Pediatric Anesthesia CME Program

Module 4

This is Module 4 of CSA's Pediatric Anesthesia Continuing Medical Education Program (CME). To receive CME credit, submit your registration page, answers to the questions, and the evaluation to the CSA office by mail or fax (650) 345-3269. Your CME certificate will be mailed to you. Alternatively, the full text of each module will be accessible through the CSA Web Site, **www.csahq.org**, in the Online CME Program section. Instructions to complete Module 4 online are given in the information pages. After completing the assessment, print your CME certificate. Members will need their usernames and passwords to do the modules online.

The following Important Information about Module 4 must be read and acknowledged before proceeding to the rest of the module. Check the acknowledgement box on the registration page.

Faculty/Disclosures

All faculty participating in continuing medical education activities sponsored by the CSA are required to disclose any real or apparent conflict(s) of interest related to the content of their presentation(s) or any of the industry sponsors of the meeting. In addition, speakers must disclose when a product is not labeled for the use under discussion or when a product is still investigational.

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Dr. Singleton has no relevant financial relationships with any commercial interests.

Registration/Instructions

Method of Participation: The physician will read and study the materials and complete a quiz and an evaluation of the module. Some modules may have slides available online. To register for and complete this module: Complete the registration page, complete the test questions and the evaluation that can be found after the article, and submit your quiz to the CSA office by mail or fax (650-345-3269). Your CME certificate will be mailed to you.

Estimated Time to Complete the Module: One hour

Please check the box on the registration page acknowledging that you have read everything in these introductory pages.

Availability

Module 4: Neurotoxicity of Anesthetic Agents in the Developing Brain

Release Date: June 14, 2011
Expiration Date: June 14, 2014

CME Sponsor/Accreditation

The California Society of Anesthesiologists (CSA) is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The CSA Educational Programs Division designates this pediatric anesthesia program for *AMA PRA Category 1 Credit(s)™* (1 credit per module). Physicians should claim credits commensurate with the extent of their participation in the activity.

Fees, Target Audience, Evaluation

The modules are free to CSA members. Nonmembers pay $30 for each module. Each module is worth *one AMA PRA Category 1 Credit™*. This program is intended for all licensed physicians, including residents. An evaluation of each module of this series is offered after the test questions.

Privacy Policy

CSA has a privacy policy that is a general policy for information obtained regarding all online interactive pages, including online CME activities. To review this policy, please go to www.csahq.org/privacy.vp.html.

Objectives

Upon completion of this activity, participants will be able to:

- Define the risks of an anesthetic procedure for long-term cognition based on review of the currently available human literature of anesthesia-induced developmental neurotoxicity
- List the most important proposed mechanisms of anesthesia-induced developmental neurotoxicity
- Inform parents of whether their child might be at risk for anesthesia-induced developmental neurotoxicity

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Neurotoxicity of Anesthetic Agents in the Developing Brain

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Greg Stratmann did his transitional internship and residency in anesthesiology at the University of California, San Diego, followed by fellowships in pediatric cardiac anesthesia and intraoperative transesophageal echocardiography at UCSF. As a highly esteemed researcher since the early days of his anesthesia training, he has been the recipient of numerous awards and honors, ranging from first prize in the CSA Resident Research Competition to the Ellison C. Pierce, Jr., MD, Research Award from the Anesthesia Patient Safety Foundation. Boarded in TEE, he is a member of the cardiac anesthesia subgroup at UCSF, performing both adult and pediatric cardiac anesthesia as well as anesthesia for heart and lung transplants. He also administers anesthesia for a wide range of pediatric surgeries. He is acknowledged as a world expert in the field of anesthetic-induced developmental neurotoxicity and widely published in this arena. In addition to his varied other clinical teaching functions, he has mentored numerous graduate and medical students in their research in the neurosciences, as well as serving as a reviewer for at least seven medical and anesthesia journals. One of his hobbies in his "spare time," unrelated to his obvious interest in brain injury, is serving as the team physician for the University of San Francisco collegiate boxing team (with which he also trains as a boxer) and as a ringside physician for boxing tournaments.

