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Anaesthesia-induced developmental neurotoxicity: reality or fiction?

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As animal evidence continues to mount, we face a real dilemma regarding the clinical relevance of anaesthesia-induced developmental neurotoxicity. In December 2016, the US Food and Drug Administration (FDA) issued an announcement stating that commonly used general anaesthetics could potentially be detrimental to very young and rapidly developing brains. This announcement was based on an extensive body of animal research.[1–24] Now we must grapple with the FDA's official recommendation that potential risks should be balanced with the benefits of appropriate anaesthesia in young children. More importantly, as we deal with the official expectation that potential risks should be discussed with families and heath-care providers, we are reminded how crucial it is to deepen our understanding of the pertinent mechanisms and potential long-lasting behavioural outcomes relating to the exposure of the young brain to anaesthesia.

Although initial studies were focused on different rodent models of anaesthesia-induced developmental neurotoxicity, certain limitations were undeniable, thus affecting their translational value. For example, rodent brain development is substantially shorter than human brain development (weeks as opposed to years).[25] The majority of rodent models used exposures considered to be lengthy (4–6 h).[1–4 6–8 11] Most importantly, the

neuronal networks in rodents are substantially less complex compared with those of primates.

This creates a dilemma for practising clinicians: how relevant are these findings to the daily clinical care of children? Are the potentially detrimental histopathological, behavioural, and cognitive outcomes in humans verifiable beyond reasonable doubt? What kind of ethically acceptable studies could be conducted to get us closer to the truth? Can early exposure to anaesthesia and sedatives be linked to poor cognitive outcomes later in life in view of the myriad of socioeconomic and emotional factors throughout life that can shape behavioural and cognitive development? Causation would be perhaps impossible to prove, but could we even attempt to prove association? As we struggle with the possibility that these questions are perhaps not answerable in humans, we simultaneously focus our attention on the rapidly growing body of work being done with non-human primates. Given that their brain development is very similar in timing, duration, and complexity to the development of the human brain,[20] studies with non-human primates may be the closest we can get to understanding the true implications of early exposure to anaesthesia in humans.

In this issue of the *British Journal of Anaesthesia*, Dr Noguchi and colleagues[26] provide an important addition to a growing body of non-human primate studies by focusing on the issue of the clinically relevant duration of anaesthesia exposure. Previous work[16–24] has focused on examining outcomes of anesthesia exposure of 5–24 h, which were often considered to be of limited clinical relevance because clinical exposures are commonly shorter. This prompted Noguchi and colleagues[26] to focus on a 3 h anaesthesia exposure, which is particularly timely considering that the recently issued FDA warning focused on exposures of 3 h or longer. The authors also reviewed clinical data from two US children's hospitals to show that ~30% of infants and 10% of children <3 yr of age are exposed to general anaesthesia lasting 3 h or longer. They remind us that this translates into several hundred thousand young children undergoing general anaesthesia every year in the USA alone.

In a systematic morphological study, they examined the neurotoxic potential of the inhaled anaesthetic isoflurane administered for 3 h to 6-day-old infant rhesus macaques. Infant monkeys were intubated and mechanically ventilated during anaesthesia, and the inhaled isoflurane concentration was tightly controlled to maintain a surgical plane of anaesthesia while physiological homeostasis was closely monitored. The histopathological findings were compared with those from animals in a control group that were not anaesthetized but underwent a mock anaesthesia procedure, such as 'insertion of an i.v. catheter, physiological measurements, and a period of handling to simulate the environment of the experimental animals'. Using activated caspase-3 staining, a well-established method for detecting neurones and glia undergoing apoptotic cell death, they reported that a 3 h exposure to isoflurane significantly increased both neuronal and oligodendroglial apoptosis by four-fold compared with controls. Although the apoptosis in oligodendrocytes was evenly distributed throughout the white matter, neuronal apoptosis was more brain region specific, including all regions of the cerebral cortex, caudate nucleus, putamen, and thalamus. Given that a substantial number of surgical procedures in children last 3 h or longer, they concluded that this protocol is relevant to clinical medicine. Based on their previous findings with longer exposure to isoflurane (5 h) they concluded that there is a direct correlation between the duration of exposure and degree of apoptotic activation. Although a similar pattern of widespread apoptotic neurodegeneration was noted, the intensity of apoptosis after a 5 h exposure was higher compared with the 3 h exposure. Moreover, this study solidifies earlier observations that monitoring and maintenance of proper homeostasis during general anaesthesia has no impact on the severity of anaesthesia-induced neuronal damage when exposure occurs at the peak of brain development.

Oligodendrocytes are responsible for myelination of axons and, as such, are crucially important for normal neuronal development and function. Their vulnerability to anaesthesia-induced apoptotic degeneration coincides with the critical time of myelination, thus suggesting that anaesthesia could be causing damage to developing neurons not only by triggering their apoptotic death but also by disturbing timely axonal myelination.

Although the focus of the present study was not on long-term behavioural and cognitive sequelae, recent evidence suggests that a single 5 h exposure to isoflurane, unlike multiple exposures (a total of three times), of infant rhesus macaques did not result in motor reflex deficits at 1 month of age and did not lead to an increased anxiety response to a new social environment.[24] Furthermore, unlike repeated exposures, a single exposure of 5 h did not result in affiliative or appeasement behaviour at 12 months of age. These early repeated exposures to isoflurane result in long-lasting and detrimental effects on socioemotional development.[24] The relevance of a single 3 h exposure to long-term behavioural outcomes remains to be examined using a wide array of sensitive behavioural approaches. Elsewhere in this issue of the *Bristish Journal of Anaesthesia*, Alvarado and colleagues[27] show that repeated exposures to sevoflurane also lead to neurocognitive deficits in macaques.

With such a large body of animal evidence, including this recent study, the question of the clinical relevance of such convincing scientific evidence gathered from several mammalian species of different phylogenic complexity remains. Is it possible that findings reported in >300 original manuscripts by numerous groups throughout the last 25 yr are not applicable to human children? The scientific community has spent a great deal of time, resources, and intellectual acumen not only on describing and understanding the phenomenon of anaesthesia-induced developmental neurotoxicity but, rightfully so, on challenging and scrutinizing every aspect of it. In the true spirit of scientific rigour and inquiry, we search for weaknesses, shortcomings, and logical explanations for the observed phenomena.

As the medical community is faced with the warning issued by the FDA, we continue to struggle with the best and most responsible course of action. As we move from doubting the relevance of an extensive body of research to perhaps accepting that our clinically used general anaesthetics might not be as innocuous as we once believed, we are reminded of Kuhn's,[28] in which he described three stages of a paradigm shift in science: (i) first it is ridiculed; (ii) then it is resisted; and (iii) finally, it is considered self-evident. The recent warning by the FDA may be challenging us to re-evaluate our position in this particular paradigm shift. Ultimately, we must leave it up to the scientific community and clinicians to decide the best course of action. Further studies of non-human primates will continue to help us evaluate the complex issues posed to our daily anaesthesia practice in very young children.

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