

**FDA Advisory Committee Background Document to the
Anesthetic and Life Support Drugs Advisory
Committee (ALSDAC)
March 10, 2011**

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the issue of the neurotoxicity of anesthetic and sedative drugs to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

MEMORANDUM

DATE: February 8, 2011

FROM: Bob A. Rappaport, MD
Director
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Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)

RE: Overview of the March 10, 2011 ALSDAC Meeting to Discuss the
Neurotoxicity of Anesthetic and Sedative Drugs in Juvenile Animals

The majority of the anesthetic and sedative drugs used today were approved many years ago, prior to the current requirements for assessing the safety and efficacy of drug products in children. In 1999, after many years of wide use of these drugs in children the first of a series of reports of neuroapoptosis in juvenile rodents exposed to these agents began to appear in the literature; and in April of 2007, our FDA colleagues at the National Center for Toxicological Research (NCTR) published the first report of neurotoxicity in juvenile monkeys exposed to ketamine in vivo. In March of 2007, the Agency convened a meeting of the ALSDAC to discuss the growing body of knowledge about the neurotoxicity of anesthetic and sedative drugs in juvenile animals and the implications of these data for children exposed to those agents. The members of the committee called upon the medical and scientific communities to undertake the research necessary to fully understand the implications of the results of the animal studies for children exposed to anesthetics and sedative drugs when undergoing surgical, medical and diagnostic procedures. They also cautioned that the animal findings should not preclude the use of these drugs in children, except in the rare and unusual case of a purely elective procedure in a child under 3 years of age.

Over the past four years, numerous additional studies demonstrating neurotoxicity in juvenile animals exposed to anesthetics and sedatives have been published, and the

NCTR has just published the results of a study that found that a single 24-hr episode of ketamine anesthesia, occurring during a sensitive period of brain development, resulted in very long-lasting deficits in brain function in primates and, thus, provided proof-of-concept that general anesthesia during critical periods of brain development can result in subsequent functional deficits. However, in primate studies that demonstrated that shorter exposure to ketamine did not result in neuronal degeneration cognitive function was not evaluated. In addition, recent epidemiological studies have shown a correlation between the number of exposures to anesthesia during early childhood and an increased incidence of learning disabilities. Whereas a single anesthesia exposure before the age of four was not associated with learning disabilities, children exposed to two or more anesthesia exposures were at an increased risk for learning disabilities. Clearly, there are many factors related to anesthesia exposure in childhood that might explain the latter findings, but they are nevertheless an additional piece of a complex puzzle that is far from completion. At this time, we don't know whether the neurotoxicity seen in juvenile animals translates to the clinical setting; and if it does, we don't know whether the toxicity will be the same, similar or completely different from what we have seen in the animal studies. More importantly, we don't know whether any temporary or permanent clinical changes would result, even if there were histopathological changes occurring as a result of exposure to these drugs.

One thing is clear, however, anesthetizing and sedating children undergoing medical and surgical procedures is rarely optional. Clinicians only perform these procedures when they are necessary for the child's health and well-being. And the procedures cannot be undertaken without these drugs, as they are essential both for the child's safety and comfort. Pain itself can result in neuronal abnormalities and behavioral disorders in infants and young children who receive inadequate analgesia; and it would be unethical to allow a child to undergo a frightening medical procedure without adequate sedation. Additional studies are ongoing, and both the medical community and the FDA have made efforts to support and expand the research necessary to find the answers to the many questions that remain. Our SmartTots *Critical Path Initiative* project, a public-private partnership with the International Anesthesia Research Society, is one important effort aimed at coordinating the best minds on the necessary research and finding the funding to support that work.

There are two issues that require our immediate attention. The first is whether it is time to provide additional information regarding what is currently known from the nonclinical and clinical studies to practitioners and parents. And if additional information is appropriate, how do we communicate prudently so that medically indicated anesthesia continues to occur. The second equally important issue is the development of a research agenda, which will allow the medical community and organizations such as SmartTots to focus their efforts on studies that are most likely to be feasible and reliable providing the most valuable data in the shortest amount of time.

At this meeting of the ALSDAC we will be bringing together some of the leading experts working in this field, as well as prominent experts in pediatric anesthesia, neurology, behavioral development, epidemiology and pediatric ethics, in order to address these two

issues. We are not likely to fully understand the risk of exposure to anesthetics and sedatives in children for many years; but with the right goals, the scientific community working together may be able to shorten that time period considerably. In the meantime, children will still need to undergo surgical and medical procedures for which these drugs are essential to their safety and comfort, and we need to communicate what we do know as clearly and effectively as possible, without engendering undue concern. If a research agenda allows us to mitigate risks, or find novel drugs that are less likely to cause neurotoxicity, we will have made a major stride toward assuring the safety of anesthesia and sedation for children. We look forward to working with you during this important meeting of the ALSDAC and to what promises to be a most interesting discussion.

