November 12, 2014

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Chair
Science Board to the FDA
c/o Martha Monser
Designated Federal Officer
Food and Drug Administration
10903 New Hampshire Avenue
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Dear Dr. Altman and Members of the Science Board:

The American Society of Anesthesiologists and the Society for Pediatric Anesthesia appreciate the opportunity to provide comments in advance of the Food and Drug Administration (FDA) Science Board meeting on the use and potential toxicity of anesthetics and sedation drugs in the pediatric population. We commend the FDA for holding this important meeting and welcome the opportunity to work with the Agency and stakeholders to further evaluate and mitigate the risks associated with the use of anesthetics and sedation drugs in the pediatric population. Below, we summarize the existing research, offer key points about the current evidence, and identify the major knowledge gaps.

Summary of existing research

Numerous preclinical and retrospective human data have questioned the safety of anesthetics on the developing human brain. Data supporting anesthetic neurotoxicity has been present in the literature for over ten years [1-3]. These data originate from mechanistic studies of fetal alcohol syndrome, an accepted, well-defined, and permanent neuro-toxidrome [4]. Exposure of developing rodents to ethanol, a known *N*-methyl-D-aspartate (NMDA) receptor antagonist and γ-aminobutyric acid (GABA) receptor agonist, during a critical period of development results in widespread neuroapoptosis [5]. Given that most anesthetic agents are believed to exert their effects via these receptors, the data were subsequently reproduced using established anesthetic agents and neurodegeneration was described using a wide variety of molecular and histological techniques [6]. These abnormalities, however, were without defined developmental significance until a landmark study reported long-term cognitive deficits in developing rodents exposed to a combination of midazolam, nitrous oxide, and isoflurane [7]. These data have subsequently been reproduced in a wide variety of species using many of the anesthetic agents in common clinical use [6].

Although criticism regarding dose, duration, degree of clinical monitoring, and generalizability of rodent data to humans remains [8,9], many of these concerns have been addressed in studies utilizing non-human primates. At present, seven published studies have reported neuroapoptosis in response to anesthetic exposure in young monkeys, all using monitoring standards similar to that of children undergoing operative procedures [10-16]. For example, one study reported long-term neurocognitive deficits in monkeys exposed to 24 hours of ketamine, effects that were persistent several years after exposure [13]. In addition to neuroapoptosis, several other potential mechanisms of injury have now been identified in animal models, including degeneration of oligodendrocytes (observed in rodents and primates), neuroinflammation, and impairment of both synaptogenesis and neurogenesis, suggesting that the spectrum of anesthetic neurotoxicity may be wider than previously assumed [10]. At the same time, there have been many attempts to prevent the histologic and developmental abnormalities induced by anesthetics, many of which have been successful in animal models. These protective techniques include, but are not limited to, hypothermia [17], melatonin [18], dexmedetomidine [19], lithium [20], erythropoietin [21], xenon [22,23], bumetanide [24], and environmental enrichment.

In contrast to the many preclinical studies in animals is the relative dearth of reports studying the neurodevelopmental effect of anesthetics in humans. The extant literature is based upon a limited number of epidemiological studies, all but one of which is retrospective [25-38]. These studies exhibit significant variability due to varying population selection, comparators, definition of anesthetic exposure, timing of anesthetic exposure, outcome measurements, and findings. Some of the retrospective studies encompassed a period during which halothane, a drug no longer used in the United States, was the primary anesthetic agent used and standard monitoring devices (such as the pulse oximeter) were not available [29,30,35,36,38]. All the retrospective studies involved analysis of databases composed of one of three primary sources: administrative data, single-center data, and data from a single geographical area (birth cohorts). While data derived from these datasets have been valuable, they also have significant weaknesses that temper conclusions [1,39]. While administrative data possess the strength of having a large number of patients available for study, such datasets have been criticized for lacking detailed information about the anesthetic and surgery and being unable to control for the effects of migration patterns, comorbidity, and educational experience [1,27,28,39]. While single center data often possess detailed medical information about the anesthetic, they are weakened by the presence of relatively small numbers as well as increased comorbidities confounding the results (referral bias) [26,31,34]. Birth cohorts have had the benefit of avoiding referral bias and providing detailed socioeconomic, educational, and medical information, but the specific constitution of such cohorts may not be generalizable to pediatric populations at large [29,30,32,33,35,36,38]. The major limitation of all retrospective data is the potential for confounding by the condition that necessitates surgery; i.e., children who receive therapeutic and diagnostic procedures are different from those who do not, and anesthesia exposure may simply serve as a marker for children at risk from their underlying medical issues. It is also not possible to mechanistically separate the potential effects of anesthesia from factors such as the physiological and psychological stresses of surgery, which may also affect child development.