From the Chair

By now most readers of this *Bulletin* are aware that recent research findings have suggested the possibility of previously unsuspected vulnerabilities of the immature, developing human brain to anesthesia. Questions subsequently have arisen, prompted largely by investigators at

the Food and Drug Administration (FDA), as to the toxicity and long-term cognitive effects of virtually every commonly used anesthetic agent in infants and young children. This is indeed a "hot topic" and one that surely will gain attention in the media and among parents. This excellent module, authored by Dr. Greg Stratmann, who is a principal investigator and expert in this field, presents an overview of the three major areas of study directed at addressing this question—human cohort studies, histological and behavioral investigations in animals, and research on mechanisms at the cellular level.

We administer anesthetics with the belief that, in appropriate doses and exposures, the effects are fully reversible and free from lasting harm. We may need to challenge our assumptions.

Mark Singleton, M.D., Editor

Introduction

For over 150 years of anesthetic practice, it was believed that as a general anesthetic wears off, the brain will return to the same state as before the anesthetic. We are now beginning to understand that this basic premise of anesthetic pharmacology may be false. In 2003 Jevtovic-Todorovic presented her sentinel findings that a combined anesthetic (midazolam, nitrous oxide and isoflurane) administered to 7-day-old rats for six hours kills neurons in the developing brain and causes long-term impairment of brain function.[1] These researchers also showed that long-term potentiation (a form of synaptic plasticity often considered the electrophysiological correlate of learning and memory) in the hippocampus (a key anatomic location in the brain for learning and memory) was impaired. They further demonstrated a progressive deficit in spatial recognition tasks administered both four weeks and four and a half months after anesthesia.[1] Immediate concern mounted about whether or not these phenomena might apply to humans. Subsequently, the histological data were reproducible not only in rodents but in virtually every species tested, including primates, further heightening the degree of concern about anesthesia in the immature human brain.[2–4] An FDA advisory committee meeting in 2007 concluded that no change in clinical practice is justified based on available data.[5]

It is uncertain if it will ever be feasible to test whether anesthesia kills neurons in the brains of children. However, this may not be entirely necessary. A focus on anesthesia-induced neurodegeneration seems appropriate if some aspect of brain function in humans was changed permanently by anesthesia, and if a causal link between neurodegeneration and long-term brain function could be demonstrated in animals.

Anesthesia and Brain Function in Humans

Until recently, speculation as to whether or not developmental anesthetic neurotoxicity might exist in humans occurred mostly on the basis of studies that were not specifically designed to address this question. Since 2009, six publications have appeared that were designed to shed light on whether or not anesthesia in humans might impair brain function long-term.[6–11] Unfortunately, for a number of reasons discussed below, the issue is still far from being resolved. The power of studying a prospective cohort must be balanced against the lead time for data to become available.[12] For example, if enrollment into a randomized, controlled trial of regional versus general anesthesia for pediatric surgical procedures were completed today, then data of remote neurobehavioral outcomes would not be available for years, maybe decades. Given the urgency with which data on developmental neurobehavioral end points after anesthesia in humans are sought, a long lag time is, arguably, unacceptable. Thus, an ideal combination of lag time and design strength would be prospective analysis of a retrospective cohort. To date, no data exist using this approach.

Wilder studied if anesthesia administered to children under 4 years of age were associated with learning disabilities between ages 5 and 19.[6] A cohort of 5,357 children born in Olmsted County, Minn., between 1976 and 1982 was assessed for the presence, type and duration of anesthesia prior to age 4. Anesthesia administered for both surgical and diagnostic procedures was included in the analysis. The school district in which the study was performed routinely administered reading, writing and mathematics aptitude tests as well as intelligence tests. In this study, learning disability was defined as performance on standardized achievement tests below a certain predicted score that was based on the child's IQ. If any of three different definitions used by the school district to identify disabled learning applied, then the primary outcome of this study—learning disability—was considered to be present, and study follow-up ceased at this point. Eleven percent of children underwent at least one anesthetic prior to age 4, of which 24 percent underwent more than one anesthetic. Learning disabilities were more common in those children that underwent more than one anesthetic, and cumulative anesthetic duration of greater than two hours was a risk factor for learning disability. Learning disability was not more common if only one anesthetic exposure occurred before age 4.

