Review of FDA’s Activities

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Ikonomidou et al. (1999)

**Saline Treatment**

**MK-801 Treatment**

Ketamine (20 mg/kg, sc), injected every 90 minutes, 7 injections
Chronology of Events

- **1999** - *Ikonomidou et al* rat data with *ketamine*
- **2000** - FDA working group + Rapid Response Team
- **2001** - FDA nominates ketamine to the National Toxicology Program (NTP)
- **2003** - *Jevtovic-Todorovic et al*;
  - First published report to suggest that in rat model, *nitrous oxide*, *isoflurane* and *midazolam* can also produce neuroapoptosis leading to persistent memory/learning impairments
- **2004** – *Scallet et al* (CDER/NCTR) confirm and extend results of Ikonomidou paper
Wang et al. (2006)

Blockade of N-Methyl-d-Aspartate Receptors by Ketamine Produces Loss of Postnatal Day 3 Monkey Frontal Cortical Neurons in Culture


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- Report from NCTR and CDER.
- First in vitro primate (rhesus monkey) data demonstrating loss of neurons
2007

• DAARP briefed CDER Center Director leading to further action:
  – Publication of a summary paper in *Anesthesia & Analgesia*
  – Meeting of the Anesthetics and Life Support Advisory Committee
Use of Anesthetic Agents in Neonates and Young Children

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BACKGROUND: Some drugs used for sedation and anesthesia produce histopathologic central nervous system changes in juvenile animal models. These observations have raised concerns regarding the use of these drugs in pediatric patients. We summarized the findings in developing animals and describe the steps that the Food and Drug Administration (FDA) and others are taking to assess potential risks in pediatric patients. The FDA views this communication as opening a dialog with the anesthesia community to address this issue.

“It is also likely that new NMDA-antagonist and GABA-agonist drug products submitted to the FDA for approval for use in humans will have to undergo further nonclinical testing in juvenile animals before clinical trials in the vulnerable segment of the pediatric population can be contemplated”
Conclusions

– Animal studies suggest that neurodegeneration, with possible cognitive sequelae, is a potential long-term risk of anesthetics in neonatal and young pediatric patients.
– The existing nonclinical data implicate NMDA antagonists (ketamine, nitrous oxide, e.g.) and GABA agonists (midazolam, sevoflurane, e.g.)
– Lack of information precludes the ability to designate any one anesthetic agent or regimen as safer than any other.
– Ongoing studies (some CDER-funded) in juvenile animals should provide additional information regarding the risks
– CDER anticipates working with the anesthesia community and pharmaceutical industry to develop strategies for further assessing the safety of anesthetics in neonates and young children
Slikker et al. (2007)

Ketamine-Induced Neuronal Cell Death in the Perinatal Rhesus Monkey


- NCTR/CDER funded studies
- First *in vivo* nonhuman primate data
- Ketamine-induced neuronal cell death in the monkey appears both apoptotic and *necrotic* in nature (vs. primarily apoptotic in rodents)
ALSDAC Meeting
March 29, 2007

• Question: Are there sufficient data to apply the findings in animals to humans?
  – 14/15 responded “NO”

• Advisory Committee members agreed:
  – Elective surgery in children 3 years of age or younger should be performed only in special circumstances
  – the data are worrisome, more studies are needed, and that this is a high priority issue
  – clinical trials could be designed to address the problem
The Problem

- A safety signal has been identified in animals for many drugs used to provide sedation and anesthesia in children.

- There are no studies or data in humans that specifically examine whether pediatric exposure to anesthetics is associated with adverse neurological outcomes:
  - Long-term neurocognitive deficits
  - Long-term behavioral deficits
  - Structural brain changes

- In U.S., millions of children receive anesthesia annually.

- The need to provide sedation and anesthesia cannot be avoided in most situations.
The Food and Drug Administration Amendments Act of 2007:


(a) Establishment

The Secretary, acting through the Commissioner of Food and Drugs, may enter into collaborative agreements, to be known as Critical Path Public-Private Partnerships, with one or more eligible entities to implement the Critical Path Initiative of the Food and Drug Administration by developing innovative, collaborative projects in research, education, and outreach for the purpose of fostering medical product innovation, enabling the acceleration of medical product development, manufacturing, and translational therapeutics, and enhancing medical product safety.
The Pieces Come Together

- **Spring 2008:** Conceptualization of the framework for a public-private partnership (PPP)
- The newly conceptualized “SAFEKIDS” Initiative receives a much needed financial kick-start from OSE: $1.5M from CDER
- FDA immediately developed RFP to solicit proposals for the needed research and PPP development
FOR IMMEDIATE RELEASE
March 13, 2009

FDA Launches SAFEKIDS Initiative with Academic and Clinical Partners
Public-Private Partnership will assess safety of anesthetics and sedatives in young children

The U.S. Food and Drug Administration today announced agreements with five partners to study the effects of anesthetics and sedatives on the neurocognitive development of infants and young children.