With regard to outcome measurement, comprehensive neurocognitive tests are the gold standard for both determining the presence or absence of neurologic deficits as well as quantifying their magnitude. However, such examinations are often prohibitively expensive and their results have been reported in only a single study utilizing an existing birth cohort assembled to study child development in Australia [33]. The remaining studies utilized data from individual or group-administered tests of achievement (GTA), teacher/parent rating scales, and diagnostic codes. Unlike individual tests of achievement, GTAs are intended to serve as sensitive tests to screen large numbers of subjects but lack the specificity necessary for diagnostic precision. Diagnostic codes, in contrast, are biased in the opposite direction; they provide specific diagnostic information, but are frequently inaccurate, lack sensitivity, and may miss cognitive delay observed in non-clinical settings. Lastly, parent/teacher reports are overtly subjective and information on their sensitivity and specificity are completely lacking with respect to the outcomes of interest.

Despite these shortcomings, of the approximately dozen significant studies seeking the presence of anesthetic neurotoxicity in children, eight report an association between neurocognitive outcome and exposure to anesthetics. However, the degree of the purported association remains weak, with the majority reporting hazard ratios of approximately 2 or less. Hazard ratios of this magnitude are frequently secondary to factors other than the exposure (confounders) and are significantly weaker than associations that are widely accepted in the pediatric literature, such as prone sleeping and sudden infant death syndrome (hazard ratio 12.9) as well as salicylate use and Reye syndrome (hazard ratio 26) [1,39]. Nevertheless, even a modest effect, if real, could have profound public health consequences given the millions of anesthetics that are provided to children around the world each year. Several studies suggest that children receiving multiple exposures to anesthesia and surgery are at the greatest risk.

Three significant studies are ongoing and are likely to add significantly to the discussion and debate around this issue. The GAS study is the only funded randomized clinical trial, comparing spinal with general anesthesia in infants undergoing hernia repair. The study is well designed and carefully conducted, but is likely to be negative given that the anesthetic exposure is short and children with multiple exposures are not included. The PANDA study is a ambidirectional study also examining the effect of anesthetic exposure using a sibling comparator. It too, is likely to be negative for the same reasons. MASK is also an ambidirectional study but includes multiple exposures and examines children at two different ages in an effort to determine whether any observed effects persist into young adulthood. MASK also employs an operant test battery, developed by the FDA to assess neurotoxicity in primates, as a part of the comprehensive neurobehavioral assessment. Because exposure of young non-human primates has been shown by FDA investigators at the Nation Center for Toxicologic Research (NCTR) to produce long-term alterations in several measures

assessed by the operant test battery, this will allow direct comparison of primate findings with human data, thus assessing their translational significance for the first time.

