CORRESPONDENCE

Anesthesia in Children — Limitations of the Data on Neurotoxicity

TO THE EDITOR: We share the concerns that Rappaport et al. express in their Perspective article in this issue of the *Journal* regarding possible relationships between anesthetic agents and neurologic damage in young children. However, clinicians are challenged with extrapolating neurodevelopmental stages and behavioral correlates from animal models to human infants. Studies in animals reveal worrisome neuronal apoptosis after anesthesia, raising questions about whether pediatric anesthesiologists should change their practice and what they should tell parents.

Studies in animals involve prolonged exposure to anesthetics in high doses with variable monitoring and no surgical stress. Furthermore, translating stages of brain development from rats to humans is problematic, given the uneven regional brain growth in human infants. Behavioral testing of rat pups after administration of various anesthetics shows deficits in some but not all models, even in the face of neuronal apoptosis.[1] Conversely, emerging data suggest that certain anesthetics (e.g., ketamine and dexmedetomidine) may actually mitigate the apoptosis that follows cerebral ischemia and reperfusion or repeated painful stimulation in newborns.[2,3]

Data from humans reveal developmental consequences in children who undergo surgery at an early age.[1] Limitations of these studies — including their retrospective nature, underpowered samples, nonrepresentative cohorts, nonstandardized anesthesia protocols, and patients' diverse coexisting conditions — preclude drawing definitive conclusions. Moreover, the studies use school performance or standardized tests as surrogates for formal neurodevelopmental assessments; these measures, although important, introduce significant biases.

Two reassuring studies in humans deserve comment. Bartels et al. reported lower educational achievement scores in monozygotic twins who underwent surgery before 3 years of age than in those who did not. Twins who were discordant for exposure to anesthesia showed no significant differences in educational outcomes.[4] Hansen et al. reported no significant differences in educational outcomes at 15 to 16 years of age between 2500 children who underwent inguinal herniorrhaphy and an age-matched population sample.[5]

We applaud the Food and Drug Administration (FDA) for its commitment to the safety of pediatric anesthesia. Current data on neurotoxic effects of anesthesia, however, do not provide definitive answers, so we must remain circumspect in our risk assessments and communications. On the basis of available data, it would be inappropriate to deny or delay necessary surgery for fear of unknown consequences of anesthe-

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sia. Similarly, the current information is insufficient to support recommendations to change the selection or monitoring of anesthetics.

Teasing out the relationship between exposure to anesthesia and neurologic effects remains difficult. Ongoing prospective, longitudinal studies won't yield outcome data for years and will require time-consuming, expensive developmental tests. Efforts to identify biomarkers may clarify individual susceptibility to potential adverse effects of anesthetics. The Society for Pediatric Anesthesia is supportive of the efforts of the FDA and other investigators to answer these important questions.

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Rifaximin for Irritable Bowel Syndrome without Constipation

TO THE EDITOR: Two issues are major drawbacks of the study by Pimentel et al. (Jan. 6 issue)[1] on rifaximin therapy for patients with irritable bowel syndrome (IBS) without constipation. First, the development of resistance was not investigated in TARGET 1 or TARGET 2 (ClinicalTrials.gov numbers, NCT00731679 and NCT00724126) or mentioned in the discussion of the two studies. The close structural relationship of rifaximin and rifampin leads to rifampin resistance; the emergence of rifampin-resistant skin staphylococci after intake of rifaximin has been reported.[2] Staphylococcal foreign-body infections are of increasing concern because of their medical and economic consequences, and rifampin susceptibility of causative staphylococci is crucial for the treatment of these conditions. Second, study patients were allowed to receive antidepressant agents. However, no information is provided regarding the distribution of patients receiving these drugs in the rifaximin and placebo groups. Therefore, the effect of rifaximin in IBS treatment without knowledge of concomitant antidepressant agents in both groups has therefore to be seriously questioned. We thus conclude that great caution should be exercised in transferring the study results reported by Pimentel et al. into clinical practice.

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1. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22-32.
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TO THE EDITOR: In the study on the treatment of IBS with rifaximin reported by Pimentel et al., we were impressed by the 31.7% improvement with placebo in the primary outcome, relief of global IBS symptoms. This gain was more than triple the 9.0% incremental gain from treatment with rifaximin over placebo, and it was sustained at 12 weeks.

This magnitude of improvement with placebo is higher than that of widely accepted interventions (such as statins to reduce future coronary events in patients with coronary artery disease).[1] We are surprised that the authors of this study and its accompanying editorial[2] do not at least