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Review Article

The Use of Anti-Seizure Medications in Neonatal Intensive Care Unit

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Abstract

Neonatal seizures are the most common emergency neurological condition. Neonatal seizures require emergency treatment to prevent further brain injury. The most effective is causal treatment, such as treatment of transient metabolic disturbances, systemic and intracranial infections. However, anti-seizure medications are important for the treatment of seizures in high-risk neonates in whom seizures are not expected to resolve spontaneously. The International League Against Epilepsy developed evidence-based recommendations about anti-seizure medication and treatment of neonatal seizures. Phenobarbital remains the first-line treatment for neonatal seizures in term and preterm neonates. If neonatal seizures do not stop to phenobarbital, levetiracetam or phenytoin may be used as a second-line anti-seizure medication, as well as midazolam or lidocaine. Midazolam is a short-acting benzodiazepine using for treatment of refractory neonatal seizures. In neonates with cardiac disorders, levetiracetam may be the preferred second-line anti-seizure medication than phenytoin. Pyridoxine is recommended in neonates with seizure unresponsive to seconde-line therapy. Carbamazepine and phenytoin, as sodium blockers channels, are preferred for neonates with characteristics suggesting a channelopathy.

Keywords: *Neonatal Seizure; Anti-Seizure Medication; Neonate*

Introduction

Neonatal seizures are the most common emergency neurological condition, but at the same time the first sign of central nervous system (CNS) dysfunction in neonates. Several factors which increase excitation and decrease inhibition contribute to higher susceptibility to seizures in the developing brain. The incidence of neonatal seizures is higher in preterm or very low birth weight neonates than in term neonates (1-3). In the term and late preterm neonates, the most common cause of seizures is hypoxic-ischemic encephalopathy (HIE), and in the preterm neonate, intraventricular hemorrhage (IVH) is the most prevalent (4).

Neonatal seizures require emergency treatment to prevent further brain injury. The most effective is causal treatment, such as treatment of transient metabolic disturbances (eg, hypocalcemia, hypoglycemia, hypomagnesemia), systemic and intracranial infections. However, anti-seizure medications (ASMs) are important for the treatment of seizures in high-risk neonates in whom seizures are not expected to resolve spontaneously (4,5).

Although numerous ASM have been registered in the last two decades, therapeutic options for the treatment of neonatal seizures remain limited, due to the paucity of data from randomized controlled studies on the use of these medications in neonates. Recommendations for the treatment of neonatal seizures are based primarily on a small number of systematic reviews and clinical experience of experts in neonatology, neuropediatrics and pharmacology (6).

In this review are presented the most commonly used ASMs in the neonatal intensive care unit (NICU), such as phenobarbital, levetiracetam, midazolam, and phenytoin, their pharmacokinetics, dosages, adverse effects, and interactions with other medications.

Phenobarbital

Phenobarbital was introduced into clinical practice as ASM in 1904. According to current recommendations, phenobarbital remains the first-line treatment for neonatal seizures in term and preterm neonates (6-8). Phenobarbital controlled seizures in approximately 78% of neonates (5,6,9). Phenobarbital acts as a gamma-aminobutyric acid (GABA) receptor (GABAA) agonist. Its mechanism of action is the synaptic inhibition through an action on GABAA receptors (10). Phenobarbitone leads to a number of neurophysiological and neurochemical effects, thought to be related to modifications of sodium and calcium ion conductivity in the neuronal membrane (8).

There is evidence that phenobarbital enhances neuronal apoptosis in animal models and have an adverse effect on psychomotor development (11). The experimental study of Barks JD, et al. (12) shown that administration of the phenobarbital in early phase of HIE, after cerebral hypoxia-ischemia, may enhance the neuroprotective efficacy of therapeutic hypothermia. There are few clinical trials about neuroprotective effect of phenobarbital in asphyxiated neonates. One of the studies that confirmed neuroprotective effect of phenobarbital in neonates with HIE treated with hypotermia was the prospective SHIVER study (13). However, the retrospective study of Meyn DF Jr, et al. (14) showed no improvement in neurodevelopmental outcome in neonates treated with whole-body cooling for HIE. According to previous research, phenobarbital is only used in asphyxiated neonates with seizures. A Cochrane review reported insufficient evidence to recommend the use of prophylactic phenobarbital in neonatal encephalopathy without seizures (15).