Because children requiring more than one anesthetic were sicker than those requiring only a single anesthetic, the authors performed a subgroup analysis of children requiring more than one anesthetic with an ASA physical status 1

and 2 (while excluding those with ASA physical status 3 and 4), but the association between learning disabilities and anesthesia persisted. Methodological advantages of this study include that studying a birth cohort does not bias surgical procedures and co-morbidities in the same way that recruitment of a cohort of patients from an academic center might. Further, controlling for IQ seems like a reasonable approach to controlling for one of the strongest confounders of a child's ability to learn. General methodological drawbacks included retrospective analysis of a retrospective cohort studying an outcome variable that is available rather than one chosen prospectively.

Learning disability is a very nonspecific outcome because many underlying pathologies may impair a child's ability to learn—for example, motivation, attention, intelligence, sensory neural problems, or other more specific functional abnormalities, all of which may have relevance to anesthetic developmental neurotoxicity. Further drawbacks include that the anesthetic almost uniformly administered to the study cohort was halothane/nitrous oxide, which is now an outdated anesthetic in most pediatric anesthetic practices. Reporting the cumulative incidence of learning disabilities requires that follow-up is stopped when learning disability is detected: once a child meets the criterion for learning disabilities, it is assumed that learning disabilities persist and never resolve. This makes it impossible to comment on the true prevalence of the outcome. It is possible that children with learning disabilities at some point may have a change in performance that places them back into the normal range, an event that could not be captured by the study design. On the other hand, it is possible that anesthesia-associated learning disability may progress, as has been suggested for anesthesia-induced neurocognitive dysfunction in animals,[1, 13, 14] but this study[6] was not able to detect progression of cognitive disability.

The same group later reported that general anesthesia for cesarean delivery does not increase the cumulative incidence of learning disabilities in the same birth cohort of children—that is, a brief general anesthesia during late fetal life is not associated with later cognitive problems.[7] This is consistent with their earlier study[6] because cesarean delivery required one rather short anesthetic. Unexplained is the finding that children born by cesarean delivery under regional anesthesia had a lower cumulative incidence of learning disability than those born by vaginal delivery.[7]

Kalkman approached the problem from a different angle, arguing that anesthesia is mostly administered to tolerate a surgical procedure.[8] Therefore, in order to draw conclusions about the effects of anesthesia versus surgery on cognitive outcome, an unanesthetized control group undergoing surgery would be required, or anesthesia would have to be administered to children who don't

need it, neither one of which is ethically feasible. Based on the assumption that there is a distinct period of vulnerability to the effects of anesthesia on neurodevelopment, as suggested by animal studies using histologic outcomes,[15] Kalkman hypothesized that children anesthetized during the period of vulnerability (earlier in life) should have a worse cognitive outcome than children anesthetized beyond a defined period of vulnerability. They defined the period of vulnerability in humans as younger than 2 years of age. This design used children anesthetized when older than 2 years to serve as controls. They used scores from the Child Behavioral Checklist to identify behavioral abnormalities, and they found that children undergoing the same (urological) procedures who were under 2 years of age tended to have a higher incidence of clinically deviant behavior than children older than 2 years old. The difference was even more pronounced between children undergoing anesthesia at less than 6 months of age compared to those more than 2 years old. However, *neither* effect was pronounced enough to reach statistical significance, which would have required thousands of children.

Moreover, the validity of defining the period of vulnerability in humans as being younger than 2 years of age is not known. A rodent study[14] suggests that the period of vulnerability to the outcome of interest—the long-term cognitive effects of anesthesia—may extend beyond 2 years of age in humans, and consequently, Kalkman's estimate of the anesthetic effect on behavior might, if anything, be an underestimate.