If you wish to read further about our initial advisory committee meeting on this subject in 2007, please follow this link: <http://www.fda.gov/ohrms/dockets/ac/07acdocs.htm>.

The Neurotoxicity of Anesthetic and Sedative Drugs in Juvenile Animals and the Implications for Pediatric Patients Undergoing Surgical, Medical or Diagnostic Procedures Requiring Exposure to These Agents

On March 29, 2007, the Food and Drug Administration (FDA) Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) met to discuss the growing body of animal data, which suggested that exposure to anesthetic agents during the period of rapid brain growth produced widespread neuronal apoptosis with long-term functional consequences (Food and Drug Administration, 2007). Prior to that meeting, the Agency published a review of the publically available literature to date and outlined the steps taken by the FDA's Center for Drug Evaluation and Research (CDER) and National Center for Toxicological Research (NCTR) to understand the impact of anesthetic drugs on the developing nervous system (Mellon, et al., 2007). Via both the review article and the meeting, the Agency invited the anesthesia community and the pharmaceutical industry to develop strategies to assess the impact of these drugs on the developing brain in order to provide appropriate guidance to clinicians and consumers regarding the clinical use of these drugs. Since that time period, tremendous efforts have been made to advance this field of research in both the nonclinical and clinical arenas.

Although there are extensive rodent data suggesting anesthesia-induced developmental neurotoxicity with long-term cognitive impairment, direct extrapolation of the published rodent neurodevelopmental toxicology data to humans is challenging. To bridge these initial findings, comprehensive nonhuman primate studies were conducted by the NCTR using the prototypical NMDA-receptor antagonist ketamine. These studies indicated that exposure of 5-day old rhesus monkeys to a dose of ketamine required to produce a surgical plane of anesthesia for 9 or 24 hours results in increased neuronal cell death (Slikker, Jr., et al., 2007; Zou, et al., 2009). Neuroapoptosis was also evident when rhesus monkeys were exposed to 24 hours of ketamine on gestation day 122, but not on postnatal day (PND) 35, or for 3 hours on PND 5 (Slikker, Jr., et al., 2007). In contrast to the rodent data, which reported widespread neuronal cell death following anesthesia administration (Ikonomidou, et al., 1999; Jevtovic-Todorovic, et al., 2003; Fredriksson, et al., 2004), studies with ketamine in the primate suggest that the most vulnerable region of the brain appears to be the frontal cortex, specifically layer II and III.

Dr. Olney and colleagues have also published results in nonhuman primates. These researchers have demonstrated that primates exposed on PND 6 for 5 hours to isoflurane at a dose that produced a surgical plane of anesthesia results in neuronal apoptosis with a slightly different neuroanatomical pattern of degeneration, noting specific vulnerability in the cerebral cortex (primary visual cortex layers II and V, and the temporal and somatosensory cortices) (Brambrink, et al., 2010a; Brambrink, et al., 2010b). Given the different pattern of apoptosis, it is plausible that different functional consequences may result for each of these drugs. These findings are consistent with reports in rodent models that demonstrated that NMDA antagonists and GABAergic drug products produce different patterns of neuronal cell death (Ikonomidou, et al., 2000; Fredriksson and Archer, 2004; Young, et al., 2005). It further suggests that an anesthetic regimen that

targets both NMDA-receptor antagonism and GABAergic augmentation would likely show greater and potentially more extensive histopathological damage as well as different functional consequences. These findings indicate that clinical trial design should take into consideration the mechanism of action of the drugs examined when determining the functional endpoints to be assessed.

Assessing for any functional consequences associated with the histopathological changes noted in the developing primate requires long-term studies involving repeated, comprehensive neurological evaluations. The FDA's NCTR initiated such studies using ketamine as a model NMDA-receptor antagonist and recently reported their findings. Paule et al. are evaluating rhesus monkeys that were exposed to a single, 24-hour, light surgical plane of anesthesia via ketamine on PND 5 or 6, using a comparator group that were not treated. Beginning at 7 months of age, animals were evaluated for their ability to complete cognitive function tasks as part of the NCTR Operant Test Battery (OTB). The OTB consists of a battery of tasks that evaluate short-term memory, attention, learning, time perception, motivation, and color and position discrimination. The OTB has been used in both primates and human children (Paule, 1990; Paule, et al., 1990), and performance on the test battery has been shown to correlate with IQ (Paule, et al., 1999). The results indicated that, compared to the control animals, the ketamine-treated animals had lower training scores that persisted for approximately 10 months suggesting a significant lag in performance of these specific tasks (Paule, et al., 2009; Paule, et al., 2011). The results of these studies support the conclusion that the ketamine-induced histopathological changes noted with the primate model translate into long-term, possibly permanent, cognitive deficits. Although it is not possible to directly correlate the long-term functional deficits noted in the primates with those reported using rodent models of learning and memory, the findings in primates reinforce the growing concern regarding the potential impact of anesthetics on the developing human brain.

