

Neurotoxicity of anesthetics in infants: should we be worried? What do parents want to know?

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Background

For the past 20 years, members of the international pediatric anesthesia and critical care medicine community have refined techniques for delivering safe general anesthesia, analgesia and sedation to newborn and older infants, be they healthy with mild anomalies or critically ill. It has long been established that pain and the stress response, if unmitigated by anesthesia and analgesia, has deleterious effects in young infants, both short- and long-term.^{1,2,3} Contrasting with these known beneficial effects, over the past 10 years a body of work has emerged documenting neurotoxic effects in young animals after exposure to anesthetic agents on which we base many of our anesthetics in these infants. How should clinicians who provide anesthesia for newborns and young infants react to this information? Should we adjust our anesthetic technique? What do we tell parents who have heard about this issue in the lay press? What would we recommend for our own children or grandchildren?

History

Since 1999 when Ikonomidou et al. published a study linking the administration of ketamine to apoptotic neurodegeneration in the brains of young rats, many other investigators have published studies linking the administration of anesthetic agents to animals early in life to histological neurodegeneration. Agents shown to have this effect have included NMDA receptor antagonists such as ketamine and nitrous oxide and GABA receptor agonists such as midazolam, isoflurane, and propofol.^{4,5,6}

| Drug | GABA _A agonist | NMDA antagonist |
|-----------------|---------------------------|-----------------|
| Benzodiazepines | +++ | |
| Ketamine | + | +++ |
| Propofol | ++ | + |
| Nitrous oxide | + | +++ |
| Isoflurane | +++ | + |
| Sevoflurane | +++ | + |

These effects have been seen in multiple animal species including rats, mice, and more recently non-human primates.⁷ An excellent tabular summary of animal evidence published to date is available in a recent review by Loepke and Soriano.⁸ In addition to histological evidence of neurodegeneration, some studies have demonstrated long-lasting effects on “cognitive” function testing and learning behavior in such animals.^{9,10}

Multiple arguments have been made questioning the applicability of this animal evidence to the clinical care of human infants. Among these arguments are:

- 1) Correspondence of phenomena observed in animals to human effects
 - a. Window of vulnerability in animals vs. humans: are studies being done in the “sweet spot”?
 - b. Animal days/months vs. human regarding neurodevelopment¹¹
- 2) Questions about relevance of study design in animals to human clinical scenarios
 - a. Prolonged duration of administration
 - b. High concentrations of agents
 - c. Combinations of multiple agents rarely used for anesthesia
 - d. Focus on agents rarely used (nitrous oxide, isoflurane) rather than those more commonly used (sevoflurane, opioids)
 - e. Lack of control of ventilatory and metabolic parameters
 - f. Isolation from maternal care¹²
 - g. Lack of surgical stimulation
- 3) Degree of apoptosis seen after anesthetic exposure vs. “normal” developmental apoptosis

Although most ketamine studies have employed doses and/or durations of ketamine exposure far in excess of that used in humans (and rarely used in human infants), adverse effects have been seen with isoflurane using clinically relevant,⁹ and in some cases, sub-anesthetic doses.⁵

Some preliminary animal work has been done to explore agents that might protect against the observed neurodegeneration. Although some positive results have been seen, the medications used (e.g. carnitine, lithium) have been given in pharmacologic doses and are impractical for administration to infants.^{13,14} Any suggestion that such agents should be employed is premature, to say the least. Interestingly, dexmedetomidine has been shown to reduce neurocognitive impairment after neonatal isoflurane exposure in rats.¹⁵

Although the mechanism of injury is unclear and the relevance for human neonates and infants is not established, it is likely that if there is an effect it might be extremely difficult to detect, especially in the population of premature and/or critically ill infants who have many confounding conditions including but not limited to hypoglycemia, sepsis, intraventricular hemorrhage, and cardiopulmonary dysfunction. In addition, if there is vulnerability, the population of sick infants exposed to days, weeks and even months of sedation using benzodiazepines may be even more at risk.

Is there evidence for adverse effects in humans?

Epidemiologic approaches

Investigators at the Mayo Clinic have reported an association between repeated exposure to anesthetics (≥ 3 times) prior to 4 years of age and subsequent identification of learning disabilities diagnosed by school testing.¹⁶ Another epidemiologic behavioral survey found a trend toward more common behavioral disturbances in children exposed to anesthesia before the age of 2 years compared to those exposed first at older ages.¹⁷ Though disturbing, these retrospective epidemiologic approaches make it impossible to distinguish between effects of anesthesia,

reasons for surgery, underlying medical conditions, and adverse events which may have taken place during the perioperative period,¹⁸ all of which are difficult to discern from this “30000 foot” view.

After the publication of a review of the pre-clinical evidence and the concern for relevance to human infant,¹⁹ the FDA convened a meeting of the Anesthesia and Life-Support Advisory Committee. The conclusion of that meeting was “there are not adequate data to extrapolate the animal findings to humans.”²⁰ Subsequently the FDA established the SAFEKIDS initiative,²¹ a public-private partnership to support further investigation into what Loeper et al. have called “the preeminent controversy in pediatric anesthesiology.”²² This collaborative of several academic institutions as well as the IARS has provided start-up funding for epidemiologic studies as described above as well as to one prospective study of spinal versus general anesthesia for hernia repair in infants <6 months of age (both full-term and premature) with subsequent neurocognitive testing (the GAS study),²³ as well as a more contemporaneous study of sibling pairs one of whom had anesthesia at less than 3 years of age and the other did not with neurocognitive and behavioral testing of both siblings (PANDAS).²⁴

At the present time, it is clear that there are no established non-invasive methods of identifying any injury that may occur after anesthesia (e.g. MRI, PET, SPECT). Established biomarkers of brain injury, (e.g. neuron specific enolase or S-100b), have been used in other clinical scenarios, such as stroke. These biomarkers are probably too insensitive to detect the small and regional increase in apoptosis that has been observed in experimental animals.

Parents may be aware of these concerns because of publicity in the lay press²⁵ and other media in response to publications in the medical literature such as the paper from the Mayo Clinic (13). Anesthesiologists should be prepared to answer questions from families about this issue. These may include:

1. Will anesthesia cause brain damage?
2. Can you give anesthetics that are less likely to cause brain damage?
3. Should my child’s surgery be postponed?
4. If surgery is postponed, when is it safe for my child’s brain to reschedule?

There are many unknowns. If these effects can be shown to occur in human infants, is there one anesthetic gas that has less effect than another? There is some suggestion that sevoflurane may cause less damage in animals than isoflurane.²⁶ Should we design “balanced anesthetics” with heavier reliance on opioids with minimization of the use of potent vapor and/or benzodiazepine for amnesia? What about Xenon? Is it the magic bullet?²⁷ It is premature to answer these questions; it is probably premature to ask them.

The benefits of affording our patients safe anesthesia care which provides analgesia and amnesia are well known. In 2010, we may conclude, as the FDA committee did in 2007 “the existing and well-understood risks of anesthesia continue to be the overwhelming considerations in designing an anesthetic, and the understood risks of delaying the surgery are the primary reasons to determine the timing”.¹⁷

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