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Anesthetic Effects on the Developing Brain

Insights from Epidemiology

Editor's Note: This is the third in a three-part series of Editorial Views regarding design of clinical trials to address the effect of anesthesia on the developing brain. Animal studies have suggested that anesthetic exposure could affect neurocognitive development, and there is an urgent need for clinical trials to determine whether this effect occurs in humans. This series presents the opinions of three world thought leaders in the possible designs of such clinical trials.

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MILLIONS of neonates, infants, and young children worldwide are exposed to anesthetic agents each year, and concerns raised by animal data regarding association of anesthesia and neurodegeneration represent an enormous potential burden to public health. The animal data reviewed in this and other journals is compelling and involves a variety of anesthetic agents, settings, and species, including most recently, primates.[1–4] Implicated are n-methyl-d-aspartate receptor antagonists and γ-amino-butyric acid agonists, including virtually all of the commonly used anesthetics for both children and adults. It is not yet clear whether the effects observed in animals are clinically relevant in humans. In his recent excellent review, Loepke *et al.* noted the numerous limitations of the few available clinical studies, none of which were specifically designed to examine anesthesia-induced neurotoxicity in the clinical setting.[5]

This is the third in a series of editorials in ANESTHESIOLOGY that considers potential study designs to answer the question of whether exposure of children to anesthesia causes detectable changes in their subsequent cognition or behavior. In the first, Sun proposed a study design that uses an historical cohort of otherwise healthy young children who have undergone a brief procedure before the age of 3 yr.[6] These children will be compared to unexposed siblings, with outcomes including a variety of prospectively measured neurodevelopmental outcomes at least 3 yr after exposure. In the second, Davidson *et al.* described a prospective trial currently underway that randomizes otherwise healthy infants undergoing inguinal herniorrhaphy to receive either a regional or general anesthetic.[7] The primary outcome is the intelligence quotient (IQ) measured at 5 yr of age, and the study is powered to detect a 5-point difference in IQ.

The approaches discussed in these editorials serve to illustrate the difficulty in determining what effect, if any, the implicated anesthetic agents may have on the neurocognitive development of children. The obstacles faced by each group in study design include: age (What is the age at risk?), duration of exposure (How much exposure is sufficient?), control of surgical procedure (Are we measuring the effects of surgery or anesthesia?), control of comorbid conditions (Does the study measure the impact of anesthesia exposure or the comorbidity that accompanies the need for surgery?), developmental endpoint (IQ, standardized test score, etc.), and duration of follow-up (How much time must be allowed for abnormalities in cognition to become manifest?). In this editorial, we describe two studies that use epidemiological methods that have proven in many settings to be powerful tools for exploring the relationship between exposure and disease and that may help overcome some of these obstacles. These studies will exploit high-quality population-based information, including the detailed medical and school records of large cohorts.

The first is an ongoing epidemiological study in Denmark comparing the educational achievement of all children operated before the age of 1 yr during the period 1977–1990, (n = 45,000+) to the background Danish population. The study is based on linkage of a series of available registries. The Danish civil registration system identifies individuals by unique social security numbers, which can be linked to a number of thematically organized population databases, called registers. Information from three registers will be used: (1) the Danish Demo-

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graphic Database, which includes information on parental identities, deaths, migrations, adoptions and education,[8] (2) the National Hospital Discharge Register, which includes information on overnight hospital stays for nonpsychiatric illnesses,[9] and (3) the Register of Compulsory School Completion Assessments and Test Scores, which is compiled from school reports by the Ministry of Education.[10] The primary outcome will be based on measures of academic achievement rather than IQ.

The second is a study being performed by investigators at Mayo Clinic that combines two unique resources. The first is a birth cohort (n = 5357) of children born in Rochester, Minnesota between 1976 and 1982. This cohort has been the subject of several publications examining the epidemiology of learning disabilities (LD) in this population. Through exhaustive review of a variety of medical and school records, LD was sought in each member of this cohort who enrolled in a Rochester elementary school. LD was defined using rigorous criteria based on individually administered test of achievement, including tests of IQ, as well as all medical, school, and neuropsychiatric testing records available for virtually every child in the cohort. The second unique resource is the Rochester Epidemiology Project, which is a medical records coding and linkage system that allows for the examination of all available medical records for Olmsted County residents (the county in which Rochester, Minnesota is located). In particular, the anesthesia records for all children undergoing surgery at one of the two surgical facilities in Olmsted County (Mayo Clinic and Olmsted Medical Center) are available for review. Thus, it will be possible in this study to compare the incidence of LD in those children in this cohort who were and were not exposed to anesthesia, while adjusting for other potentially relevant variables such as birth weight using available birth records.

Such epidemiologic approaches are ideal for the examination of rare problems/complications that occur remotely from the time of exposure because they produce information quickly and at a relatively low cost.[11] Examples of the power of epidemiologic studies to either establish or conclusively refute a critical association include studies that established the link between salicylates and Reye syndrome, defined the relationship between prone sleeping and sudden infant death syndrome, and conclusively refuted any link between thimerosal used in childhood vaccines and autism.[12–14] The problem faced in the study of anesthetic toxicity is similar to those cited in that it is rare (the risk of exposure is low) and the effects are subtle, are readily attributable to alternative causes (reductions in school performance), and are potentially delayed or not discernible for many years.