Since the 2007 ALSDAC meeting, the number of publications examining the potential impact of anesthetics on the developing brain has increased substantially. Although it is not possible to review all of the findings in this forum, the collective nonclinical data raise several challenging questions summarized in the table below:

Table 1: Key Recent Nonclinical Findings Reported in Literature

Key Nonclinical Finding
1. Anesthesia exposure during early brain development results in apoptosis of immature oligodendrocytes, “oligoapoptosis” (Olney, et al., 2009; Brambrink, et al., 2010a).
2. Anesthesia exposure during early brain development results in alterations in synaptic architecture (Tan, et al., 2009; De Roo, et al., 2009; Briner, et al., 2010; Lunardi, et al., 2010).
3. Anesthesia exposure during early brain development results in decreased neurogenesis (Stefovska, et al., 2008; Stratmann, et al., 2009; Zhu, et al., 2010).
4. Exposure to anesthetic agents (inhaled isoflurane or spinal ketamine) during early brain development results in apoptosis of the dorsal horn of the spinal column; whereas, spinal morphine did not (Sanders, et al., 2008; Westin, et al., 2010; Walker, et al., 2010).
5. An analgesic dose of ketamine protects against pain-induced neuroapoptosis in the rat inflammatory pain model (Anand, et al., 2007; Rovnaghi, et al., 2008).
6. Several drugs have been reported to not result in increased neuroapoptosis: <ul style="list-style-type: none">• fentanyl (Rizzi, et al., 2008),• morphine (Black, et al., 2008), and• dexmedetomidine (Sanders, et al., 2009; Sanders, et al., 2010)
7. A growing number of nonclinical reports suggest that the following drugs or approaches could either ameliorate or prevent anesthesia-induced neuroapoptosis in vivo: <ul style="list-style-type: none">• β-estradiol (Bittigau, et al., 2002; Asimiadou, et al., 2005; Lu, et al., 2006),• erythropoietin (Dzietko, et al., 2004; Shang, et al., 2007),• melatonin (Yon, et al., 2006),• xenon (Ma, et al., 2007; Cattano, et al., 2008; Shu, et al., 2010),• L-carnitine (Zou, et al., 2008),• lithium (Xia, et al., 2008),• dexmedetomidine (Sanders, et al., 2009; Sanders, et al., 2010) and• hypothermia (Creeley and Olney, 2010)

Results of the above studies raise numerous questions that would require further nonclinical and clinical studies to address, such as:

1. Would the loss of immature oligodendrocytes impact long-term myelination in the brain?
2. Are changes in synaptic architecture more sensitive endpoints than neuronal apoptosis? What are the functional consequences of changes in neuronal architecture, if any? Are changes in synaptic architecture permanent or would adaptation occur more readily to such changes so that long-term functional consequences may not be of clinical concern?
3. As there are regions of the brain that undergo neurogenesis throughout life, such as the hippocampus, do these findings expand the currently perceived window of vulnerability?
4. Do the spinal cord findings have functional consequences and are there implications with respect to a potential reduction in dorsal horn neuronal reserve? What is the effect of spinal local anesthetic agents on dorsal horn neuronal development?
5. Do the findings of oligoapoptosis, decreased neurogenesis, altered synaptic architecture or degeneration of the spinal cord change the currently perceived window of vulnerability?
6. What is the impact of surgical stress/pain on anesthesia-induced neuroapoptosis? Will primate studies reproduce what has been reported using the rodent model? Will anesthetic doses show the same neuroprotective effect as reported for analgesic doses of ketamine or other agent?
7. Are there adequate data to suggest that some FDA-approved drug products such as fentanyl, morphine or dexmedetomidine may be better than others? Given the reports of diverse prenatal opioid neurodevelopmental effects reported (Handelmann and Dow-Edwards, 1985; Hammer, Jr., et al., 1989; Schrott, et al., 2008; Mei, et al., 2009), would the clinical use of more opioids only result in different safety concerns? As opioids are rarely used alone for anesthesia, what is the effect of an opioid combined with low doses (i.e., non-apoptotic doses) of other anesthetic drugs?
8. How can compounds suggested to ameliorate or block anesthesia-induced neurotoxicity be tested in humans in the absence of a monitorable endpoint? Would animal efficacy data impact the practice of medicine?

The finding that some drugs or interventions may reduce or eliminate anesthetic-induced apoptosis in animals raises challenging clinical questions, especially when there is no solid evidence to date that exposure to anesthetic drugs either causes neuronal apoptosis or results in adverse neurological consequences in pediatric patients. In addition to the clinical questions, there are also regulatory issues that would have to be addressed if such treatments were to be considered for approval by FDA, e.g., demonstration of safety and efficacy, determination of proper dosing.

