EDITORIAL

Discontinuing Antiseizure Medication in Neonates With Acute Symptomatic Seizures—Primum non nocere

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In the field of epilepsy treatment, we are often caught between the proverbial rock and hard place: our seizure medications can cause harm but so can seizures. Glass and colleagues[1] provide important and robust evidence to address this contentious issue. Their data from 9 American Neonatal Seizure Registry centers suggest that prolonged antiseizure medication (ASM) treatment is unnecessary for most neonates and support routine discontinuation of ASMs after resolution of acute symptomatic neonatal seizures prior to hospital discharge.

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A total of 305 term and preterm neonates with acute symptomatic seizures, including 43% with hypoxic-ischemic encephalopathy, 26% with ischemic stroke, and 18% with an intracranial hemorrhage, were included if seizures were confirmed with conventional continuous electroencephalography (cEEG) or if they were treated with ASM for clinically suspicious events consistent with seizures. This EEG confirmation is particularly important given that even experienced bedside caregivers often misdiagnose neonatal seizures based on semiologic features alone.[2] The study primary outcome (functional neurodevelopment assessment at age 24 months) was evaluated in 270 children using the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS) 50-item questionnaire administered to parents via a standardized telephone survey. Scores were similar for the 34% whose ASMs were discontinued prior to discharge vs the 64% with ASMs maintained at discharge. The risk for developing epilepsy was also similar between groups.

As noted by Glass et al,[1] a prior prospective trial that aimed to randomize neonates with acute symptomatic seizures to receive either phenobarbital or placebo for 4 months was halted because of a lack of recruitment. Approximately half of families and clinicians were concerned about the sequelae of further seizures if medication was stopped too early and the other half was worried about the adverse effects of more prolonged phenobarbital exposure. The strong tendency even at major academic centers to continue ASMs with neonates with seizures at discharge persists, evidenced by the nearly two-thirds of infants whose ASMs were continued in the current study.[1]

Neonatal seizures are a common neurological problem, affecting approximately 1 to 4 per 1000 full-term infants, and up to 10-fold more preterm infants.[3] Unlike many seizures that occur in childhood, neonatal seizures are usually the sequelae of underlying brain injury such as hypoxic-ischemic encephalopathy, stroke, intracranial hemorrhage, infection (meningitis, encephalitis, or congenital viral infections), or metabolic disorders.[4] As a result, infants with neonatal seizures are already at high risk of neurodevelopmental disability long term. Data from 1982 from the National Collaborative Perinatal Project found that a child with neonatal seizures had a 30-fold to 40-fold higher rate of cerebral palsy (including a 55-fold to 70-fold higher rate of disabling cerebral palsy), a 5.3-fold higher rate of intellectual disability, and an 18-fold higher rate of epilepsy compared with a child without neonatal seizures.[5] A 2019 study shows intellectual disability and/or cerebral palsy in up to half and postneonatal epilepsy in up to 25% of infants who survive.[3]

Antiseizure medication does not mitigate brain injury that has already occurred. Studies suggest that drug exposure during critical periods of brain development may adversely affect nervous system function. The most commonly used medication for neonatal seizures is phenobarbital, and a recent randomized clinical trial documented its superior efficacy compared with levetiracetam.[6] Similarly in the current study,[1] although the selection, dosing, and duration of ASMs were at the discretion of the local clinician, phenobarbital was the first loading ASM for 90%. Yet studies in immature rodents have shown that phenobarbital, as well as benzodiazepines, phenytoin, and valproate, result in neuronal apoptosis in the developing brain, at plasma concentrations relevant for seizure control in humans, and that this neuronal death is associated with decreased expression of neurotrophins and reduced concentrations of survival-promoting proteins.[7] Phenobarbital has also been shown to disrupt synaptic development in the striatum[8] and GABAergic synaptic maturation in the CA1 region[9] and lead to apoptosis in the developing white matter in the rodent brain.[10] Notably, these changes have been shown to correlate with learning and behavioral impairment. Further, in preterm neonates, exposure to midazolam was associated with hippocampal structural alterations and worse neurocognitive outcomes at 18 months.[11] In addition, a landmark randomized placebo-controlled study comparing phenobarbital with placebo in children with febrile seizures demonstrated a significantly lower IQ in the phenobarbital-treated cohort after 2 years of treatment, confirming its negative outcomes in humans.[12] Furthermore, phenobarbital did not result in reduced seizure freedom rates in children with febrile seizures, just as it did not protect against development of postneonatal epilepsy in the study by Glass et al.[1]