Numerous studies have analyzed the first-line therapy of neonatal seizures of various etiologies. The first study of Painter MJ, et al. (16) compared phenobarbital and phenytoin for treatment of neonatal seizures confirmed by electroencephalography (EEG) and there was no difference in efficacy between these ASM as first-line treatment. The combined use of phenobarbital and phenytoin has a similar effect in controlling neonatal seizures (in about 80% of neonates), regardless of which medication is administered first. Another open-label randomized controlled study of Pathak G, et al. (17) showed that phenobarbital is more efficacy than phenytoin in control clinical neonatal seizures of any cause in term and late preterm neonates. Similarly, a multicenter controlled study of Sharpe C, et al. (18) evaluated the efficacy of levetiracetam compared with phenobarbital as first-line treatment for neonatal seizures irrespective of etiology. The results of this study showed that phenobarbital was more effective than levetiracetam as first-line treatment. There was no difference in efficacy between phenobarbital and levetiracetam as second-line treatment. Akeel NE, et al. (19) were conducted comparative study of phenobarbital and levetiracetam for treatment of neonatal seizures and showed that levetiracetam is an effective and safer alternative to phenobarbital as a first-line ASM.

Phenobarbital is primarily metabolized in the liver, and conjugated metabolites are eliminated by the kidneys. A quarter of the administered dose of phenobarbital is excreted unchanged in the urine. In preterm neonates, the elimination half-life is longer than in term neonates. Renal and hepatic excretion of phenobarbital can be affected in HIE. Phenobarbital interacts with numerous medications because it induces liver enzymes. In the past, this enzyme inducing property has been used to speed hepatic conjugation, excretion of bilirubin and treatment indirect (unconjugated) hyperbilirubinemia (6,8,10).

The initial loading dose of phenobarbital in neonates with seizures is 20 mg/kg. If the initial loading dose of phenobarbital is not effective in controlling seizures, it is necessary to administration additional doses of 10-20 mg/kg until seizures stop, so the total daily dose does not exceed 40 mg/kg. If a second loading dose of 20 mg/kg is given, monitoring of the neonate's respiratory function is necessary, and respiratory support should be available. The maintenance dose is 5 mg/kg/day intravenously or orally divided into two doses and is administered 12 to 24 hours after the loading dose. If the neonates receive a maintenance dose, serum levels of phenobarbital should be measured. The therapeutic serum level of phenobarbital is 25 – 40 μg/ml (5,6). The adverse effects of phenobarbital are dose dependent. Serum levels of phenobarbital above 40 μg/ml may give sedation, hypotonia, somnolence, depressed consciousness, and poor feeding, while plasma levels above 60 μg/ml may cause respiratory depression (8).

Levetiracetam

Levetiracetam is a second generation ASM, the active, water-soluble S-enantiomer of pyrrolidine acetamide. It's a member of the nootropic class of medications which are considered to be "pharmacologically safe" (20). Over the last decade, levetiracetam has been increasingly used in the treatment of neonatal seizures. Initial case reports and small series reported that seizures cessation or decreased in frequency in about 52% to 80% of neonates after receiving levetiracetam. Several studies have been published on the efficacy of levetiracetam in the treatment of neonatal seizures, most commonly in neonates who have not responded to previously administered ASMs (5). Khan O, et al. (21) reported immediate seizure cessation in 86% of included neonates within one hour of receiving levetiracetam. Similarly, Abend NS, et al. (22) showed that after receiving of levetiracetam, the number of seizures within 24 hours decreased by more than 50% in 35%, and the seizures completely stopped in 30% of neonates. No significant adverse effects were noted in any of the studies. The efficacy of levetiracetam in the treatment of neonatal seizures was evaluated in a systematic review of Sharma D, et al. (23). Levetiracetam has shown to have promising better efficacy in the treatment of neonatal seizures and less or no adverse effects. Neonatal seizures secondary to HIE treated with therapeutic hypothermia were better controlled with levetiracetam compared to phenobarbital.

The precise mechanism of action of levetiracetam is still not fully understood, but studies in animal models of epilepsy have shown that levetiracetam has a mechanism of action that differs from other ASMs. In the mid-nineties of the 20th century, the mechanism of action of levetiracetam was proposed, which implied the existence of a site on a specific protein localized in the region of the synaptic membrane in the CNS. That protein was identified as synaptic vesicle protein-2 (SV2). The SV2A isoform is the most widespread in the neurons, as well as in endocrine cells (24,25). Receptors for levetiracetam appear in human neurons as early as 26 weeks of gestation, reaching near-adult levels by 37 weeks of gestation. Levetiracetam binds to the SV2A protein and inhibits N-type presynaptic Ca2+ channels and the release of Ca2+ from intracellular depots, which affects the process of Ca2+-mediated exocytosis and reduces the release of neurotransmitters from synaptic vesicles. Also, levetiracetam leads to changes in neuronal hypersynchrony and thus reduces neuronal excitability (20,26-28). Several studies in animal models have shown that levetiracetam does not cause neuronal apoptosis in the immature brain, does not disturb the development of synapses, and can have a neuroprotective effect, especially in neonates with HIE (29-32).

