



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

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**MEMORANDUM**

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DATE: March 2, 2007

FROM: Bob A. Rappaport, MD  
Director  
Division of Anesthesia, Analgesia and Rheumatology Products  
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 29, 2007 ALSDAC Meeting to Discuss the  
Preclinical Neurotoxicity of Anesthetic Drug Products

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In 1999, Dr. Ikonomidou and colleagues published an article in Science describing apoptotic neurodegeneration in juvenile rats exposed to NMDA-receptor blocking agents. The potential importance of the findings described in this article led to numerous investigations and reports of similar findings in rodent models over the next few years. Reports by Drs. Jevtovic-Todorovic, Olney and others added to the concerns over potential clinical relevance by providing further evidence of neurotoxicity in the developing rodent brain associated with not only ketamine and other NMDA-receptor blocking agents, but the majority of general anesthetic and sedative drug products currently employed in pediatric anesthesia. Additional studies documented that in addition to histopathologic changes, subtle and prolonged behavioral changes could be seen in rodents exposed to these agents as juveniles.

While the academic community and the FDA acknowledged that there was insufficient human data to either support or refute the clinical relevance of these findings, it was clear that further investigation was essential. An Expert Working Group was established by the Agency soon thereafter to review the issue. A preliminary study performed by the Division of Applied Pharmacology Research confirmed the earlier reports of ketamine-induced apoptosis in 7-day-old rats. As a result, FDA's Center for Drug Evaluation and Research (CDER) and National Center for Toxicological Research (NCTR) developed a collaborative effort that provided further confirmation in rodent models. CDER and

NCTR, with the assistance of other government agencies, then initiated studies in juvenile monkeys to determine the susceptibility to ketamine-induced neurotoxicity in a primate model during the period of synaptogenesis. While these studies were being developed and performed, further details of the effects of anesthetic agents in rodent models continued to be reported by academic researchers. Recently, the preliminary results of FDA's non-human primate studies were submitted for publication. These early studies have demonstrated the presence of apoptotic neurodegeneration in juvenile monkeys which appears to be similar to that seen in the rodent studies.

These findings raise many concerning questions regarding the effects of exposure to general anesthetic and sedative drugs on the developing human brain. While we have no evidence to date that supports detrimental CNS effects in pediatric patients who have been exposed to these agents, the reality is that there have been no well-designed studies to look at the possibility of neurological toxicity after exposure to anesthesia in this patient population. Indeed, planning and performing these types of studies would involve enormous challenges in terms of design, assurance of validity, and ethical considerations. Nevertheless, the histologic evidence of neurotoxicity documented in the Agency's non-human primate studies mandates further investigation into the toxicity of these agents and to help inform their use in the clinical setting. It has also become essential that we clearly inform practitioners and parents on the growing body of evidence, with as rich and relevant a database as possible, so that they can make informed decisions regarding the use of these products in these most vulnerable of patients, our children.

During this meeting of the Anesthetic and Life Support Drugs Advisory Committee, the preclinical studies that have been undertaken to date will be described by the scientists who performed them. Additionally, our recently published review of the available data on this topic has been included in this background package in order to provide you with an overview of the topic and FDA's current perspective on this important issue. Following the presentations, you will be provided with an opportunity to discuss these findings, their implications for the practice of clinical pediatric anesthesia, and the need for (and potential designs of) further preclinical and clinical studies to assess anesthetic-induced neurotoxicity in the developing brain.

I would like to thank you in advance for your participation in this important discussion. Your comments and recommendations will provide a foundation for both the academic and regulatory communities to move forward in assessing the clinical implications of the available animal data, and for the development of appropriate recommendations to the clinical anesthesia community, and to patients and their families.

## **Bibliography**

Mellon, RD, Simon, AF, and Rappaport, BA. Use of Anesthetic Agents in Neonates and Young Children. *Anesthesia & Analgesia*. 2007; 104:509-520.

## Draft

Questions for discussion – March 29, 2007 Anesthetic and Life Support Drugs Advisory Committee meeting:

1. Are there sufficient data to determine whether the findings for ketamine and other anesthetics in nonclinical models are applicable to humans?  
If not, what other data would be needed for ketamine? For other anesthetics?
2. To what extent do the doses and durations of exposure to the anesthetics used in nonclinical studies inform the clinical use of these drugs?
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 potential neurologic toxicity of combination use?
4. Are there feasible study designs to assess the potential neurological toxicities of exposing pediatric patients to anesthetic agents?
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?