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Review

Antiseizure medications for neonatal seizures: Insights from ILAE guidelines

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ABSTRACT

The International League Against Epilepsy (ILAE) has made significant efforts to standardize the management of neonatal seizures by providing evidence-based recommendations for antiseizure medication in neonates. This is important because managing seizures in neonates can be complex, and evidence-based guidelines help clinicians provide the best care. There were six main recommendations. The phenobarbital should be the first- line antiseizure medication regardless of etiology, unless channelopathy is likely the cause for seizures (e.g., due to family history), in this case phenytoin or carbamazepine should be used. Among neonates with seizures not responding to first-line antiseizure medication phenytoin, levetiracetam, midazolam, or lidocaine may be used as a second-line antiseizure medication. In neonates with cardiac disorders, levetiracetam may be the preferred second-line antiseizure medication. This article provides guidelines and consensus-based recommendations for six priority questions related to neonatal seizure management: (1) first-line antiseizure medication, (2) second-line antiseizure medication, (3) duration of antiseizure medication treatment, (4) impact of therapeutic hypothermia on seizure burden in neonates with hypoxic-ischemic encephalopathy (HIE), (5) impact of electrographic seizure treatment on outcome, and (6) administration of pyridoxine.

Keywords: antiseizure medication, neonatal seizure, evidence-based guideline

INTRODUCTION

Seizures in newborns are often considered a neurological emergency due to the vulnerability of their developing brain. The most common causes of neonatal seizures are acute and provoked by various factors, such as hypoxic-ischemic brain injury this occurs when the baby doesn't get enough oxygen during or around the time of birth, leading to potential damage to the brain. Intracranial hemorrhage is a bleeding within the brain that can result from traumatic birth, vascular malformations, or prematurity, causing seizures. Arterial ischemic stroke is a blockage or narrowing of the arteries supplying the brain, leading to restricted blood flow, which can result in a stroke and seizures. Intracranial infections like meningitis or encephalitis can irritate the brain and cause seizures.[1-3]

In 10%–15% of neonates, seizures are the result of neonatal epilepsy, which can be due to several factors such as cortical malformations these are structural abnormalities in the brain that can lead to abnormal electrical activity. Conditions like focal cortical dysplasia or polymicrogyria can be associated with neonatal seizures. These malformations often impair the brain's normal development and function, leading to recurrent seizures. Genetic defects like genetic mutations can cause disorders that affect the brain's electrical activity and metabolism, leading to neonatal epilepsy. Some examples include mutations in ion channels or neurotransmitter receptors, which can cause disorders like channelopathies or other genetic epilepsies. These conditions might be inherited or occur de novo (new mutations). Inborn errors of metabolism are rare genetic conditions where the body is unable to process certain chemicals or compounds properly. Conditions like phenylketonuria (PKU), glutaric aciduria, or maple syrup urine disease can lead to metabolic disturbances that affect brain function and lead to seizures. These are typically diagnosed early through newborn screening. In cases of neonatal epilepsy, seizures may present as recurrent or resistant to treatment, requiring long-term management. Identifying the underlying cause is crucial for directing treatment, as some conditions might benefit from specific therapies, such as dietary modifications, metabolic treatment, or genetic counseling.[4-6]

This article presents guidelines and recommendations from the International League Against Epilepsy regarding the treatment of neonatal seizures. The clinical practice guideline group consisted of an international team of experts, including neurologists, neonatologists, pediatricians, epileptologists, and a parent representative. Recommendations are based on a systematic review and expert-based consensus via Delphi methodology if insufficient evidence was available. Recommendations include a choice of first- and second-line medication, treatment duration, the effect of therapeutic hypothermia on seizures, and the use of pyridoxine. This article provides guidelines and consensus-based recommendations for six priority questions related to neo-natal seizure management: (1) first-line antiseizure medication, (2) second-line antiseizure medication, (3) duration of antiseizure medication treatment, (4) impact of therapeutic hypothermia on seizure burden in neonates with hypoxic-ischemic encephalopathy (HIE), (5) impact of electrographic seizure treatment on outcome, and (6) administration of pyridoxine.[7-9]

Recommendation 1: First-line antiseizure medication

Evidence-based recommendation: In neonates with seizures requiring antiseizure medication, phenobarbital should be the first-line antiseizure medication. The strength of the recommendation is moderate. Consensus-based recommendations: Phenobarbital should be the first-line antiseizure medication regardless of etiology (including hypoxic-ischemic encephalopathy, stroke, and hemorrhage). The level of agreement is high. If channelopathy is the likely cause for seizures due to family history, then phenytoin or carbamazepine (sodium channel blocker) may be the first-line antiseizure medication. The level of agreement is high.

Phenobarbital: The dosage should be 20mg/kg IV as the first loading dose. 10–20 mg/kg IV as the Second loading dose if required, If a second loading dose of 20 mg/kg is given, respiratory support should be available; the maintenance dose should be 5 mg/kg/day IV or orally in one dose, consider plasma levels if on maintenance. Common adverse effects include respiratory depression, somnolence, depressed consciousness, poor feeding, and hypotension.[10-17]

Phenytoin/fosphenytoin: The loading dose should be 20 mg/kg PE IV over 30 min; the maintenance dose should be 5 mg/kg/ day IV or orally in two divided doses, adjusted according to response and plasma concentration to a maximum per dose of 7.5 mg/kg, target level: 10–20 μg/ mL. The common adverse effects include Infusion site irritation/necrosis, hypotonia, arrhythmia, bradycardia, and respiratory depression/arrest. Phenytoin has poor oral bioavailability levels, likely higher in infants receiving

therapeutic hypothermia, thus adjusting dosage according to local target levels. Cardiac monitoring is required. If used for channelopathies, switch to carbamazepine for maintenance once oral administration is possible.[15]

Carbamazepine: The dosage should be 10 mg/kg/day orally in two divided doses. The common adverse effects include transient somnolence, gastrointestinal symptoms, hyponatremia, and skin reactions reported in safety studies in children 1 month to 17 years. It is usually well tolerated, but there is limited information regarding dosing and adverse effects for the neonatal population.[12,16,18,19]

Recommendation 2: Second-line antiseizure medication

Consensus-based recommendations: In neonates with seizures not responding to first-line antiseizure medication, Phenytoin or Levetiracetam may be used as a second-line antiseizure medication for most etiologies (hypoxic-ischemic encephalopathy, stroke, or hemorrhage). Other possible options include Midazolam or Lidocaine. This level of agreement is moderate.