SUMMARY OF CLINICAL DATA

As the animal evidence indicating some anesthetic agents induce neurocognitive deficits in the very young continues to accumulate, efforts have been made to assess what effects these agents may have in the pediatric patient population. A number of studies, including retrospective and prospective epidemiology studies and prospective clinical trials, have been conducted or are in progress. These are described below.

Hansen and colleagues (Hansen and Flick, 2009) at the Odense University Hospital, Denmark, and the Danish Registry Study Group are conducting a nationwide epidemiological study comparing the educational achievement of all children who have undergone a surgical procedure before one year of age to that of their counterparts in the general population. The focus for this case-control study is on the time period from 1977-1990, during which, more than 45,000 cases have been identified. The study will use social security numbers to collect data from three registries, one of which will be the Register of Compulsory School Completion Assessments and Test Scores, compiled from school reports by the Ministry of Education. Data from this registry will be used to assess the primary outcome: measures of academic achievement other than IQ. This study is ongoing at the present time.

At Columbia University, investigators have been involved in several epidemiological efforts assessing the risk of exposure to anesthetics with adverse developmental outcomes. Results from two of their studies have been published; a third study is in progress.

In 2009, DiMaggio et al. reported their retrospective cohort analysis of children who were enrolled in the New York State Medicaid program during the years 1999 through 2002 (DiMaggio, et al., 2009). In this study, they followed a birth cohort of 383 children who underwent inguinal hernia repair during the first three years of life, and compared them to a sample of 5050 children, frequency-matched on age, who had no history of hernia repair before age three. They were able to control for gender, age, race and certain birth-related conditions, e.g., low birth weight and perinatal hypoxia, which could confound the analysis. A diagnosis of behavioral and developmental disorder was predicated on the presence of a diagnostic code for unspecified delay or behavioral disorder, mental retardation, autism, and language or speech problems that did not precede the diagnostic code for the hernia repair. They found that children who

underwent hernia repair were more than twice as likely as children in the comparison group to be subsequently diagnosed with a developmental or behavioral disorder (adjusted hazard ratio 2.3; 95% confidence interval (CI): 1.3, 4.1).

In 2009, DiMaggio and colleagues reported on their analysis of a cohort of twins used to assess the association between exposure to a general anesthetic prior to three years of age and the risk of developmental and behavioral disorders (Dimaggio, et al., 2010). The New York State Medicaid program served as a database from which they constructed a retrospective cohort of 5,824 twin pairs born between 1999 and 2005. Exposure status was based on the presence of a surgical procedure record for each child less than three years of age. Developmental and behavioral outcomes were determined using screening diagnosis codes and following each subject from birth up to the time that either a diagnosis for developmental or behavioral disorder was made, or censoring due to study end or loss to follow up. They controlled for gender, complications at birth, and medical care utilization and performed both matched and unmatched analyses to determine relative risk estimates. Of the 5,824 pairs of twins they identified, 668 (6%) were exposed to anesthesia before the age of three years. A total of 2,168 (19%) children were diagnosed with developmental and behavioral disorders, the majority of which were classified as unspecified developmental delay. The incidence of developmental and behavioral disorders was 341 per 1000 anesthesia-exposed children and 157 per 1,000 for the unexposed children resulting in a crude relative risk of 2.5 (95% CI: 2.2, 2.7). Adjusting for birth complications and gender (there was no difference based on medical care utilization), the estimated relative risk of developmental and behavioral disorders was 2.2 (95% CI: 1.9, 2.4).

The research team at Columbia continues its investigations in this area with an ongoing study of mixed epidemiologic design (Sun, et al., 2008). The study uses a retrospective historical cohort of children who had exposure to an anesthetic before the age of three years and conducts a prospective follow-up for direct assessment of neurodevelopmental outcome. The outcome measures include global IQ and several targeted areas of neurocognitive function: attention, memory, behavior, and motor function. The comparison group will consist of developmental age-matched siblings without history of anesthesia exposure. The investigators will perform direct assessments of neurodevelopment at prespecified age ranges, at least three years following the anesthetic exposure, for both the index and the comparison groups. They will use validated, age-specific instruments selected based, in part, on the findings in the preclinical studies. They will also make assessments of social, behavioral, and family function in an effort to evaluate any impact these may have on the two cohorts.