Key points regarding current evidence

1. A large volume of accumulated data in rodents demonstrates that agents with actions on NMDA and GABA receptors, which include most of the anesthetics in current clinical use, produce profound apoptotic and other neurodegenerative changes in the developing brains of animals.
    a. These effects vary by dose, duration, and species.
    b. They are associated with long-term deficits in learning and behavior.
    c. They may be mitigated by a variety of pharmacological agents and by behavioral means such as enriching the animals' environment.
2. Eight studies in non-human primates appear to produce similar histologic effects and are also associated with adverse cognitive effects.
    a. Adverse cognitive effects of exposure in non-human primates have been demonstrated at the NCTR using the operant test battery, a tool that has not yet been used or validated by other investigators.
    b. Doses and durations of exposure appear to be clinically relevant.
3. "Safe" anesthetic agents have not been identified, although several studies have identified adjuncts that may reduce or eliminate the neuronal injury.
4. Human studies to date are confined to retrospective cohort studies of existing databases. Results are mixed, however there are consistencies across the strongest of these studies.
    a. Single brief exposures do not seem to produce an effect.
    b. Multiple exposures are consistently associated with adverse cognitive effects, even after analytic adjustment for co-morbidity.
    c. Those studies with the most robust outcome measures are uniformly positive. Those with weak or non-discriminative outcomes are typically negative.
    d. The effect size is small with hazards typically around 2. However, given the relatively high incidence of many of the outcomes examined (such as learning disabilities and attention-deficit hyperactivity disorder) in the general population, even these modest hazard ratios may imply profound effects on population health.
    e. Adverse effects on speech and language have been identified in 3 studies.
    f. A significant potential for confounding exists in all human studies.
        i. Effect of surgery is difficult to separate from anesthesia, although a single study suggests that surgery itself does not produce an effect.
        ii. Co-morbidity remains a potential confounder although several studies have used a variety of means to adjust for this, albeit imperfectly. Most studies adjusted for co-morbidity are positive.
5. Three comprehensive studies are currently underway using a prospective comprehensive battery of neurocognitive tests to measure effect.
    a. GAS: The GAS study is the only randomized clinical trial currently funded to study this problem. The study compares infants undergoing hernia repair either under spinal or general anesthesia with regard to performance on neurocognitive testing at age 5 years. Results will be reported in 2016 or 2017 depending on whether additional funding is secured.
    b. PANDA: An ambidirectional study of children exposed to general anesthesia for hernia repair matched to siblings not so exposed. PANDA also uses a prospectively administered comprehensive battery of neurocognitive tests. It will likely report results in 2016.
    c. MASK: The MASK study is also ambidirectional but differs in that it measures comprehensive outcomes at two separate ages, includes children with single and multiple exposures and includes the OTB as a means of translating existing non-human primate findings to children. The study is likely to report results in 2017.

Major Knowledge Gaps

The following is a general outline of what needs to be accomplished.

1. Establish or refute a causal link between anesthesia and adverse neurodevelopmental outcomes and use this information to improve care. Broadly speaking, the following tasks need to be accomplished:

a. Define injury phenotype in children (if it exists), which includes the question of whether there is a unique injury phenotype.
b. Continue to characterize the injury phenotype(s) and mechanism(s) in animal models.
c. Establish or refute links between injury phenotype(s) in children and animals.
    i. It is still possible that the associations between adverse outcomes and anesthesia/procedure exposure are not caused by anesthesia.
    ii. The links would be strengthened by randomized trials comparing different anesthetic regimens, but only if differences in outcomes are found (GAS, etc.), and results are likely highly dependent upon the study population, the experimental anesthetic regimen chosen, and the procedures included.
d. Evaluate effects of translational mitigation strategies (e.g., "safe" anesthetics, drugs, etc. that have been evaluated in animal models, preferably non-human primates) on phenotype in children.
    i. Positive findings would perhaps be the strongest possible evidence for causal links, especially because these studies could be performed in a wide variety of children and surgical procedures.

2. Focus on defining and improving overall outcomes after anesthesia/procedures, without exclusively concentrating on the potential role of anesthesia. Regardless of mechanism, multiple studies have now shown an association between anesthesia/procedures and adverse neurodevelopmental outcomes under some circumstances for some outcomes. Anesthesia is one potential mechanism to explain this apparent association; there are several others. Two questions arise:
    a. Under what circumstances is this association present (i.e., are there moderators of the association such as single vs. multiple exposures? Intensity and length of procedures? Patient-specific factors? etc.), and;
    b. Whether some event(s) occurring in the process of anesthesia/procedure is (are) causal of adverse outcomes, or whether the underlying conditions that necessitate surgery are themselves causal. Even if anesthesia is eventually exonerated, we still need to understand what is responsible for this apparent association, and what are moderating factors, so that mitigation strategies can be developed to alter those factors amenable to intervention.

   Answering these questions will likely require large multicenter prospective cohort studies that would allow for the prospective collection of patient- and procedure-specific information, as well as carefully-defined, patient-oriented outcomes. This cohort could potentially be used to address a variety of neurotoxilogic concerns in addition to that related to anesthetic exposure.

We appreciate your consideration of our comments and look forward to working with the FDA and stakeholders to ensure that anesthetic care provided to children is as safe as possible.

Respectfully yours,

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