

Pharmacologic Management of Neonatal Seizures

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The purpose of this article is to review the etiology and pharmacologic management of neonatal seizures.

ABSTRACT

Seizures are most often the only sign of a central nervous dysfunction in the neonate. Neonatal seizures are a symptom of a specific disease entity. The search for a cause of neonatal seizures should focus on perinatal history or acute metabolic changes in the neonate. There are four classifications of neonatal seizures: clonic, tonic, myoclonic, and subtle. Simultaneous electroencephalogram and video recording are tools to assist the practitioner in the evaluation of difficult-to-assess subtle behaviors. Although many seizures may be prevented by careful attention to metabolic changes and the neonate's overall condition, those that cannot be prevented may require pharmacologic treatment. First-generation antiepileptic drugs such as phenobarbital and phenytoin are still the first and second lines of therapy, even as questions concerning their limited clinical effectiveness and concern for potential neurotoxicity continue.

Keywords: neonatal; seizures; antiepileptic; phenobarbital; phenytoin; midazolam; lidocaine; levetiracetam

SEIZURES ARE OFTEN THE ONLY SIGN OF a central nervous dysfunction in the neonate.¹ Seizures require prompt medical attention and raise concerns about the cause and clinical condition of the neonate as well as effects on the developing brain from seizure activity and the use of anticonvulsants.¹⁻² Identifying an exact incidence in neonatal seizures is difficult. It is estimated that the incidence of clinical seizures in the newborn is 1-3 per 1,000 live births. Seizures occur more frequently in the preterm newborn especially in lower gestational ages and birth weights. Various reports identify rates of 2-3 per 1,000 live births in the general population and term babies, 4.4 per 1,000 live births between 1,500 and 2,500 g, 55-130 per 1,000 live births <1,500 g, and up to 64 per 1,000 live births in infants <1,000 g birth weight.¹⁻⁹

Neonatal seizures are a symptom of a specific disease entity.¹⁰ Seizures may be associated with any disorder directly or indirectly affecting the central nervous system (CNS) and may be caused by various acute and

chronic stresses on the brain.¹ General causes of neonatal seizures are included in Table 1.

Primary intracranial conditions that may cause neonatal seizures include meningitis, intracranial hemorrhage, encephalitis, and tumor, whereas secondary processes include hypoglycemia, hypoxic-ischemia, hypocalcemia, hypomagnesemia, hyponatremia, and drug withdrawal.^{1,10,12} There has also been a link identified between intrapartum fever and unexplained neonatal seizure activity, increasing the risk of these seizures by fourfold even when the presence of infections was not found.¹³

Clinical symptoms may or may not be associated with surface electroencephalogram (EEG) changes. Seizures in the neonatal period are considerably different as compared with seizures in older children and adults, which are well organized. Seizure activity is less organized in the preterm infant as compared with a term infant because of incomplete neurophysiologic development. This makes detecting seizure activity in any neonate considerably more difficult, and it may oftentimes go unnoticed.¹

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TABLE 1 ■ Common Causes of Neonatal Seizures

Classification	Causes
Acute metabolic conditions (pH, HCO ₃ , Na, K, Ca, Mg, glucose, blood urea nitrogen)	Hypocalcemia Hypoglycemia; hyperglycemia Hypomagnesemia Pyridoxine dependency or deficiency Hyponatremia; hypernatremia
Inherited metabolic conditions (acidosis is common; assess urine amino acids, organic acids, NH ₃ , galactose)	Maple syrup urine disease Nonketotic hyperglycemia Hyperprolinemia Hyperglycinemia Galactosemia Urea cycle abnormalities Organic acidemias
Infections (12% of cases; assess cerebrospinal fluid [CSF]; culture blood, CSF; polymerase chain reaction assay in CSF; imaging)	Viral encephalitis; herpes or enterovirus infection Congenital infections Bacterial meningitis Sepsis Brain abscess Septic venous thrombosis
Intracranial hemorrhage (15% of cases; imaging; CSF examination)	Subdural hematoma Cerebral contusion Subarachnoid hemorrhage Epidural hemorrhage Intraventricular hemorrhage (premature)
Hypoxic ischemia (0–3 days) most common (60%)	
Congenital malformations	
Neonatal drug withdrawal (e.g., opiates)	
Local anesthetic intoxication	
Kernicterus	
Specific nongenetic syndromes	
Benign familial neonatal seizures	
Idiopathic (in only 10%, no cause is found)	

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The search for a cause for neonatal seizures should be focused on known history of perinatal problems or acute metabolic changes to narrow the differential diagnoses. Blood glucose should be checked at the bedside and confirmed in the laboratory. Lumbar puncture is another critical procedure to do as soon as the neonate is clinically stable in order to rule out meningitis. Both hypoglycemia and meningitis are dangerous but very treatable causes of neonatal seizures.^{1,12}

