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The new FDA drug safety communication on the use of general anesthetics in young children: what should we make of it?

Editorial

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Recently, the US Food and Drug Administration (FDA) issued a warning related to the use of general anesthetics in children younger than 3 years of age and in women during their third trimester of pregnancy (http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm). What is the available evidence behind this drug safety communication and, most importantly, how should it influence our daily practice?

The pediatric anesthesia community is already well aware of this issue. Indeed, the plausible association between the perioperative period and subsequently impaired neurocognitive or behavioural outcome in young children had been suggested decades ago (1). Over the last decade, high quality experimental and clinical research has resulted in hundreds of publications and has considerably advanced our knowledge and understanding in this field.

There is now strong evidence that most general anesthetics can modulate brain development in all animal models studied; ranging from the nematode to the non human primate (2). The degree and nature of morphologic and functional change is dose dependent and probably greater in younger animals, with effects varying from the subtle to the profound. There is also increasing evidence that young animals with a long exposure to anaesthesia have a variety of neurobehavioural problems when they are older. However, even though we are beginning to unpick some of the mechanisms that underlie these effects, we still haven't directly linked morphologic changes to neurobehavioural changes. From the animal studies it is reasonable to conclude that if you give enough anaesthetic for long enough there will be some morphologic changes in humans, but whether or not that would translate to neurodevelopmental changes in humans is unknown and cannot be determined solely by further animal studies.

Identifying any causal effect in humans is not easy. Nevertheless several large human studies have been published. Very large population based cohort studies have consistently found evidence for a very small association between anesthesia exposure and neurodevelopmental outcomes (3-5). Potential confounding makes it impossible to infer that this relationship is causal. Interestingly several studies did not see a stronger association in those exposed at a younger age compared to an older age (3); increasingly the likelihood that the association is indeed unlikely to be related to the changes seen in animal studies. Importantly, PANDA, the most robust cohort study available so far, found no evidence for any association with detailed psychometric assessment (6). Similarly the GAS

trial found no evidence for a difference between general or awake-regional anesthesia (although the children are yet to be fully assessed at an older age) (7). The majority of children in all these studies had less than 2 hours of anesthesia, and given the effect in animal studies is duration dependent, it is perhaps not surprising that no evidence for a causal relationship has yet emerged in human studies. From the animal data and the human data it is now reasonable to conclude that less than 2 hours of anesthesia does not directly cause any detectable neurodevelopmental change in the majority of humans. It is possible that some sub groups may still be at risk but there is no strong evidence to support this speculation.

There are a few cohort studies looking at outcomes after longer exposures in infant humans. These are mostly published outside the anesthesia journals (8). They show strong evidence for an association between major surgery in neonates and poor neurodevelopmental outcome. These children have numerous substantial confounding factors that could explain the association. Indeed many of these papers don't even mention anesthesia as a possible causative factor. In human studies we simply don't know if long exposure to anaesthesia in infancy is a problem or not. Well designed trials are needed but these trials will not be quick, cheap or easy.

So what do we make of the FDA warning? Given the wealth of animal data the FDA was obliged to make some statement. We think that most of the warning is sensible, evidence based and balanced. The warning alerts the public to the issue, but also provides some reassurance. The second sentence says "relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning". The first sentence is perhaps the one which will cause most alarm amongst our profession: "that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains". Yes that's true, it *may* affect the brain. There *may* also be long term effects but the only clinical evidence we have to suggest this is weak and indirect.

The evidence for choosing 3 years of age as a "cut off" is extraordinarily weak. Choosing an age makes the warning easier for clinicians to act on, but it is very difficult to understand why the FDA chose this age. Translating animal developmental age to human developmental ages is an imprecise science. Younger animals do seem to have greater effects but even within the limitations of translation some effects are still seen in relatively older animals (9). The human studies do not support there being an upper age where there is no longer an association. Similarly the evidence

concerning the impact of multiple versus single exposure is limited in animal studies and weak in human studies. The stronger association seen with multiple exposures in some studies may simply be explained by confounding. In later paragraphs the warning goes to some length to explain the limitations of our knowledge and the weak nature of the evidence, but we suspect many readers of the warning will only remember the first sentence.

The warning does not suggest anaesthesia is avoided but rather suggests "Health care professionals should balance the benefits of appropriate anesthesia in young children and pregnant women against the potential risks, especially for procedures that may last longer than 3 hours or if multiple procedures are required in children under 3 years". Determining this balance will not be difficult for the vast majority of cases. We rarely have 3 hour cases in pregnant women or young children that can be delayed or performed without appropriate anaesthesia, without adding material and substantial risk. There will however be some grey areas. Can some craniofacial cases be delayed? Can we perform a laparotomy in a neonate with just high dose opioids? In these cases a more careful evaluation of risk/benefit is indeed warranted.

Medicine is all about making decisions that are driven by balancing our mechanistic understanding of the biology underlying the disease or therapy, with empiric population based evidence and what the patient wants. In some cases the empiric evidence and/or mechanistic understanding is strong enough to make general guidelines and recommendations; however when it comes to the effect of anaesthesia on neurodevelopment we are certainly not there yet. The FDA needed to issue a warning and was wise to emphasize the uncertainty of our knowledge. What you do with the FDA warning will depend on whether you look at the evidence in its entirely or just read the first sentence. We recommend you do the former.

Disclosures

A Davidson is Editor-in-chief for this journal and L Vutskits is a section editor. Both A Davidson and L Vutskits have published research in this area and have research grants to research this area.

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