As expected, infants in whom ASMs were discontinued prior to hospital discharge had decreased exposure to phenobarbital as inpatients (28 mg/kg less on average) and 94% fewer days of phenobarbital treatment overall, as it was the most common ASM continued at discharge.[1]

All neonates in this study underwent cEEG monitoring per American Clinical Neurophysiology Society guidelines and EEG-seizure burden and worst EEG background were calculated.[1] As expected, EEG seizure frequency was high among this cohort of extremely vulnerable neonates—15% experienced status epilepticus (>30 minutes of seizure in any 1-hour epoch) and 21% had frequent recurrent seizures. In neonates, an increased seizure burden is associated with both short-term and long-term neurocognitive outcomes. Among a large cohort of full-term neonates with hypoxic-ischemic encephalopathy who underwent cEEG monitoring, a maximum hourly seizure burden of greater than 13 minutes was associated with an 8-fold odds of abnormal neurocognitive outcomes at 24 to 48 months.[13] In addition, in a randomized clinical trial of neonates with moderate to severe hypoxic-ischemic encephalopathy, cEEG monitoring and treatment of electrographic seizures led to significant reduction in seizure burden, and was associated with improved performance across cognitive, motor, and language scores at 18 to 24 months.[14]

Glass and colleagues[1] also revealed that physicians tailored ASM discontinuation decisions based on certain clinical factors. As may be expected, infants with high EEG seizure burden, complex clinical course (ie, congenital heart disease, extracorporeal membrane oxygenation, diaphragmatic hernia), and abnormal findings on discharge neurological examination had a higher propensity for ASM maintenance at the time of hospital discharge. Infants who underwent therapeutic hypothermia were more likely to have use of ASMs halted prior to discharge. However, propensity for ASM maintenance was defined by a logistic regression model including seizure causes, gestational age, therapeutic hypothermia, worst EEG background, days of EEG seizures, and discharge examination.

Thirteen percent of infants developed epilepsy before age 24 months. Median age at epilepsy onset was 7 months, and no infants with a normal EEG background developed epilepsy, and 7% of those with a normal findings on neurological examination at discharge developed epilepsy. The risk of epilepsy did not differ by ASM treatment duration group nor did the timing of epilepsy onset. All 11 children with epilepsy onset before age 4 months had ASM maintained at hospital discharge, including 4 of 11 (36%) with infantile spasms. Thus, ASM treatment duration did not affect development of postneonatal epilepsy or gross motor function at 24 months.[1]

West syndrome (infantile spasms) is the most common developmental and epileptic encephalopathy in infants, but evolution to this syndrome occurred in only 5% of cases in the study by Glass et al.[1] Phenobarbital neither prevents West syndrome nor effectively treats infantile spasms, and sodium channel blocking agents may even induce them.[15] Specific factors associating higher risk of spasms in infants with neonatal seizures have been identified.[16] Counseling of families regarding the risk and semiologic features of spasms to allow early recognition is a better option than maintaining an ineffective and potentially harmful therapy.

Glass and colleagues[1] also highlight the need to further understand and how best to intervene during the latent period of epileptogenesis that occurs between neonatal seizures and onset of postneonatal epilepsy. As the authors note, larger long-term studies are needed. Follow-up was limited to 24 months and some children may develop epilepsy after, although this study suggests that more than 2 years of ASM maintenance is unlikely to modulate the risk of childhood-onset epilepsy. Although powered to assess their primary outcome (noninferiority of functional outcomes at 24 months), postneonatal epilepsy was a rare outcome, and the authors cannot exclude a difference of up to 3.4 times the odds of developing epilepsy before age 24 months.

