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

Quick Minutes
Anesthetic and Life Support Drugs Advisory Committee Meeting
March 29, 2007

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.

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Quick Minutes
Anesthetic and Life Support Drugs Advisory Committee Meeting
March 29, 2007

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: Anesthestic-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, dexametatomidine) 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, remifentanil, 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 Cesarian 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.