In 2009, Wilder et al. at the Mayo Clinic reported the results of their population-based, retrospective, birth cohort study (Wilder, et al., 2009). The investigators utilized the extensive educational and medical records kept of all children born in Olmsted County, Minnesota. They examined the databases to identify children born in the county between 1976 and 1982 and who still resided there at five years of age. Among these, they identified children with learning disabilities and performed a Cox proportional hazards regression to calculate hazard ratios for anesthetic exposure as a predictor of the

disabilities. They were able to adjust for gestational age at birth, sex, and birth weight. A total of 593 of the 5,357 children in the cohort had undergone at least one general anesthetic before four years of age. Compared with those who never received anesthesia, children with a single exposure to anesthesia (n = 449) had no increased risk of learning disabilities (hazard ratio = 1.0; 95% CI: 0.79, 1.27). However, children who had undergone two anesthetics (n = 100) or more than two anesthetics (n = 44) were found to be at an increased risk for learning disabilities (hazard ratio = 1.59; 95% CI: 1.06, 2.37, and hazard ratio = 2.60; 95% CI: 1.60, 4.24, respectively). They also found that the risk for learning disabilities increased with longer cumulative exposures to anesthesia ($P < 0.02$).

The only prospective, randomized, controlled clinical trial being conducted to assess the effects of anesthetic agents on neurocognitive function involves an international collaboration of institutions from Australia, the United States, Canada, Italy, the United Kingdom, and the Netherlands (McCann, et al., 2010). The trial is an investigator-blinded, open-label investigation in which infants over 26 weeks gestational age and up to 60 weeks post-menstrual age presenting for unilateral or bilateral inguinal hernia repair (with or without circumcision) are randomized to either a general anesthetic with sevoflurane or a spinal anesthetic with bupivacaine. Subjects' neurocognitive development is evaluated at two years corrected age, using the Bayley Scales of Infant Development examination score, and then reassessed at five years corrected age, using the Wechsler Preschool and Primary Scale of Intelligence Full Scale IQ score. A total enrollment of 660 infants is planned for the study. Recruitment is anticipated to be complete by the end of 2010 or early 2011, with 2-year data available in 2013 and 5-year data available in 2016.

Each of the studies described above has limitations, whether it is in the interpretation of the findings due to potential confounding issues or in the sensitivity and duration of the neurocognitive testing. Nevertheless, these studies do and will provide some insight into impact that medical conditions requiring surgery, surgical interventions and anesthesia can have on the neurocognitive development of the youngest of patients. They also demonstrate the need for continuing animal studies to guide clinical investigations as well as the importance for conducting clinical studies in parallel with those in animals to resolve this issue more expeditiously. Clearly, many studies spanning many years will be required to fully elucidate the impact, if any, that anesthesia drug products have on neurocognitive development.

Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)

Discussion Points

March 10, 2011

1. Please discuss the nonclinical and clinical data presented to you, and whether or not it can be applied to the clinical setting.
2. Given the risks that may be associated with the delay of a surgical, medical or diagnostic procedure, or with the use of sub-optimal anesthetic or sedative doses or techniques, how should the medical community incorporate the current knowledge base into the practice of pediatric anesthesia?
3. Please discuss how to best communicate these findings to both health care practitioners and parents.
4. Please discuss what studies should be included in a research agenda that would complement the currently ongoing, nonclinical, clinical and epidemiological studies. Please consider each of the following issues as part of your discussion:
 - a. Are there additional nonclinical or clinical studies that would be useful to better evaluate the relationship between specific neurodevelopmental stages and the development of neurotoxicity associated with exposure to these drugs?
 - b. How important is it to conduct research on the commonly used combinations of anesthetic and sedative agents?
 - c. Are controlled, comparative studies critical to our understanding of the effects of sedative and anesthetic exposure in pediatric patients?
 - d. Is it important to conduct studies in all settings of use, including general anesthesia for surgery, procedural sedation, and prolonged ICU sedation?
 - e. What level of priority would you give to studies of drugs, procedures or techniques that might mitigate the risks associated with exposure to anesthetics and sedatives.

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**Food and Drug Administration
Center for Drug Evaluation and Research**

Doubletree/Hilton Hotel and Executive Meeting Center, 1750 Rockville Pike, Rockville, Maryland

Summary Minutes of the Anesthetic and Life Support Drugs Advisory Committee meeting on March 29, 2007.

On March 29 2007, the committee did the following: 1) received presentations regarding neurodegenerative findings in juvenile animals exposed to anesthetic drugs (e.g., ketamine); and 2) discussed the relevance of these findings to pediatric patients and provide guidance for future preclinical and clinical studies.

These summary minutes for the March 29, 2007 meeting of the Anesthetic and Life Support Drugs Advisory Committee were approved on Wednesday, April 4, 2007.

I certify that I attended the March 29, 2007 meeting of the Anesthetic and Life Support Drugs Advisory Committee and that these minutes accurately reflect what transpired.