If channelopathy as an etiology for the seizures is suspected because of clinical or EEG features, then a sodium channel blocker may be used as a second-line antiseizure medication. This can be Phenytoin or Carbamazepine, depending on the clinical state of the neonate (critically ill or otherwise well baby) and the regional availability of antiseizure medication and monitoring of drug levels. The level of agreement is high. In neonates with cardiac disorder(s), Levetiracetam may be preferred as a second-line antiseizure medication. The level of agreement is moderate.

Levetiracetam: The first loading dose is 40 mg/ kg IV, the second loading dose is 20 mg/kg IV if required, and the maintenance dose is 40–60 mg/ kg/day IV or orally in three divided doses. The common adverse effects include mild sedation and irritability. It is usually well tolerated, but there is limited information regarding dosing and adverse effects for the neonatal population.[16,20-24]

Midazolam: The loading dose is 0.05 to 0.15 mg/kg, followed by the maintenance dose of 1 μg/kg/ min (=60 μg/kg/h) continuous infusion, titrate up in steps of 1 μg/kg/min (=60 μg/ kg/h) to max. of 5 μg/ kg/min (=300 μg/ kg/h). The common adverse effects include respiratory somnolence, depressed consciousness, and poor feeding hypotension. It needs to be tapered when maintenance treatment has been used.[25,26]

Lidocaine: The loading dose is 2 mg/kg IV over 10 min, the maintenance dose is 7 mg/kg/h IV for 4 h, reduced to 3.5 mg/kg/h for 12 h, reduced to 1.75 mg/ kg/h for 12 h, then stop Adapt dose for birth weight, PMA, and therapeutic hypothermia. The common adverse effects include cardiac (arrhythmias, atrioventricular block, cardiac arrest) hypotension, and methemoglobinemia. It is not to be given to a patient with congenital heart disease and/or who was or is on proarrhythmic drugs like (fos)phenytoin, additionally, cardiac monitoring is required.[25,27]

Carbamazepine: 10 mg/kg/day orally in two divided doses. The common adverse effects include transient somnolence gastrointestinal symptoms, hyponatremia, and skin reactions reported in safety studies in children 1 month to 17 years. It is usually well tolerated, but there is limited information regarding dosing and adverse effects for the neonatal population.[26,28]

Recommendation 3: Duration of treatment with Antiseizure medication

Consensus-based recommendations: Following cessation of acute provoked seizures (electroclinical or electrographic) without evidence for neonatal-onset epilepsy, antiseizure medications should be discontinued before discharge home, regardless of MRI or EEG findings. This level of agreement is high.[29,30]

Recommendation 4: Impact of therapeutic hypothermia on seizure burden

Evidence-based recommendation: Therapeutic hypothermia may reduce seizure burden in term neonates with hypoxic-ischemic encephalopathy. However, the impact of therapeutic hypothermia as a specific seizure therapy was not assessed. The strength of the evidence is weak. Consensus-based recommendations: Therapeutic hypothermia may reduce the seizure burden in neonates with hypoxic-ischemic encephalopathy. The level of agreement is high.[31,32]

Recommendation 5: Associations between seizure burden and outcome

Consensus-based recommendations: Treating neonatal seizures (including electrographic-only seizures) to achieve a lower seizure burden may be associated with improved outcomes (neurodevelopment, reduction of subsequent epilepsy). The level of agreement is moderate.[33,34]

Recommendation 6: Treatment with pyridoxine and pyridoxal 5-phosphate

Consensus-based recommendations: A trial of pyridoxine (add-on to antiseizure medication) may be attempted in neonates presenting with clinical features or EEG characteristics suggestive of vitamin B6-dependent epilepsy and neonates with seizures unresponsive to second-line antiseizure medication without an identified etiology. The level of agreement is high.

Pyridoxine: The loading dose is 100 mg IV or orally, followed by 30 mg/kg/day IV or orally in two divided doses for 3-5 days. The common adverse effects include respiratory depression, hypotension, prolonged treatment with high dosages may cause peripheral neuropathy. Ventilatory support should be available when the loading dose is administered. If effective, continue until genetic results are available.[35]

Pyridoxal 5′-phosphate: 30 mg/kg/day orally in three divided doses for 3-5 days. The common adverse effects include respiratory depression, hepatotoxic, and cirrhosis described in prolonged use. It is not licensed as a medical product, but the most promising approach in pyridox(am)ine 5′-phosphate oxidase-deficient patients. If effective, continue until genetic results are available.[36]

CONCLUSION

Based on the conclusions of the above recommendations, a sample neonatal seizure management pathway provides suggested antiseizure medications. As with all pathways, adaptation is needed based on individual patient characteristics and practice settings. All experts agreed that neonatal units should have a standardized pathway for the management of neonatal seizures. The International League Against Epilepsy recommends that guidelines be updated every 5 years, and the International League Against Epilepsy Task Force on Neonatal Seizures is developing an approach to periodically update these recommendations.

Conflict of Interest

The authors declare no conflicts of interest relevant to this article.

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