Another study investigated whether hernia repair at age 3 years or less is associated with subsequent behavioral and/or developmental disorders.[9] A set of 383 Medicaid records listing procedure codes related to hernia repair was compared to a control set of 5,050 age- and sex-matched Medicaid records not listing these procedure codes. The behavioral outcome was defined as a diagnostic code for unspecified delay or behavioral disorder, mental retardation, autism, or language and speech disorder. If the behavioral outcome preceded the surgery, then the record was excluded. After controlling for age, sex, race, and the presence of confounding diagnoses at birth, procedure codes indicating the occurrence of hernia repair were more than twice as likely to be associated with the behavioral outcome codes as compared with when procedure codes for hernia repair were absent. The study design did not allow for assessing the type, frequency and duration of the anesthetic in either the hernia repair or the control group. Nor was it possible to exclude children in the control cohort who did not have an anesthetic for surgeries other than hernia repairs.

Recently, the academic performance of a national cohort of Danish 15–16-year-old children (n=2,689) who had undergone inguinal hernia repair between 1986 and 1990 at the age of 1 year or less was compared to a random sample of

14,575 age-matched controls.[10] When important confounders such as gender, birth weight, and parental age and education were controlled for, there was no evidence that the relatively brief (presumed to be 30–60 minutes) general anesthetic had affected academic achievement scores. All of the above confounders more strongly affected academic achievement than surgery plus anesthesia. In light of the fact that children in this study were younger than 12 months of age, they might be considered to have been more sensitive to the effects of anesthesia than the significantly older children of the other studies. However, these reassuring results cannot exclude deficits in more particular cognitive domains. It is understood that the effects of longer anesthetic durations were, likewise, not detectable with this study design. Furthermore, the anesthetic duration was short and, based on animal studies,[16] it might have been predicted that brief exposure to anesthesia might not be a problem.

Another human trial was designed to test if a causality exists between anesthesia at less than 3 years of age and cognitive performance in children.[11] Here, 1,143 pairs of monozygotic twins were investigated, and it was hypothesized that if anesthesia, and not the underlying disease, caused cognitive disabilities, then the exposed twin of a pair should have a higher incidence of underachievement than the unexposed twin of the pair. Most pairs in this study consisted of twins that were either both exposed or both not exposed to anesthesia. However 71 twin pairs (15 percent) were discordant (one twin exposed, the other not exposed to anesthesia). Anesthesia was administered mostly for surgical procedures. On a nationwide test given when the children were 12 years of age, exposed twins had similar achievement scores as unexposed twins. There was also a similar incidence of cognitive problems, as assessed by a teacher questionnaire. The study concluded that the combination of anesthesia and surgery was not the cause of the cognitive problems. If these results can be duplicated, then they would make a convincing argument that neither anesthesia nor surgery is a problem for the cognitive development of children.

In summary, the human literature is controversial as to whether or not anesthesia in infancy causes the most worrisome feature of developmental anesthetic neurotoxicity, namely, cognitive problems later in life. Furthermore, it is unclear as to what the period of vulnerability to anesthetic neurotoxicity is. We do not know if there is a safe anesthetic technique or duration. The specific cognitive deficit caused by anesthesia, if any, that may underlie outcomes such as learning disability has not been defined. None of the studies, alone or in combination, forms a basis for guiding our clinical practice.

Animal Studies

Animal models of anesthesia further our understanding of the phenomenology, pharmacology, and mechanisms of anesthesia-induced neurocognitive

dysfunction. Implicit in the concept of a mechanism is the concept of causality, and the mechanism of anesthesia-induced cognitive dysfunction—or decline, as the case may be—is a lot less clear than previously thought. There are three cellular phenomena that would qualify as a mediating mechanism of anesthesia-induced cognitive decline—neurodegeneration, synaptogenesis, and hippocampal neurogenesis.

Neurodegeneration

Overwhelming experimental evidence indicates that anesthesia causes neurodegeneration in a variety of animal species, including primates.[2–4] Yet, whether or not anesthesia-induced neurodegeneration also happens in humans is not nearly as important as whether or not anesthesia causes cognitive decline in humans. When anesthesia was first shown to cause both neurodegeneration and cognitive decline in rats, a causal link between the two outcomes must have appeared so plausible that it was not as rigorously scrutinized as other, less intuitive potential mechanisms may have been.