The Safety of Key Inhaled and Intravenous Drugs in Pediatrics (SAFEKIDS) Initiative is a multi-year project designed to address major gaps in scientific information about the safe use of anesthetics and sedatives received by millions of children each year.

"The long-term benefits of these studies will inform risk-benefit decisions that both anesthesiologists and parents must make when considering the choice of anesthesia in pediatric patients," said FDA Acting Commissioner Frank M. Torti, M.D., M.P.H.

The FDA’s research partners in the SAFEKIDS Initiative include:

- The International Anesthesia Research Society (Cleveland, Ohio), which will be responsible for leading the administrative oversight and the overarching framework for the partnership.
- Children’s Hospital - Harvard University (Boston), which is conducting a long-term study of neurodevelopmental outcomes in pediatric patients administered regional or general anesthesia as neonates or infants.
- Arkansas Children’s Hospital Research Institute (Little Rock, Ark.), which will research the pharmacokinetics, pharmacodynamics, and neurotoxic effects of an anesthetic agent in infants undergoing various surgical procedures.
- Columbia University (New York), which will evaluate the effects of anesthetic exposure on neurocognitive, emotional and behavioral outcomes in pediatric patients.
- Mayo Clinic (Rochester, Minn.), which will study long-term cognitive development following exposure to general anesthetic agents during infancy.
Why Public-Private Partnerships?

• Any single party: limited resources (staff, funds, infrastructure, equipment…), time and expertise

  – Leverage resources and expertise among stakeholders to minimize costs (time and money)
  – Align missions toward mutually beneficial goals
  – Open new lines of communication among partners
  – Create value added for all stakeholders: optimizing economies of scale…advancing public health

• Whole = Greater than sum of individual parts/partners
Basic Funding Mechanisms

Whole is greater than sum of the parts…

Private Only

Individually or in groups launch project/s

Private

Launch PPPs with combination of public/private resources with mutually beneficial goals and objectives

Public

Public Only

FDA, NIH, CMS Other government

Data, new guidances, best practices, informed clinical decisions, evidence based medicine Effective & safe medical products to patients faster, and more efficiently
FDA/IARS Partnership
A Public Private Partnership
ALSDAC Meeting
March 10, 2011

• Update
  – on clinical and nonclinical data that had emerged since the 2007 advisory committee meeting
  – on epidemiological study and clinical trials that were underway at the time of the meeting
• Discuss whether it was time to provide additional information to parents and practitioners and, if so, in what manner
• Discuss development of a research agenda
CONSENSUS STATEMENT ON THE USE OF ANESTHETICS AND SEDATIVES IN CHILDREN
December 2012

Each year, millions of young children require surgery and other procedures for serious or life-threatening medical conditions or to improve their quality of life. Anesthetic and sedative drugs are widely used to help ensure the safety, health, and comfort of children undergoing these procedures. However, increasing evidence from research studies suggests the benefits of these agents should be considered in the context of their potential to cause harmful effects.

Previous research in young animals and children has raised concerns that exposure to commonly used anesthetics may produce neurobehavioral effects. However, these studies had limitations that prevent experts from drawing conclusions on whether the harmful effects were due to the anesthesia or to other factors, including surgery, hospitalization, or pre-existing conditions. Furthermore, the findings in children have been mixed, with some studies of infants and young children undergoing anesthesia or sedation finding long-term deficits in learning and behavior while others have not.

Clearly, additional research is urgently needed to identify any possible risks to young children. In the absence of conclusive evidence, it would be unethical to withhold sedation and anesthesia when necessary. Instead, healthcare providers should do the following:

- Discuss with parents and other caretakers the risks and benefits of procedures requiring anesthetics or sedatives, as well as the known health risks of not treating certain conditions.
- Stay informed of new developments in this area.
- Recognize that current anesthetics and sedatives are necessary for infants and children who require surgery or other painful and stressful procedures.

Endorsed by:

IARS
American Academy of Pediatrics
American Society of Anesthesiologists
Society for Pediatric Anesthesia
SNACC
European Society of Anesthesiology
ESA
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Scientific Advisory Board
2014

• Update
  – on clinical and nonclinical data that had emerged since the 2011 advisory committee meeting
  – on epidemiological study and clinical trials that are currently underway

• Discuss the applicability of the nonclinical data to humans

• Discuss potential components of a communication strategy

• Discuss the design of a proposed clinical study