Aneseizure: Is the Neonatal Brain Asleep?

GENERAL anesthesia decreases brain activity and eliminates consciousness.1,2 Almost all intravenous and volatile anesthetics are γ-aminobutyric acid (GABA)-ergic.3 A number of these agents, including barbiturates, propofol, and benzodiazepines, are potent anticonvulsants as well. Interestingly, many modern anesthetics, including sevoflurane, have been implicated in epileptiform brain activity or even frank seizures.4,5 The mechanism by which anesthetics cause brain excitation is poorly understood. In this month’s issue of Anesthesiology, Edwards et al.6 propose a possible mechanism for one type of sevoflurane-induced seizure, namely GABAergic brain excitation in the immature brain. This type of seizure is common (50% of 4- to 6-day-old rats), is nonconvulsive, and occurs at clinically relevant inspired concentrations of sevoflurane (2.1%). It is distinct from the well-recognized sevoflurane emergence seizures, which these authors6 also found. In contrast to convulsive emergence seizures, these nonconvulsive “maintenance” seizures occurred in young rats and were prevented by bumetanide pretreatment.

Why should a GABAergic anesthetic cause seizures in immature rats and why should a diuretic prevent them? The answer to both these questions is that GABA is excitatory during development. The immature Na/K/2Cl transporter NKCC1 imports chloride into the cell, creating an inside-to-outside chloride gradient.7,8 When GABA receptors are activated, chloride crosses the cell membrane down this concentration gradient, depolarizing immature brain cells, such as neural progenitors, neuroblasts, and immature neurons.7,9 GABAergic excitation is the earliest and the most important excitatory and trophic signal that developing neurons receive and is critical to brain development.9–11 By increasing intracellular calcium, GABA signals a number of important neurogenic and synaptogenic events.7–9,11–18 During a brief period from just before to just after birth, maternal oxytocin temporarily renders GABA inhibitory, possibly by reducing NKCC1 activity, which protects the developing brain from peripartum hypoxic insults.19 Thereafter, GABA remains excitatory until GABA itself causes a switch from excitation to inhibition of GABA by inducing expression of the mature chloride transporter, KCC2.12 KCC2 transports chloride out of the cell, thereby reversing the concentration gradient of chloride, causing hyperpolarization in response to GABA-A receptor activation. This switch of GABA phenotype proceeds in a caudal-to-rostral fashion.20 GABA is inhibitory in the spinal cord and brainstem in utero20,21 but does not become inhibitory in the cortex and the hippocampus until 14–21 days of postnatal age.22 It follows that during this vulnerable period of development, GABA excites the cortex and the hippocampus while inhibiting the subcortical areas causing nonconvulsive seizures.23 This “electroclinical uncoupling” underlies the difficulty in detecting and treating neonatal seizures. Phenobarbital, a GABAergic agent and anticonvulsant of choice for neonatal seizures,24 inhibits subcortical areas where the GABA phenotype is mature (inhibitory) and thus abors the convulsive aspects of neonatal seizures but is ineffective in aborting seizures in the cortex and the hippocampus.22,23,25,26 Bumetanide, a loop diuretic, inhibits the NKCC1 transporter and renders GABA inhibitory.22,23,27 By itself, bumetanide is a more effective anticonvulsant than phenobarbital for neonatal seizures.22 Bumetanide improves the efficacy of phenobarbital in aborting neonatal seizures.27

Given this background, the existence of anesthesia-induced nonconvulsive seizures demonstrated by Edwards et al.6 seems rather plausible.