Cathy A. Groupe Miller, M.P.H., R.N.
Designated Federal Official



Steven L. Shafer, M.D.
(Acting) Chair

The following are the final minutes for the March 29, 2007 Anesthetic and Life Support Drugs Advisory Committee meeting. A verbatim transcript will be available in approximately two weeks, and posted on the FDA website at <http://www.fda.gov/ohrms/dockets/ac/cder07.htm#AnestheticLifeSupport>.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Anesthetic and Life Support Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on March 29, 2007 at the Doubletree/Hilton Hotel and Executive Meeting Center, 1750 Rockville Pike, Rockville, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Steven L. Shafer, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Cathy Groupe, M.P.H. (Designated Federal Official). There were approximately 125 persons in attendance. There were nine speakers for the Open Public Hearing sessions.

Issue: The committee did the following: (1) Received presentations regarding neurodegenerative findings in juvenile animals exposed to anesthetic drugs (e.g., ketamine); and (2) Ddiscussed the relevance of these findings to pediatric patients and provide guidance for future preclinical and clinical studies.

Attendance:

Anesthetic and Life Support Drugs Advisory Committee Members Present (Voting):

James C. Eisenach, M.D.; Srinivasa N. Raja, M.D.; Sulpicio de Guzman Soriano, III, M.D.; Thomas K. Henthorn, M.D.; David J. Wlody, M.D. ; Kanwaljeet Anand, M.D.,D.Phil.

Special Government Employee Consultants (Voting):

Jayant K. Deshpande, M.D.; Vesna Jevtovic-Todorovic, M.D., Ph.D.; Jeffrey R. Kirsch, M.D.; Donald R. Mattison, M.D.; Steven L. Shafer, M.D.; Wayne R. Snodgrass, M.D., Ph.D.; L. Daniel Armstrong, M.D.; Julia E. Pollock, M.D.; Daniel Zelterman, Ph.D.; Athena F. Zuppa, M.D.

Anesthetic and Life Support Drugs Advisory Committee Members Present (Non-voting):

Charles H. McLeskey, M.D. (Industry Representative)

Participant Guest Speakers (Non-voting):

John W. Olney, M.D.

Anesthetic and Life Support Drugs Advisory Committee Members Not Present:

Robert H. Dworkin, Ph.D.; John T. Farrar, M.D.; David G. Nichols, M.D., M.B.A.;

FDA Participants:

Robert J. Meyer, M.D.; Bob A. Rappaport, M.D.; Arthur F. Simone, M.D., Ph.D.; R. Daniel Mellon, Ph.D.; William Slikker, Jr., Ph.D.

Designated Federal Official:

Cathy A. Groupe, M.P.H.

Open Public Hearing Speakers:

Peter Jackson; Roderic G. Eckenhoff, M.D.; Art Van Zee, M.D.; Huafeng Wei, M.D., Ph.D.; Lewis Coleman; Scott Kelley, M.D.; Reid Rubsamen, M.D.; Zhongcong Zie, M.D., Ph.D.; Gregory Crosby, M.D.

The agenda was as follows:

Call to Order and Introductions

Steven L. Shafer, M.D.
Acting Chair,
Anesthetic and Life Support Drugs Advisory Committee

Conflict of Interest Statement

LCDR Cathy Groupe, M.P.H.
Designated Federal Official
Anesthetic and Life Support Drugs Advisory Committee

PRESENTATIONS:

Introductory Remarks
Background

Bob A. Rappaport, M.D.
Director, Division of Anesthesia, Analgesia and
Rheumatology Products, FDA

Overview and Regulatory Issues
Regarding Anesthetic Agents for
Pediatric Patients

Arthur F. Simone, M.D., Ph.D.
Medical Officer, Division of Anesthesia, Analgesia and
Rheumatology Products, FDA

History of Preclinical Data:
Anesthetic-Induced
Neuroapoptosis

Dan Mellon, Ph.D.
Supervisor, Pharmacology and Toxicology, Division of
Anesthesia, Analgesia and Rheumatology Products, FDA

Preclinical Developmental
Neurotoxicity

John Olney, M.D.
Department of Psychiatry and Neuropathology
Washington University School of Medicine

Preclinical Model of
Anesthetic-Induced Neurotoxicity

Vesna Jevtovic-Todorovic, M.D., Ph.D.
Associate Professor of Anesthesiology and Neuroscience
University of Virginia Department of Anesthesiology

Break

Overview of FDA (CDER/NCTR)
Studies to Evaluate the Potential
For Anesthetic-Induced Neurotoxicity

William Slikker, Jr., Ph.D.
Director, Division of Neurotoxicology
National Center for Toxicological Research (NCTR), FDA

Clinical Perspective: Implications
Of Non-Clinical Findings

Sulpicio de Guzman Soriano III, M.D.
Senior Associate, Department of Anesthesia
Children's Hospital – Boston, Massachusetts

Clarifying Questions from the Committee

Lunch

Open Public Hearing

Break

Committee Discussion and Questions

Adjourn

Questions to the Committee:

1. Please discuss whether there are sufficient data to determine the applicability of the findings for anesthetics in nonclinical models to humans? If not, what other data would be needed?