While neonatal care clinicians seek to avoid unnecessary harm to their vulnerable patients—especially to the rapidly developing brains of their patients—what may constitute unnecessary harm often remains unclear. Glass and colleagues[1] have provided clarity through data that support the 2011 World Health Organization recommendation to consider stopping ASMs without a taper after 72 hours of seizure freedom for neonates with normal findings on neurological examination and/or EEG. The current study suggests this recommendation should include all neonates with acute symptomatic seizures, even in the setting of an abnormal EEG and neurological examination results. Perhaps a little wiggle room might be created out from under that proverbial rock if centers are willing to adopt this practice change.

ARTICLE INFORMATION

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REFERENCES

1. Glass HC, Soul JS, Chang T, et al. Safety of early discontinuation of antiseizure medication after acute symptomatic neonatal seizures. *JAMA Neurol*. Published online May 24, 2021. doi:10.1001/jamaneurol.2021.1437

2. Malone A, Ryan CA, Fitzgerald A, Burgoyne L, Connolly S, Boylan GB. Interobserver agreement in neonatal seizure identification. *Epilepsia*. 2009;50(9):2097-2101. doi:10.1111/j.1528-1167.2009.02132.x

3. Shellhaas RA. Seizure classification, etiology, and management. *Handb Clin Neurol*. 2019;162:347-361. doi:10.1016/B978-0-444-64029-1.00017-5

4. Pressler RM, Cilio MR, Mizrahi EM, et al. The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. *Epilepsia*. 2021;62(3):615-628. doi:10.1111/epi.16815

5. Holden KR, Mellits ED, Freeman JM. Neonatal seizures. I. Correlation of prenatal and perinatal events with outcomes. *Pediatrics*. 1982;70(2):165-176.

6. Sharpe C, Reiner GE, Davis SL, et al; NEOLEV2 INVESTIGATORS. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. *Pediatrics*. 2020;145(6):145. doi:10.1542/peds.2019-3182

7. Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci U S A*. 2002;99 (23):15089-15094. doi:10.1073/pnas.222550499

8. Forcelli PA, Janssen MJ, Vicini S, Gale K. Neonatal exposure to antiepileptic drugs disrupts striatal synaptic development. *Ann Neurol*. 2012;72 (3):363-372. doi:10.1002/ana.23600

9. Al-Muhtasib N, Sepulveda-Rodriguez A, Vicini S, Forcelli PA. Neonatal phenobarbital exposure disrupts GABAergic synaptic maturation in rat CA1 neurons. *Epilepsia*. 2018;59(2):333-344. doi:10.1111/epi.13990

10. Kaushal S, Tamer Z, Opoku F, Forcelli PA. Anticonvulsant drug-induced cell death in the developing white matter of the rodent brain. *Epilepsia*. 2016;57(5):727-734. doi:10.1111/epi.13365

11. Duerden EG, Guo T, Dodbiba L, et al. Midazolam dose correlates with abnormal hippocampal growth and neurodevelopmental outcome in preterm infants. *Ann Neurol*. 2016;79(4):548-559. doi:10.1002/ana.24601

12. Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures–effects on intelligence and on seizure recurrence. *N Engl J Med*. 1990;322(6):364-369. doi:10.1056/NEJM199002083220604

13. Kharoshankaya L, Stevenson NJ, Livingstone V, et al. Seizure burden and neurodevelopmental outcome in neonates with hypoxic-ischemic encephalopathy. *Dev Med Child Neurol*. 2016;58 (12):1242-1248. doi:10.1111/dmcn.13215

14. Srinivasakumar P, Zempel J, Trivedi S, et al. Treating EEG Seizures in Hypoxic Ischemic Encephalopathy: A Randomized Controlled Trial. *Pediatrics*. 2015;136(5):e1302-e1309. doi:10.1542/peds.2014-3777

15. Hussain SA, Heesch J, Weng J, Rajaraman RR, Numis AL, Sankar R. Potential induction of epileptic spasms by nonselective voltage-gated sodium channel blockade: Interaction with etiology. *Epilepsy Behav*. 2021;115:107624. doi:10.1016/j.yebeh.2020.107624

16. Glass HC, Grinspan ZM, Li Y, et al; Neonatal Seizure Registry Study Group. Risk for infantile spasms after acute symptomatic neonatal seizures. *Epilepsia*. 2020;61(12):2774-2784. doi:10.1111/epi.16749