Next, the authors attempt to mechanistically link anesthesia-induced seizures to anesthesia-induced neurotoxicity by showing that 3 h of sevoflurane increases cleaved caspase 3, a cell death marker, in 4-day-old rats. This was prevented by bumetanide, suggesting that the immature GABA phenotype may have caused “excitotoxicity” in the immature brain.24 Thus far, it has been thought that neuronal quiescence mediates developmental neurotoxicity of anesthetic agents.28 The study by Edward et al.6 challenges this concept by suggesting that GABAergic excitation causes developmental neurotoxicity. However, their data are difficult to interpret. Undoubtedly, anesthesia kills cells in the developing brain,29 but the duration required for this effect (at least 2 h for isoflurane,30 unknown for sevoflurane) exceeds the anesthetic duration (33 and 60 min) used to demonstrate seizures in this study.6 It is unknown whether seizures occurred at anesthetic durations sufficient to cause brain cell death (3 h). Furthermore, attempting to causally link seizure- and anes-
Anesthesia-induced brain cell death would require, at the very least, a correlation between the degree of cell death and the occurrence of seizures. In other words, the animals that suffered sevoflurane-induced seizures should have more cell death and rats without seizures should have less cell death in their brains. It was not tested whether such a correlation exists. The literature suggests otherwise. The neonatal brain is less sensitive to seizure-induced brain cell death but more sensitive to anesthesia-induced brain cell death than the adult brain. Seizure-induced brain cell death supposedly does not occur until after 14 days of age in rats. However, only in rats younger than 14 days do seizures change brain development and impair hippocampal-dependent learning and memory long-term. The animals suffering from anesthesia-induced brain cell death were 4 days old in the study by Edward et al. The Fio₂ of 1.0 used in this study may have caused further brain cell death. Finally, even if seizures mediated the anesthesia-induced brain cell death, the question would be, does it matter? Bumetanide, despite preventing seizures and anesthesia-induced brain cell death, did not prevent anesthesia-induced decrease in hippocampal long-term potentiation, the electrophysiologic correlate to learning and memory. A similar discrepancy between brain cell death and outcome has been described previously, suggesting that anesthesia-induced brain cell death does not necessarily mediate anesthesia-induced long-term functional outcome. This is underscored by seizure-induced long-term hippocampal dysfunction in the absence of brain cell death. It would be important to confirm that bumetanide does not affect the behavioral outcome of sevoflurane anesthesia because long-term potentiation and behavioral outcomes may differ.

Could the described GABAergic excitotoxicity be important in humans? Two pieces of information are required to answer this question. First, we must know whether sevoflurane causes maintenance seizures in babies. Researchers should be able to provide this information relatively easily. In case sevoflurane does cause maintenance seizures in babies, we need to know whether a single anesthetic with a sevoflurane-genic agent causes long-term effects on brain development and brain function. This question is not easily answered. Although human data in this regard remain inconclusive, animal data may be the best basis for an informed guess, fully recognizing the obvious limitations of extrapolating animal data to humans. In animals, neonatal seizures, independent of their cause, change developmental programs, decrease neurogenesis, alter synaptogenesis, and impair long-term neurocognitive function (reviewed by Holmes). In rats, even a single neonatal seizure lasting for 3 h causes long-term molecular, cellular, and behavioral changes, specifically of hippocampal-dependent memory, a set of circumstances reminiscent of a single episode of neonatal anesthesia. In humans, down-regulation of the immature Cl transporter NKCC1 seems to be completed by the 15th postnatal week, whereas KCC2 transporter expression does not reach adult levels until 1 yr of age. Because down-regulation or inhibition of the NKCC1 transporter seems to be sufficient to render GABA inhibitory, the period of vulnerability to GABA-induced excitotoxicity in humans would end around 4 months of life. Whether this is also true for the period of vulnerability to anesthesia-induced neurotoxicity is unclear.

Edward et al. have discovered a previously unknown and potentially important mechanism by which GABAergic anesthetics may harm the neonatal brain. They have also described an easily translatable treatment, bumetanide, that may prevent both seizures and sevoflurane-induced brain cell death. Does this call for a change in clinical practice? Until more is known about this phenomenon and data from clinical studies are available, no change in clinical practice is justified. However, this work fully justifies such studies.

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References

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