

To The Question of Safety of Neonatal Anesthesia

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A rapidly increasing number of prematurely born and sick babies with different pathophysiological conditions survive due to the progress of modern medicine. Clinical procedures for most of these patients require general anesthesia; frequently repeated exposures are needed. Although, the advances in pediatric anesthesiology play a crucial role in this success, numerous laboratory studies provide evidence that exposure to general anesthesia of even healthy animals during the early postnatal period may result in immediate and long-term brain related abnormalities, such as neurodegeneration and impaired cognition [1-5]. Even though these adverse effects of neonatal anesthesia were demonstrated across various species, from rodents to non-human primates, the results of human studies are not conclusive at this time. Thus, on the one hand, signs of learning disabilities, developmental and behavioral complications have been detected in children who were exposed to general anesthetics before 4 years of age [6-8]. On the other hand, other human studies were not able to find significant differences in cognitive performance in children that were exposed to general anesthesia early after birth and when compared to age-matched counterparts that did not have such exposure [9-12]. All these human studies were retrospective epidemiological assessments, and for this reason suffer from lack of detailed planning and other weaknesses discussed in detail in recent excellent reviews [13-15]. Specifically designed human studies are definitely needed to better assess the risk of long-term consequences that the youngest patients may face after exposure to general anesthesia. It is plausible that neonates with (or predisposed to) certain diseases that share mechanisms with the side effects of general anesthetics are more vulnerable to the harmful effects of general anesthetics than patients with other conditions. The problem is that the mechanisms that mediate the adverse actions of general anesthetics in the early stages after birth and the pathophysiological conditions, which, in combination with the anesthetic actions, may produce synergistic or additive adverse effects, are essentially unknown even in animal models. A better understanding of such additive and synergistic effects may allow the identification of groups of neonatal patients to whom general anesthesia, especially with certain types of anesthetics, may not be safe, and, on the other hand, may give a green light to other patients who are tolerant of the long-term effects of the anesthetics. Therefore, new laboratory investigations that identify the whole spectrum of the side effects of neonatal anesthesia and their underlying mechanisms can be an important component in the combined efforts to answer the question whether neonatal anesthesia is safe to human patients. One of the weaknesses of the published animal studies investigating the side effects of general anesthetics is that they all, almost exclusively, focus on neurodegeneration, neurogenesis, synaptogenesis and a limited number of behavioral paradigms. Given that pharmacologic targets for general anesthetics are present not only in the central nervous system, it is plausible that the side effects that the general anesthetics may cause in neonates and pathophysiological conditions that specifically interact with those side effects are not necessarily restricted to the brain.

As an example, let's consider a hypothetical case involving GABA_A receptors and aldosterone, a major target for general anesthetics and an important component of the neuro-humoral perioperative

stress response, respectively [16]. High expression of the Na⁺-K⁺-2Cl⁻ (NKCC1) co-transporter in late embryonic and early neonatal cortical neurons is a unique feature of neonatal physiology that may contribute to increased susceptibility of neonates to the adverse effects of general anesthetics. The NKCC1 activity is responsible for the elevated levels of intracellular Cl⁻ that provide the basis for the depolarizing and excitatory action of GABA [17]. The GABA_A receptor-mediated excitation, especially when further enhanced by anesthetics, may result in neurotoxic effects [4, 18]. However, the depolarizing action of GABA is not restricted to the neonatal brain. GABA_A receptor-mediated depolarization also plays an important stimulatory role in different peripheral tissues, for example in hormone synthesis by the adrenal gland. Thus, isoflurane elicits catecholamine secretion by activating GABA_A receptors in bovine adrenal medullar chromaffin cells [19]. The GABA machinery was also found in adrenal cortex cells [20], which are responsible for synthesis of the mineralocorticoid hormone aldosterone. These findings are indirectly supported by our unpublished observations of a more than 30-fold increase in serum levels of aldosterone in postnatal day 4-5 rats anesthetized with sevoflurane for 6 hrs. Regardless of the exact mechanisms whereby sevoflurane stimulates the production of aldosterone in neonatal rats, the increase in aldosterone levels may represent a potential peripheral component in the neonatal anesthesia-caused side effects. Aldosterone is known to induce oxidative stress, inflammation and apoptosis [16, 21-23]. Importantly, aldosterone is more likely to produce these effects in neonatal brain than in adult brain because high expression of the enzyme 11-β-hydroxysteroid dehydrogenase 2 in this period provides conditions for modulation of mineralocorticoid receptors by aldosterone by removing the glucocorticoid shield [23]. Furthermore, aldosterone-induced oxidative stress and inflammation [24], have profound peripheral effects contributing to cardiovascular disorders, insulin resistance, obesity and other disease states [16, 21-23]. Therefore, it is plausible that neonates with higher plasma aldosterone levels, such as low birth weight preterm infants [25-27], or those predisposed to the above mentioned disorders may be more vulnerable to the anesthetics with GABA_A receptor agonistic properties (such as sevoflurane or isoflurane) when compared to those that have minimal or no effect on GABA_A receptors (such as xenon).

This hypothetical case should serve as an invitation to look at the neonatal anesthesia toxicity phenomenon not as strictly brain related, but rather as a systemic phenomenon which includes the possibility

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that neonatal anesthesia may specifically exacerbate some disease states more than others. A multidisciplinary approach would help to expedite the resolution of this startling and potentially dangerous problem. An open access platform, such as the one provided by the Journal of Pain and Relief, can facilitate attracting clinical and basic science researchers with the requisite diversified expertise.

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