SmartTots: what you should know right now

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Faculty Disclosures

- no commercial relationships to disclose
Objectives

upon completion of this lecture participants should be able to

- delineate basic science driving concern that sedatives may harm the developing brain
- describe recent epidemiologic evidence of potential postoperative neurotoxicity
- identify SmartTots and its role in addressing scientific and clinical gaps regarding the safe use of anesthetics in young children
animal studies w/anesthetics *unequivocally* demonstrate developmental neurotoxicity

some epidemiologic evidence links surgery in small children with later learning disabilities and developmental disorders
US – estimated 1M surgical anesthetics < 4
  ▶️ ↑↑↑ in the use of anesthesia* for children

AIDN (anesthetic–induced developmental neurotoxicity) is therefore a major health issue of concern to the public, government agencies and the medical community

* spectrum of sedation (imaging, procedures, ICU)
Doctor, is the anesthesia safe for my child?  

- assessment through institutional audits, closed claims, cardiac arrest registry \(^1\)
- major morbidity exceedingly rare
  - 1990’s → monitoring, ↓ halothane
- minor morbidity increasingly on our radar

\(^1\) Paterson N. *Pediatric Anesthesia* 21:848;2011
Leap of faith: complete anesthetic reversibility

- coma → assume brain emerges unscathed  **BUT**
- changes in gene & protein expression beyond emergence suggest the possibility of more durable effects, both positive and negative

1 Hudson AE. *Br J Anaesth* 107:30;2011
Anesthesia is complex and incompletely understood

- amnesia, unconsciousness & immobility from a heterogeneity of agents which are potent modulators of neuronal activity throughout CNS
- emerging evidence that this may result in both positive and negative non-anesthetic effects
Ligand-gated ion channels: molecular targets of anesthetic action

NMDA (excitatory)

GABA_A (inhibitory)

All anesthetics / sedatives either block NMDA &/or enhance GABA_A to a degree

CNS morphogenesis involves complex cellular processes (neurogenesis, differentiation, migration & synaptogenesis) – dependent on GABA and NMDA mediated neuronal activity.

In humans, rapid brain growth (RBG) or peak synaptogenesis (likely) 3rd trimester → 2–3 yrs; ~ in small rodents to first 2 weeks.
Apoptosis: a key to normal development

- natural and ongoing pruning process for redundant cells (up to 50–70% of neurons)
- “programmed” through a variety of stimuli with both physiologic and pathologic roles
- extrinsic (death–receptor mediated) & intrinsic (mitochondrial) pathways exist
Apoptosis
(Programmed Cell Death)

Normal cell → Cell shrinkage → Membrane Blebbing

Chromatin Condensation → Apoptotic Body Formation → Lysis of Apoptotic Bodies

Nuclear Collapse → Continued Blebbing
Blockade NMDA receptors and apoptotic degeneration in the developing brain

- NMDA antagonists, such as ketamine, trigger apoptosis in developing (P7 rat) brain
- similar response to GABA\textsubscript{A} agonists
- anesthetic “cocktail” ↑ apoptosis & correlation w/ persistent behavioral changes in animals

1 Ikonomidou et al. *Science* 283:70;1999
Caspase-3 activation in caudate nuclei P7 mice 5° after exposure

Young C et al. *Br Journ Pharm* 146:190;2005
Neuroapoptosis and AIDN

- mechanism unclear; untested hypothesis ↓ neural traffic → synaptic connection lost
  - but GABA_A is excitatory, not inhibitory in immature neurons
- ? ↑ NMDA receptor Ca^{2+} influx
- ? modulation of trophic factors such as BDNF±AKT

Young et al. *Cell Death and Differentiation* 2003

1 Ben–Ari. *Physiol Rev* 87:1215;2007
3 Lu. *Apoptosis* 11:1603;2006
apoptosis normal development of the CNS
neuroapoptosis ↑ by a variety of exposures including NMDA antagonists / GABA_A mimetics
we assume (but aren’t certain) this is bad (not just acceleration of normal process), although causality w/neurocognitive Δ’s not established
Researchers found common drugs used in pediatric surgery could harm children exposed to anesthesia for long periods... brain damage in infant rats...children may be at risk for brain damage when exposed to anesthesia for long periods...elective surgeries for infants and toddlers ...postponed long as possible...