If months after anesthesia the brain of a formerly anesthetized human or animal were indistinguishable from a brain that was not exposed to anesthesia, then it would be difficult to argue that anesthesia caused the brain to become dysfunctional. Applied to neurodegeneration, this means that several months after anesthesia, causality between anesthesia-induced neurodegeneration and anesthesia-induced cognitive dysfunction would be difficult to accept unless neurodegeneration had somehow altered the brain of anesthetized animals. If the neurons destroyed by anesthesia resulted in a detectable gap in the brain, or if the neuronal number were different from unanesthetized animals, then a reasonable argument could be made that neurodegeneration qualifies as a potential mediating mechanism for the cognitive outcome.

The most compelling evidence that acute neurodegeneration causes lasting neuronal deletion comes from two rat studies.[17, 18] These results would be strengthened if it could be demonstrated that the total number of neurons (as opposed to the neuronal density[17, 18]) decreased long-term, but this research has yet to be performed. The results would be stronger yet if animals with a proven learning and memory deficit suffered neuronal deletion, and strongest, if those animals with the worst brain function were those with the greatest degree of neuronal deletion. Again, such experiments have not yet been carried out.

An important prediction required by the concept that anesthetic neurodegeneration is responsible for later cognitive dysfunction is that interventions preventing anesthesia-induced neurodegeneration also prevent anesthesia-induced long-term neurocognitive sequelae. Examples of such ameliorating

interventions include melatonin, lithium, dexmedetomidine, inhibitors of the p75 neurotrophin receptor, hypothermia, and bumetanide.[19–25] All of these agents or conditions have been shown to prevent anesthesia-induced neurodegeneration, by various suggested mechanisms that are not well understood. Bumetanide failed to rescue the functional deficit conferred by infantile anesthesia[25] and it is not known if any of the other interventions are more effective.

Synaptogenesis

If anesthesia-induced neurodegeneration does not cause anesthesia-induced neurocognitive decline, then what does? It is possible that the age-dependent anesthetic effects on synaptogenesis[22, 23, 26, 27] can have functional relevance independent of whether or not they cause neuronal apoptosis. In order to make this claim it would have to be demonstrated that these effects persist until the time of neurocognitive testing, and that an intervention that prevents the anesthetic effects on synaptogenesis also prevents the anesthetic effect on cognitive function.

Hippocampal Neurogenesis

Another possible mechanism is an anesthetic effect on postnatal hippocampal neurogenesis.[13, 14] Postnatal neurogenesis occurs only in two brain areas, one of which is the hippocampus. Inhibition of hippocampal neurogenesis is sufficient to impair learning and memory, in a manner similar to that effected by anesthesia.[28, 29] Of particular interest in this regard is the time course of the deficits. Neurogenesis is exquisitely sensitive to brain irradiation, and children who underwent brain irradiation developed progressive cognitive decline over a number of years.[30] The deficit caused by anesthesia is hippocampus-dependent and appears to progress.[1, 13, 14] Isoflurane has been shown to impair neurogenesis,[13, 14] and these effects do persist until the time of neurocognitive testing.[14] If anesthesia does indeed induce neurocognitive decline, then interventions that restore neurogenesis should rescue the behavioral phenotype.

Which Anesthetic Is Safest?

This question is beginning to be addressed in comparative toxicity studies in animals. Human studies have not addressed this issue, and given the controversy as to whether or not functional sequelae of anesthesia in infancy even exist in humans, the argument might be made that comparative studies are not yet indicated. In animal models, where anesthetic developmental neurotoxicity has been clearly demonstrated, these studies hold the caveat that anesthetic equipotency is vitally important for interpretation of comparative results. Minimal anesthetic concentration (MAC) is used to express anesthetic potency and anesthetic depth, but unlike with adult rodents, MAC in immature rodents is not a stable anesthetic concentration, but rather decreases steadily with

increasing duration of anesthesia.[31, 32] This makes comparative studies of volatile anesthetic agents a challenge. Moreover, it is not known if MAC also is unstable in human neonates and infants. The situation becomes even more complex when an inhaled agent is to be compared with an intravenous drug because of the daunting challenge to achieve constant plasma and brain concentrations of the drugs. Furthermore, it is not known if MAC for intravenous agents changes with time in immature animals.