Sepsis should never be overlooked as a cause of neonatal seizures. Systemic infections can cause seizures because of the complications of shock, coagulopathy, hypoxia, and multisystem organ failure. Appropriate cultures to be obtained include blood, urine, cerebrospinal fluid (CSF), and tracheal aspirate. CSF should be examined for red blood cells and white blood cells, organisms by Gram stain, glucose, and

protein.^{1,14} Cranial ultrasounds are particularly helpful in identifying and following intraventricular bleeding or hydrocephalus. Computed tomography (CT) scan or magnetic resonance imaging (MRI) may also be indicated as a follow-up to the original cranial ultrasound.¹

Neonatal seizures are classified into four types: clonic, tonic, myoclonic, and subtle (more common in the premature neonate; Table 2). Volpe notes that “a seizure is defined clinically as a paroxysmal alteration in neurologic function, that is behavioral, motor or autonomic function” and is a manifestation of an underlying disorder rather than being an isolated disorder.^{1(p211)} Simultaneous EEG and video recording allows the practitioner to evaluate difficult-to-assess subtle behaviors, apnea, bradycardia, jerks, and twitches commonly seen in the preterm neonate who has seizures.¹

TABLE 2 ■ Traditional Categorization of Neonatal Seizures

Classification/Types	Clinical Manifestations	Definition/Description
Clonic	Rhythmic jerks (1–3/s)	Focal: well localized to a body part
Focal clonic	Rate slows during seizure	Multifocal: several body parts jerking simultaneously or in migrating order
Multifocal clonic	+ Electroencephalogram (EEG) seizure activity	
Tonic	Characterized by posturing	Focal: continued posturing of limb or a posturing (asymmetric) of trunk or neck
Focal tonic	Focal: + EEG seizure activity	Generalized: extension of lower limbs with either upper limb extension (looks like decerebrate posturing) or upper limb flexion (looks like decorticate posturing)
Generalized tonic	Generalized: usually no EEG seizure activity	
Myoclonic	Faster jerking than in clonic seizures	Focal: flexor jerking of upper limbs
Focal myoclonic	Flexor muscles (limbs) involved	Generalized: bilateral jerking of upper extremities; sometimes lower limbs are involved; often single or irregular jerks
Generalized myoclonic	Focal: usually no EEG seizure activity Generalized: + EEG seizure activity	
Subtle (more common in the premature infant)	Abnormal behavioral, autonomic, or motor activities that do not result from the other three seizure classifications + EEG seizure activity with only some of the seizure activities	Ocular: nystagmus, horizontal or vertical deviation of eyes, staring episodes, eyelid flutter or blinking Facial: repetitive sucking, mouth movements, tongue protrusion, chewing, drooling Limb: bicycling, swimming movements, “boxing” or “hooking” motions, stepping Apnea: only 2% result from seizures Autonomic or vasomotor changes

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Focal clonic and multifocal clonic seizures are commonly manifested in eye blinking or nystagmus. Focal clonic seizures are also an important manifestation of cerebral infarct in the neonate. Apnea, associated with electrical seizures, is more commonly seen in the full-term neonate. Most apneic episodes in the preterm neonate are not related to seizure activity.^{1,15} Seizures classified as tonic or subtle are more likely seen in the preterm neonate and quite commonly associated with intraventricular hemorrhage. Clonic and multifocal clonic seizures are more common in term infants. Myoclonic seizures are often related to a metabolic cause.¹¹

Many types of neonatal seizures can be prevented with careful attention to metabolic changes and the neonate's condition, such as anticipating hypoglycemia, hypocalcemia, hypomagnesemia, and hypoxia. Seizures that occur as a result of infections, prenatal injury, intracranial malformations, or inherited metabolic disorders often cannot be prevented until after initial symptoms appear and may require pharmacologic treatment.¹⁵

PHARMACOLOGIC MANAGEMENT OF SEIZURES

Unfortunately, no evidence-based guidelines exist for the pharmacologic management of neonatal seizures.¹⁶ There remains a lack of data from randomized controlled trials to

support the choice of antiepileptic drug (AED) for use in this population. Despite the lack of data regarding optimal treatment, rapid administration of medication is preferred because acute symptomatic seizure burden is highest at the onset. First-generation AEDs, such as phenobarbital and phenytoin, are still considered the first- and second-line drugs because of extensive clinical expertise. This is despite the fact that there has been limited clinical effectiveness and a concern for potential neurotoxicity seen with these agents.^{17,18} There has been a recent push to use newer, less toxic medications such as levetiracetam; however, there is still a lack of data on clinical effectiveness and long-term outcomes with these agents. See Table 3 for a list of common antiepileptics used in neonatal seizures.