“Doctor, will the anesthesia make my child stupid?”

“I’m right there in the room, and no one even acknowledges me.”
Difficulty extrapolating the animal data to humans (early criticisms) (I)

- morbidity lightly anesthetized neonates
  - ketamine ↓ pain–related cell death in rats
- humans are not rats! in terms of RBG→
  - much longer period relative to the exposure
  - ? different recovery profile & vulnerability
  - human equivalent to rat P7 really not well known; 32–36 wks vs. 17–20 wks PC

1 Anand KJ. Lancet 1:62;1987
3 Clancy B. Neurotoxicology 28:931;2007
animal studies are otherwise flawed \(^1\)
- physiological monitoring lacking
- malnutrition, glucose control
- temperature homeostasis
- dose/duration related effects
- the neuronal excitation ass’d w/surgery or pain (which is lacking) is “protective”

\(^1\) Anand KJ, Soriano SG. *Anesthesiology* 101:527;2004
..not adequate data to extrapolate the animal findings to humans...existing and well-understood risks of anesthesia continue to be the overwhelming considerations in designing an anesthetic, and the understood risks of delaying surgery are the primary reasons to determine the timing

Anesthesia and Life Support Drugs Advisory Committee
"The evidence for anesthetic-induced neurodegeneration in animal models is compelling... anecdotal data point toward the possibility of neurological impairment after surgery & anesthesia"

**“LIGHT” KETAMINE ANESTHESIA**

- P5 or 3rd trimester rhesus monkeys: neuroapoptosis @ 9 & 24° but not @ 3°
- P35 monkeys: no neuroapoptosis

* plasma levels 5–10 X human for similar anesthesia

OTB: persistent neurocognitive defects
short-term memory, attention, color & position discrimination and time perception

Paule MG et al. *Neurotoxicol Teratol*; 2011
neurons and oligodendrocytes affected with isoflurane 4x as potent as ketamine
implications for growth & process formation

P6 monkeys exposed to either “light” isoflurane or ketamine for 5^0 w/control physiologic parameters

• neurons *and* oligodendrocytes affected with isoflurane 4x as potent as ketamine
• implications for growth & process formation

Brambrink AM et al. ISS:A10;2010
2010: IARS* and FDA (PPP) sign a formal memorandum of understanding

- **SmartTots** (Strategies for Mitigating Anesthesia–Related neuroToxicity in Tots)
- collaborative effort to ensure the safety of anesthetic drugs in children
- multiple stakeholders: professional societies, academic research institutions, patient advocacy groups, industry and non-profit

* International Anesthesia Research Society
SmartTots has mission to coordinate research and place outcomes and practice guidelines in public domain.
precise elucidation of human synaptogenesis
better understanding of AIDN mechanism
potential co-therapies that ↓ toxicity

1 Lemkuil. *Anesthesiology* 114:49;2011 (RhoA ↑ w/actin depolymerization)
2 Creeley CE. *Anesth Analg* 110:442;2010 (dantrolene)
3 Inan. *Anesth Analg* 111:1400;2010 (lithium)
4 Sanders RD. *Anesthesiology* 110:1077;2009 (dexmedetomidine)
5 Yon JH. *Neurobiol Dis* 21:522; 2006 (melatonin)
6 Ma D. *Anesthesiology* 106:746;2007 (xenon)
The real question for SmartTots

WHAT ABOUT US??
Clinical studies of neurodevelopmental effects of anesthesia exposure during early childhood: evaluation of early “data”

- 5 retrospective studies published 2007–2010
- Precise information about exposure (age, agent, duration and dose) often lacking
- Outcome measures (learning disability, parent report of behavior) lack validation & specificity
  - Unlike fetal alcohol syndrome, manifestations of AIDN subtle & nebulous, with multiple confounders
Pathology
- genetic anomaly
- malformations
- prematurity
- sepsis

Surgery
- hormonal stress
- inflammation
- cardiorespiratory ↓ temperature

Anesthesia
- protective effects vs. toxic effects
- other "toxic" exposures, such as oxygen