The use of the Mayo Clinic and Danish cohorts have several strengths; they are of unprecedented size, they are population-based, and the important covariates, such as age, gestational age, birth weight, parental age, and parental education, are available for practically all participants in the studies. Study designs that rely on a single procedure assume *a priori* that the children requiring the procedure are reflective of the population at large. This may or may not be the case. Large population studies such as those planned by the Danish group and the Mayo group involve a variety of procedures with a broad range of exposures and therefore have the advantage of examining the effect of multiple procedures and a range of durations of anesthetic exposure. The types of surgery examined will span from major neurosurgical and cardiac procedures, where the pathology necessitating operation may itself have long-term cognitive consequences, to surgery for pyloric stenosis and inguinal hernias, which should not have cognitive costs. Such a disease severity–cognitive cost dose–response curve could demonstrate the validity of the data, and a critical test will be if the "simplest operations," such as pyloric stenosis or inguinal hernias, will have educational achievement comparable to the background population. Exposures of varying duration also allow for the construction of a dose-effect curve that may also serve to lend credibility to the findings. Birth cohorts such as those used by the Mayo Clinic and Danish studies avoid the bias inherent in convenience samples derived from administrative databases, hospital records, etc. The retrospective nature of the study ensures that all relevant events have occurred at the time of the study, avoiding selection and observational bias. Retrospective studies typically suffer from a lack of the complete health information necessary to control for comorbidity. Such access is available to the Mayo Clinic and the Danish cohorts.

The choice of endpoint is critical. The animal data are, for the most part, confined to the pathologic effects, with only a few studies demonstrating negative effects on behavior and learning.[15–17] Translating the ability of a rodent to negotiate a water or radial arm maze into a human behavioral correlate is obviously difficult. Detailed neurocognitive testing is feasible in smaller studies, such as that of Sun and colleagues, but not in larger epidemiologic studies.

The Mayo Clinic investigators chose to examine LD as the endpoint (1) because it was already completely ascertained in this cohort on the basis of rigorous criteria based on achievement tests normed across a variety of populations and settings, (2) because it is clinically relevant, and (3) because it has a plausible link to the assessments of learning performed in the animal behavioral studies. LD as defined within the incidence studies performed using the Rochester birth cohort encompasses all of the criteria contained within specific domain testing as described in Sun's editorial,[6] although testing was selective (based on academic difficulties perceived by students, parents, or teachers) rather than

universal among cohort members. Access to the entire educational record of cohort members in the Mayo Clinic study will allow for the repeated measures of achievement that are typically required to determine the presence or absence of a persistent learning disability. Differences in IQ may be statistically significant but not clinically relevant because the standard error of measurements of IQ are highly variable over time, making single tests of IQ potentially misleading. These problems are most pronounced when determining IQ in young children.

The Danish investigators chose academic achievement tests as the endpoint rather than IQ. These measurement differences are not, however, likely to be a major factor in accounting for the differences in findings. The recent review by Naglieri and Bornstein found that the correlation between IQ and standardized achievement tests is quite high, averaging 0.70–0.74.[18] The correlation between IQ and national achievement tests, like the test used here, appear to be nearly this high.[19] The high correlation between the two types of assessments suggests that they would produce similar results. In any case, assessments of academic achievement have a pragmatic advantage over IQ measures because parents are likely to be more interested in how their child will do in school than in how they will do on a test of intelligence.

The studies from the Mayo Clinic and Danish Registry represent one approach that takes advantage of unique local resources. It is likely that other investigators will have access to other data resources that can also bring additional insights. Although potentially powerful, the proposed methodologies have inherent limitations, and multiple studies from all over the world will be needed to provide mutually supporting (or refuting) evidence. In particular, even if associations between anesthetic exposure and relevant neurocognitive outcomes are found, these study designs cannot exclude two possibilities: (1) that it is the surgical experience, and not anesthetic exposure, that is causative and (2) that the need for anesthesia is a marker for other factors (such as comorbid conditions) that are responsible for the neurocognitive changes.

The issues raised by the data derived from animal studies are compelling and represent the great challenge within the practice of pediatric anesthesiology. The challenge, however, extends well beyond pediatric anesthesiology because the implicated drugs are widely used in a variety of settings in infants and young children around the world. The enormous scope of this problem requires substantial resources and efforts by the international anesthesiology community, national governments, organizations including the American Society of Anesthesiologists, Association of Pediatric Anesthetists, Great Britain and Ireland, Federation of European Associations of Pediatric Anesthesia, the Society for Pediatric Anesthesia, American and International Associations/Academies of Pediatrics, and the World Health Organization. The role of the US Food and Drug Administration and similar governmental agencies around the world is central in coordinating research efforts and assembling sufficient funding to support a variety of projects over a period of many years. No data source is complete with regard to the critical elements necessary to address this question; therefore, cooperation amongst many institutions, investigators, and governments around the world will be needed to adequately address this critical issue.

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