at age 5 years. The secondary outcome is the composite cognitive score of the Bayley Scales of Infant and Toddler Development III at age 2 years. The initial 2-year follow-up results were published in January 2016. Data were evaluated from 238 children treated with awake-regional anesthesia and 294 children administered general anesthesia. The median duration of sevoflurane in the general anesthesia cohort was 54 minutes. The authors reported no difference in Bayley III development scores between the two study arms. They suggested these data support the conclusion that sevoflurane anesthesia of less than 1 hour duration does not appear to increase the risk of adverse neurodevelopmental outcome at age 2 years compared to awake-regional anesthesia. The GAS study still needs to be completed to evaluate the primary WPPSI-III IQ outcome measure at age 5 years.[42]

The PANDA study is a sibling-matched observational cohort study that examined whether a single anesthesia exposure in healthy children younger than 3 years is associated with an increased risk of impaired global cognitive function (IQ) as the primary outcome, and abnormal domain-specific neurocognitive functions and behavior as secondary outcomes at ages 8 to 15 years. Exposed children (n=105) had a single episode of general anesthesia before 3 years for elective inguinal hernia surgery and were 36 weeks gestational age or older at birth. The mean duration of anesthesia in the exposed group was 84 minutes, with 17 children having exposures more than 2 hours. Ninety percent of the exposed children were boys. The unexposed cohort (n=105) were biologically related siblings closest in age (within 3 years) to the exposed child, also 36 weeks gestational age or older at birth but with no anesthesia exposure before 3 years. The study found that mean IQ scores were not significantly different between the exposed and unexposed siblings, with both groups scoring somewhat higher than average. There were no significant differences in mean scores on any of the secondary assessments, although exposed children were significantly more likely to have abnormal "internalizing" scores on the Child Behavior Checklist. This may have been a chance finding, as analyses did not adjust for multiple endpoints.[43]

The PANDA study addressed many of the limitations of the previous epidemiologic studies. However, as designed, the study was not able to evaluate effects of prolonged or repeated anesthesia exposures, or possible effects in more vulnerable subgroups (e.g., less healthy children). The study also may not have been sufficiently powered to evaluate

meaningful differences in all secondary outcomes or for analyses examining age at exposure, duration of exposure, or gender differences.

The PANDA study, along with the preliminary GAS trial findings, provide some clinical evidence that a single, relatively brief early exposure to general anesthesia in generally healthy children is unlikely to cause clinically detectable deficits in global cognitive function or serious behavior disorders. These findings are consistent with animal data, which have not predicted an increased risk with anesthesia exposures less than 3 hours. However, the GAS trial has not yet been completed, and additional high-quality research is needed to investigate the effects of repeated and prolonged anesthesia exposures in children, including vulnerable populations. Research is also needed to explore possible subtle behavioral effects, vulnerable ages of exposure, potential gender differences, and potential variability among specific anesthetic drugs and protocols.

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Related Information

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