Though not a voting question, the chair first identified the FDA backgrounder 'abstract' and asked the committee to comment in agreement or disagreement, with the statement "the lack of information to date precludes the ability to designate any one anesthetic agent or regimen as safer than any other" – All [16] voting panelists agreed with this statement. When addressing Question 1, [15] of the [16] committee participants supported the statement that there were not sufficient data to determine the applicability of the findings for anesthetics in nonclinical models to humans.

The Committee discussion identified the following important additional nonclinical data that should be obtained to further characterize the applicability of the findings in nonclinical models to humans:

- The window of vulnerability in humans and monkey's is not clearly delineated. Further delineation of this window of vulnerability in various species should be obtained. The suggestion was made that the use of microarray data to define the duration and timing of synaptogenesis should be considered.
- The animal studies should determine the concentration vs. time exposure profile for the drug tested rather than attempting to extrapolate exposure based on doses. Such data are critical to understand how the exposures relate to humans.
- Nonclinical studies must evaluate multiple inhaled anesthetics individually and not assume that one inhaled agent is representative of all inhaled agents. Specifically, studies with sevoflurane are necessary, as sevoflurane is far more commonly used than isoflurane in children. Studies of the influence of nitrous oxide and xenon are also important, as their effects on neuroapoptosis may differ from the halogenated inhaled anesthetics and from ketamine and other NMDA antagonists.
- Although some anesthetic drugs are used for short duration, nonclinical studies should also examine the effects of extended exposure to mimic the extended use of these products in critical care and examine the potential cumulative effects on brain development.
- Nonclinical models should employ a continuous intravenous infusion rather than repeated bolus SC or IM dosing to mimic the clinical use of IV agents.
- In terms of prioritization of drugs to be evaluated, consideration should be given to those drugs that are most commonly used in practice (i.e. propofol, sevoflurane) as well as looking to promising anesthetics that may be used in the future (i.e. xenon, dexmedetomidine) rather than focusing exclusively on the older drugs.
- Studies should be conducted to delineate the extent to which concomitant use of opioids can decrease the doses of other agents.
- Very little data exist on the effects of opioids on neuroapoptosis, Opioids should be characterized for their potential to produce long-term consequences. It was noted that there are animal data in literature that indicate that neonatal opioid exposure can result in tolerance to opioids in the adult.
- Several members of the Committee emphasized the need to keep ketamine on the list of drugs needing further data due to the increase in the use of this drug in the Emergency Room and continued use in the ICU and OR setting.
- The committee recommended characterization of potential gender differences in susceptibility to neurodegeneration.
- Further evaluation of additional age ranges, including the 'adult' brain (i.e., what are the effects of anesthetics on the elderly) should be completed. The committee noted that it is not known whether or not there is any mechanistic linkage between anesthetic risk to the developing brain and anesthetic risk to the elderly brain.
- There is a need to identify a clinical signal when giving these agents that could be used as a biomarker for the neuronal degeneration noted in the animals. Consideration to finding a biomarker in adults may guide further studies in children.
- The studies being conducted to identify an imaging technique to monitor this potential toxicity were strongly endorsed.
- Evaluation of the potential for anesthetic agent-induced neurodegeneration at the level of the spinal cord should be evaluated, particularly with respect to the local anesthetics and opioids administered neuraxially.
- The list of drugs that should be evaluated should be expanded to include: sevoflurane, xenon, barbiturates, propofol, etomidate, dexmedetomidine, fentanyl, remifentanyl, morphine and methadone. In addition, the magnesium should be added to the list of agents requiring further study because of the common use of high doses in parturients.
- Studies to determine the potential impact of concomitant therapies, for example, hypothermia, would be desirable.
- Studies should include assessments of the impact of surgical stimulation on the apoptotic effect of anesthetics in order to mimic the clinical use of these drugs. The existing studies have not been conducted in an animal model requiring

surgical intervention, and thus do not control for the influence of nociceptive input on the developing brain. It is possible that results would be different given the different activation state of the brain experiencing pain or surgical stress.

- Studies should characterize the impact of concomitant medications on the susceptibility to anesthesia-associated neurodegeneration (i.e., anticonvulsants) Focus should be on drugs that pediatric patients are given on a routine basis.
- The committee recognized the burden that these further studies present, and expressed hope that research competitively funded through the NIH could lead these efforts. The committee felt that this should be given high priority for research funding.

(See transcript for detailed discussion)

2. To what extent are the doses and durations of exposure to the anesthetics used in nonclinical studies relevant to the clinical use of these drugs?

The committee agreed that they had provided sufficient comments on this topic during previous discussions.