# AIDN: what do we “know” so far?

<table>
<thead>
<tr>
<th>STUDY</th>
<th>RESULTS</th>
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<tbody>
<tr>
<td><strong>OLMSTEAD CTY BIRTH COHORT</strong> 1976–1982</td>
<td>GA during delivery – ND ¹&lt;br&gt;multiple GA &lt; 4 – ↑ LD ²</td>
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<tr>
<td>“Learning Disability” as diagnosis</td>
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<tr>
<td><strong>NY STATE MEDICAID</strong> (retrospective)</td>
<td>↑ diagnosis developmental or behavioral disorder (OR 2.3) ³</td>
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<td>383 IH repair &lt; 3 vs. 5050 matched controls</td>
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<td><strong>NETHERLANDS TWIN REGISTRY</strong></td>
<td>ND in teacher evaluations or educational achievement ⁴</td>
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<td>twins discordant surgery &lt; age 3</td>
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1 Sprung et al. *Anesthesiology* 111:302;2009  
2 Wilder et al. *Anesthesiology* 110:796;2009  
3 DiMaggio et al. *J Neurosurg Anesthesiol* 21:286;2009  
Early childhood exposure to anesthesia & risk of developmental disorders: sibling birth cohort

- retrospective NYS Medicaid 10,450 sibs born 1999–2005; 304 exposed to surgery < 3
- ↑ likelihood behavioral disorder in those who had surgery BUT
  - if “only” 1 procedure, essentially the same risk
  - twins discordant for surgery showed no difference

DiMaggio. Anesth Analg 2011;113:1143
Long-term differences in cognitive and language ability after exposure to surgery and anesthesia in infancy

- prospective cohort (1989–92) 2868 children
- longitudinal neuropsychological testing (Raine)

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<tr>
<th>NO DIFFERENCE</th>
<th>IMPAIRMENT (odds ratio)</th>
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<tr>
<td>cognitive function</td>
<td>receptive language (2.3)</td>
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<td>perceptual reasoning</td>
<td>expressive language (1.7)</td>
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<tr>
<td>fine motor skills</td>
<td>abstract reasoning (3.4)</td>
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<tr>
<td>gross motor skills</td>
<td></td>
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<tr>
<td>behavior</td>
<td></td>
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<tr>
<td>vocabulary</td>
<td></td>
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<tr>
<td>verbal ability</td>
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surgery < 3; testing at age 10 (CI >95%)

DiMaggio.IARS S336;May 2011
where is this going??
GAS (GA – Apnea/Apoptosis – Spinal) *
- international RCT (660) GA (sevo) vs. regional for IH
- evals at 2 & 5 years standardized neuropsych, IQ

PANDA (Ped Anesthesia NeuroDev Assessment) *
- sibling-matched cohort study (500 pairs) ASA I–II with single exposure GA for IH repair < 36 months
- extensive neuropsych testing between 8 & 15 years

* FDA/SmartTots funding
AIDN: current prospective studies (II)

- Danish Registry Study Group (Odense Univ)
  - nationwide epidemiologic study using educational achievement scores age 15–16
  - surgery < 1 vs. general population
  - retrospective data base (1986–1990): ND

1 Hansen TG et al. *Anesthesiology* 114:1076;2011
A dilemma for years to come

- isolation of potential neurotoxic effects related to anesthesia from other cofounders
- prospective studies underway but studies will take years and may be ultimately inconclusive
- single exposure (↓ power) vs. practical difficulty of prospective cohort w/↑ exposure
“generating definitive data about the effects of anesthetics on the developing brain will most likely take numerous animal and human studies spanning many years.. will pose enormous challenges to the medical and scientific community. It seems unlikely that any single individual or organization will be able to muster the resources to take on this project.”

What do I tell the parents??
while investigations are underway, harm to children remains unproved; animal studies ..must not prompt changes with undue consequences .. such as postponing necessary surgery
while there is no practical and safe alternative to general anesthesia for most procedures in children < 4, balanced techniques often allow for reduced exposure to those agents with potential harm.
OR DESK      444–6030
I am the wisest man alive, for I know one thing, and that is that I know nothing.

Socrates
469–399 BCE