Phenobarbital

Phenobarbital is a long-acting barbiturate, which is an agonist at gamma aminobutyric acid (GABA) receptors in the CNS. GABA is the primary inhibitory neurotransmitter found in the CNS, which suppresses seizure activity.¹⁹ Seizure response rates are thought to be 33 to 40 percent after an initial loading dose of 15–20 mg/kg. Continued rapid-sequence loading with total doses up to 40 mg/kg are reported to increase the response rate up to 77 percent in 120 neonates between 26 and 42 weeks gestational age.^{20,21} Despite these relatively promising response rates,

TABLE 3 ■ Common Antiepileptics Used in Neonatal Seizures

Antiepileptic	Dosing	Route	Adverse Effects
Phenobarbital	20 mg/kg	IV	Hypotension, CNS depression, respiratory depression, neurotoxicity
Fosphenytoin	20 mg/kg	IV	Hypotension, CNS depression, arrhythmias
Midazolam	0.1–1 mg/kg/h	IV	Severe hypotension, CNS depression, respiratory depression
Lidocaine	4–7 mg/kg/h	IV	Arrhythmias, hypotension, respiratory depression
Levetiracetam	20–30 mg/kg	IV	Rare

Abbreviations: IV = intravenous; CNS = central nervous system.

phenobarbital is known to cause hypotension, respiratory depression, and CNS depression shortly after administration. There is also concern for neurotoxicity with long-term exposure.^{18,19}

Phenytoin and Fosphenytoin

Phenytoin works on sodium channels in the CNS, which stabilizes neuronal membranes by increasing or decreasing influx of sodium ions across cell membranes in the motor cortex during generation of nerve impulses. Fosphenytoin is the water-soluble prodrug of phenytoin given intravenously, which was created to avoid adverse effects such as severe hypotension seen with intravenous phenytoin administration. The combination of fosphenytoin and phenytoin has been shown to be effective in neonatal seizures; however, a poor side effect profile and narrow therapeutic index make it a less attractive choice. It also carries the adverse effects of hypotension and CNS depression and requires close therapeutic drug monitoring because of nonlinear pharmacokinetics and a narrow therapeutic index.¹⁹

Administering a medication with a narrow therapeutic index and nonlinear pharmacokinetics increases the risk of toxicities because the level between efficacy and toxicity is very narrow and the drug concentration level causing toxicity is unknown and different in each patient.

Phenobarbital Versus Phenytoin

Painter and colleagues randomized 59 neonates from 26 to 42 weeks gestational age to receive either phenobarbital or phenytoin for treatment of seizures.¹⁷ The standard dosing of 20 mg/kg was used for both agents. Equal efficacy was seen between groups: phenobarbital (43 percent) versus phenytoin (45 percent). In each treatment group, patients were allowed

to cross over to the other antiepileptic if seizure control was not achieved. Fifteen patients in the phenobarbital group and 13 in the phenytoin group crossed over to the other treatment arm. After crossover, efficacy rates for seizure control increased to 57 percent in the phenobarbital-treated infants and 62 percent in the phenytoin-treated infants.¹⁷ Pathak and colleagues randomized 109 neonates >36 weeks gestational age to receive 20 mg/kg of either phenobarbital or phenytoin and were allowed to cross over if seizure control was not achieved.²² Infants were being treated for seizures secondary to intracranial bleeding, CNS infections, and ischemic injury. Seizure control was achieved in 72 percent receiving phenobarbital compared with 14 percent receiving phenytoin ($p < .001$). After crossover, 91 percent and 80 percent were controlled, respectively. It seems as though phenobarbital was much more effective in this last study compared with those previously reported. It is hard to explain why these results were found. It could be because of underlying etiology for the seizures; however, this is commonly not reported. Larger studies would need to be conducted in order to find a difference between these two agents regarding efficacy.

Midazolam

Midazolam is a benzodiazepine, which is a GABA agonist in the CNS leading to increased release of inhibitory neurotransmitters and an overall less excitable state. It is commonly used for refractory seizures because of its undesirable side-effect profile and needs to be given via continuous infusion. It is known to cause frequent hypotension, CNS depression, and respiratory depression, sometimes resulting in patients requiring additional support to tolerate therapy.¹⁹ These adverse effects commonly requiring medical intervention are what keep midazolam from being a first-line agent. In a small, nonrandomized study, 13 full-term neonates who were considered nonresponders to phenobarbital were all rapidly controlled with midazolam.²³ Sheth and colleagues reviewed a small cohort of six neonates unresponsive to both phenobarbital and phenytoin, found that all patients were seizure free within one hour of starting a midazolam infusion, and 67 percent had seizure cessation immediately after the loading dose of midazolam.²⁴ Another cohort of 15 full-term neonates with uncontrolled seizures after receiving phenobarbital and lidocaine were given a midazolam infusion. Seventy-three percent of patients experienced seizure cessation within 24 hours.²⁵ The last study reported three patients with status epilepticus refractory to phenobarbital and phenytoin, who all responded to therapy with midazolam.²⁶