(See transcript for detailed discussion)

3. Combinations of anesthetic drug products are frequently used in the setting of pediatric anesthesia. Most of the preclinical data are derived from studies of drugs examined in isolation. Does the Committee have any advice on how FDA may best approach the issue of neurologic toxicity of combination use? (Please discuss)

The committee suggested the need for studies combining these drugs in a way that makes sense to clinical practice. They further discussed that there are some drugs that offer some degree of neuroprotection and the need to study these drugs concomitantly with other medications to determine if the net effect is less neurotoxicity. Committee members suggested the study of response surfaces, where each drug is studied alone and in combination with other drugs at varying concentrations rather than single points of maximum response, would provide more useful information. Additionally, nonclinical models should be studied at different ages, given that the stage of development could significantly alter the results obtained. However, the committee acknowledged that the choice of developmental period to study would be rather empiric given the data obtained to date. The committee noted that studies to determine the mechanism(s) mediating these responses may help direct studies to define the age-dependency of these findings. The committee felt that characterization of the mechanism mediating these effects would also be useful to direct studies of these drugs in combination. Once we have mechanism, we will be in a better position to determine dose response and susceptible time points.

The Agency requested clarification of the Committee recommendations on the approach to characterize the drug combination studies. Specifically, did the Committee agree that the approach taken to-date characterizing the effects of ketamine with respect to determining the effects of exposure duration, vulnerability period, and dose response relationships that may produce these responses versus doses that do not produce these responses is useful, and if the Committee agreed that characterization of isolated compounds prior to combinations is appropriate given the various differences in these compounds, prior to starting combination-drug studies. The Committee agreed that individual compounds must be studied in isolation first and then explored in combinations. The Committee further clarified the need to differentiate between 'exposure response' versus 'dose response' relationships. Specifically, the committee emphasized the need to measure concentration in the experimental animals. It noted that concentration, or a derivative measurement of drug exposure (e.g., AUC) is likely a better predictor of risk than is dose, and is a better metric than dose for comparison with human exposure.

(See transcript for detailed discussion)

4. Are there feasible clinical or other study designs to assess the potential neurological toxicities of exposing pediatric patients to anesthetic agents? (Please discuss)

Feasible clinical study designs and issues surround these studies discussed by the committee included:

- The Committee stated that the most convincing evidence would come from a randomized controlled trial. They referred to ongoing cohort studies showing a difference in outcomes (i.e., compare children undergoing medical treatment versus surgical intervention), and identified the GAS trial (Frank McGowan study) as one such study. The committee further discussed the design of this trial and how investigators would identify the appropriate level of equivalence in this trial (delta). The issue was raised whether IQ would be the only parameter that may be altered by anesthesia-induced neurodegeneration or if there were other parameters that should be monitored.
 - A second potential clinical study design could be to enroll neonatal ICU subpopulations (RSV, ARDS, pneumonia), who could be randomized to continuous infusion of midazolam or intermittent diazepam or morphine, for example. This would also require long-term developmental follow-up studies to determine if there were differences in the effects of these various treatment regimens.
 - A third possibility would be to compare the outcome of children of pregnant women who were treated with magnesium vs. those not treated with magnesium as a tocolytic agent. Alternately, a comparison of pregnant women given a general anesthetic vs. a neuraxial anesthetic for Cesarean section could be performed, although the nature of obstetric anesthesia practice might result in greater number of infants with perinatal hypoxia in the general anesthesia group.
 - The population of patients with in utero operations could be a feasible population to study, especially as inhaled anesthetics are used for prolonged periods at very high concentrations during these procedures. A study could look at development outcomes as a function of anesthetic regimen in this population.
 - Comments included the need for a validated battery of tests to be used as endpoints in these clinical studies given the lack of a clear phenotype to allow selection of an appropriate metric.
 - The committee identified the need for specific cognitive/behavioral outcome assessments for long-term strategies.
 - The committee urged consideration of brain development time. One possible study design is a retrospective chart review of children exposed to anesthetics at different ages, looking for evidence of neurological, developmental, or cognitive abnormalities 10-15 years post-operatively.
 - Prospectively, a non-invasive approach (e.g., MRI, fMRI, gene arrays etc) to assess neuroapoptosis in children in response to anesthetic exposure would be ideal. However, it was acknowledged that such methods have not been developed.
5. Given the risks associated with delay of surgical intervention or with the use of sub-optimal anesthesia techniques, how does one incorporate the current knowledge base into the practice of pediatric anesthesia?

The committee commented that the existing and well-understood risks of anesthesia (loss of airway control, hypoxia, and cardiovascular collapse) in conjunction with the risks of delaying surgery should continue to be the primary considerations in designing an anesthetic plan and determining the timing of surgical intervention. The committee did note that truly elective studies in the most vulnerable age group, children less than 6 months of age, should be delayed whenever possible. The committee further noted that almost no surgeries in very young children are truly elective. Therefore, delay of surgery would rarely be a viable option in this population.

(See transcript for detailed discussion)

The committee adjourned at approximately 4:15 P.M.