Conclusion

Knowledge of developmental anesthetic neurotoxicity is rapidly accumulating, but clarity about the mechanisms or the significance of this phenomenon for human pediatric anesthesia is not emerging. A change in clinical anesthetic practice is *unwarranted* based on the currently available human literature, but also, such action probably never should be based solely on animal studies. More research is urgently needed in order to determine if anesthesia impairs brain function in humans, what the specific deficit is, and how it can be prevented and/or treated. This will require both human trials and good translational animal models.

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Questions

1. The question of whether anesthetic agents may cause harmful effects on the developing brains of infants and children:
    a. Has been answered by combined results of animal and human studies
    b. Is a current focus of the FDA
    c. Should be of little concern to parents because results from the animal studies are not relevant to humans

2. The existence of anesthesia-induced neurodegeneration in humans would be supported by demonstration of *(Choose one: a, a+b, a+c, b, b+c, c):*
    a. A permanent change in human brain function following anesthesia
    b. A causal connection between neurodegeneration and long-term brain dysfunction in animals
    c. Ketamine or isoflurane increasing the size of the hippocampus

3. The 2009 Minnesota study (Wilder, et al) of children less than 4 years old who were anesthetized for either surgical or diagnostic procedures showed that:
    a. Learning disabilities did not occur in children who were anesthetized after 4 years of age
    b. Cumulative anesthetic duration of greater than two hours was a risk factor for learning disability
    c. Learning disability was more likely in those who received even one anesthetic, and increased with more anesthetic administrations

4. Potential drawbacks of the Wilder et al study include all of the following <u>except</u>:
    a. Learning disability is a nonspecific outcome because several underlying pathologies may impair a child's ability to learn
    b. Retrospective studies like this one are inherently invalid
    c. Temporary learning disabilities that may have later improved or normalized would not be detected
    d. The majority of anesthetics were halothane, which has virtually disappeared from modern anesthetic practice

5. In a separate study, these researchers also showed that general anesthesia exposure for cesarean delivery, but not regional anesthesia, is associated with cognitive dysfunction later in life.
    a. True
    b. False

6. In an attempt to determine the period of vulnerability of the developing human brain to harmful effects of anesthesia in children undergoing similar urologic procedures, and assuming that the period of vulnerability ceases at the second year of life, it was found that *(Choose one: a, b, or a + b):*
    a. Children anesthetized under 2 years old tended to have an increased incidence of clinically deviant behavior, compared with children older than 2 years of age (the "controls")
    b. This difference was statistically significant only for children anesthetized at an age of less than six months

7. Neurobehavioral outcomes may require study duration of many years, making the length of time required for purely prospective studies prohibitive to meet the urgent questions that have been identified.
    a. True
    b. False

8. A recent study in Denmark of a large sample population of 15–16-year-old children who had general anesthetics for repair of an inguinal hernia at the age of 1 year or less demonstrated adverse effects on academic achievement compared to controls.
    a. True
    b. False

9. An investigation of monozygotic twins that focused on cases where one received an anesthetic, while the other did not, showed that:
    a. Achievement scores for the exposed twin were worse than those for the nonexposed twin
    b. Incidence of cognitive problems was the same for both the exposed and the nonexposed twin
    c. Because most twin pairs were either both exposed to anesthesia or not exposed to anesthesia, discordant pairs did not account for a statistically significant sample

10. Cellular phenomena that may qualify as a mediating mechanism of anesthesia-induced cognitive decline are *(Choose one: a, b, c, or all of the above):*
    a. Neurodegeneration
    b. Synaptogenesis
    c. Hippocampal neurogenesis

Evaluation of Module 4

As part of the CSA Educational Programs Division's ongoing efforts to offer continuing medical education, the following evaluation of this program is requested. This is a useful tool for the EPD in preparing future CME programs.

1. How well were the learning objectives of this program met?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

2. How relevant was the information in this program to your clinical practice?

Very Relevant	5	Above Average	4
Average	3	Below Average	2
Not Relevant	1		

3. How would you rate this program overall?

Excellent	5	Above Average	4
Average	3	Below Average	2
Poor	1		

4. Did you detect any commercial bias in this module? Yes No

Neurotoxicity of Anesthetic Agents in the Developing Brain

By Greg Stratmann, M.D., Ph.D.,
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