Lidocaine

Lidocaine is an antiarrhythmic agent that also has activity in the CNS by blocking both the initiation and conduction of neuronal membranes' permeability to sodium ions, leading to inhibition of depolarization, which results in blockade of conduction and decreased seizure activity.¹⁹ Shany and colleagues administered lidocaine to 22 neonates

>36 weeks gestational age with seizures who failed to respond to phenobarbital.²⁷ These investigators reported a good or partial response to lidocaine infusion (4–6 mg/kg/hour) in 17 (77 percent) of the 22 neonates. Another small group of 21 neonates with seizure activity refractory to phenobarbital and midazolam were given lidocaine and found to have a 76 percent success rate (52 percent with complete response).²⁸ Even though lidocaine has been shown in several small studies to be effective for refractory seizures, its use remains minimal because of concerns for cardiac toxicity and arrhythmias. This risk increases if the patient has also received fosphenytoin, which also can cause cardiac toxicities. Arrhythmias are reported to occur in 4.8 percent of patients receiving continuous lidocaine infusion.²⁹ Lidocaine when given as a continuous infusion (generally 4–7 mg/kg/hour) seems to be effective in treating refractory seizures. However, concerns for cardiotoxicity, especially when combined with fosphenytoin (a common first-line agent), leads to its infrequent use.

Midazolam Versus Lidocaine

Midazolam has been compared with lidocaine as a second-line therapy in three trials. In a small, randomized trial of 11 patients with seizures all refractory to phenobarbital, five were given lidocaine, and six were given midazolam as second-line agents. None of the patients responded to midazolam; however, 60 percent of patients receiving lidocaine experienced seizure control.³⁰ In another study by Shany and colleagues, 30 neonates with seizures secondary to hypoxic-ischemic encephalopathy received treatment with midazolam or lidocaine for refractory seizures.²⁷ Fifty percent of neonates treated with midazolam showed a partial response, whereas 77 percent of those receiving lidocaine had a partial response. Cessation of all seizure activity for at least six hours was seen in 50 percent of lidocaine patients compared with no patients receiving midazolam.²⁷ Despite these few small studies showing increased efficacy with lidocaine compared with midazolam for refractory seizures, midazolam remains the most commonly used agent. The perceived contraindication between giving fosphenytoin and lidocaine simultaneously and risk of arrhythmias continues to prevent the common usage of lidocaine for refractory seizures.

Levetiracetam

Levetiracetam is an anticonvulsant with an unknown mechanism of action. It is thought to inhibit calcium channels, facilitate GABAergic inhibitory transmission through displacement of negative modulators, reduce or delay potassium current, and bind to synaptic proteins that modulate neurotransmitter release. It has recently become a popular choice for both acute and chronic management of seizures because of its attractive side-effect profile, lack of drug interactions, and large therapeutic index.¹⁹ A small retrospective cohort of 23 neonates received levetiracetam for first-, second-, or third-line seizure control. Overall, 35 percent of

patients had seizure improvement after receiving levetiracetam.³¹ This is comparable to the initial response rate for the common first-line agent phenobarbital. A second cohort of 22 neonates received levetiracetam either first line or second line (after phenobarbital), and 86 percent of patients showed immediate seizure cessation within one hour after treatment. Thirty-two percent had seizure cessation after just the loading dose, with all patients achieving seizure cessation by 72 hours after treatment initiation.³² Lastly, a cohort of 12 preterm neonates were given levetiracetam, and 82 percent experienced seizure cessation within 24 hours of drug initiation.³³ Levetiracetam appears to have efficacy against neonatal seizures, despite only a few small studies. Larger randomized trials should be performed with the hopes of finding efficacy of levetiracetam as a first-line agent for the treatment of neonatal seizures.

SUMMARY AND CONCLUSIONS

The optimal duration of therapy for acute symptomatic seizures in neonates remains unknown. There is a high degree of variability in practice despite good evidence showing no harmful effects of early discontinuation of therapy and no difference in recurrence of seizures for those who remain on maintenance therapy.^{34–36} Because there is a lack of guidance on this topic, each institution should create its own consensus-based protocols, in conjunction with neonatology and neurology services. This should prevent delays in treatment and allow for consistency in patient care.

Seizures in the neonatal period are a serious problem, and, over the last decade, a lot of research attention has been given to improve recognition, treatment, and outcomes related to neonatal seizures. New randomized controlled trials are needed to help establish better protocols for diagnosis as well as trialing new generation antiepileptic medications and determining optimal duration of treatment to obtain the best outcomes for these patients.

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