Levetiracetam have the favorable pharmacokinetic profile characterized by rapidly and almost completely absorbed after oral administration (>95%), linear pharmacokinetics and minimal (2.5%) hepatic metabolism by cytochrome P450 system. This ASM is mainly metabolised by enzymatic hydrolysis by type-B plasma esterases. Approximately, the most part of the administered (66%) of levetiracetam is excreted unchanged in the urine by the kidney. The volume of distribution is higher in neonates (more in preterm than terms) compared to older children and adults. The maximum plasma concentration of levetiracetam is reached approximately 1 to 1.5 hours after administration. Given the renal function immaturity, the elimination half-life of levetiracetam is higher in neonates compared to children and adults. There is little plasma protein binding (<10%), resulting in fewer interactions with other medications (20,34-36).

It is recommended that the loading dose of levetiracetam in neonates with seizure be 40 mg/kg and if required, the second loading dose is 20 mg/kg. The maintenance dose is 40-60 mg/kg/day intravenously or orally divided into two to three doses. The therapeutic serum levels of levetiracetam is 12 – 46 µg/ml. Known adverse effects of levetiracetam in neonates are mild sedation and irritability. Given the usually well tolerated, routine monitoring of serum level concentration is not necessary. Levetiracetam is particularly suitable for use in neonates with heart failure and liver dysfunction. neonates with renal impairment may need dose adjustments (5,6,20,35).

Midazolam

Midazolam is a short-acting benzodiazepine used for treatment of neonatal seizures refractory to phenobarbital and phenytoin, as well as for the treatment of status epilepticus. According to the results of several studies, seizures cessation was achieved in 67-80% of neonates (5,37). In addition to anti-seizure activity, midazolam has anxiolytic and muscle relaxant effects. Also, midazolam is one of the most widely used sedatives in the NICU (38,39).

The main mechanism of action of midazolam, like other benzodiazepines, includes its interaction with the GABAA receptors in the brain. Midazolam mainly metabolizes in liver by hydroxylation to form 1-hydroxymidazolam by CYP3A4 and CYP3A5 enzymes.

This metabolite of midazolam, 1-hydroxymidazolam, is glucuronidated before excretion into urine. However, CYP3A4 enzyme activity increases in the liver during the first weeks of life, resulting in reduced clearance of midazolam in the neonatal period. The activity of CYP3A4 and CYP3A5 enzymes reaches adult-like values between 3 and 12 months of age. The elimination half-life of midazolam can be variable, on average it is 4-6 hours, but in preterm neonates it can be longer, up to 22 hours. There is highly (98%) binding midazolam to plasma proteins (38).

The loading dose of midazolam is 0,05 to 0,15 mg/kg followed by intravenous infusion 0.06 mg/kg per hour. If seizures persist, then additional loading doses may be administered, and the intravenous infusion may be increased by 0.05 to 0.1 mg/kg per hour to maximum doses of about 0.5 mg/kg per hour. The most common adverse effects of midazolam in neonates are respiratory depression, somnolence, depressed consciousness, poor feeding and hypotension (5,6,40).

Phenytoin

Phenytoin is a medication used in the treatment of neonatal seizures that persist despite the administration of the maximum dose of phenobarbital, or its adverse effects occur. Unlike phenobarbital and midazolam act on chloride channels, phenytoin's mechanism of action involves blocking of sodium channels in neurons (5). As first-line therapy, phenytoin may control seizures in up to 45% of neonates (41).

Phenytoin has non-linear pharmacokinetics, variable rate of hepatic metabolism by CYP2C9 and CYP2C19 enzymes, as well as decreased elimination rates during the first weeks of life. It is highly plasma protein bound and induces hepatic metabolism, resulting in interacting with numerous medications. Also, phenytoin has poorly absorbed after oral administration in neonates and infants (5,7,42,43).

Phenytoin is given in a loading dose of 20 mg/kg intravenously over 30 minutes. The maintenance dose is 5 mg/kg/day intravenously or orally divided twice per day (for intravenous formulations) or three times per day (for enteral formulations). Maximum daily dose of this ASM is 8 mg/kg/day. The therapeutic serum levels of phenytoin are 10 – 20 µg/ml. Due to the high pH value (pH = 12) of the parenteral solution, phenytoin has an irritating effect to the vein, and if extravasation occurs, surrounding tissue injury may occur. Due to precipitation in standard glucose intravenous solutions, 0.9% sodium chloride solution is used to dilute phenytoin. The known adverse effects of phenytoin are hypotonia, disturbance in cardiac rhythm (arrhythmia, bradycardia), and respiratory depression or arrest. Heart rate and cardiac rhythm should be monitored during the phenytoin infusion. Fosphenytoin, a phosphate ester prodrug of phenytoin, has fewer adverse effects in neonates (5,6).

Therapeutic hypothermia significantly reduces phenytoin elimination in children with traumatic brain injury. Similar studies in neonates with HIE treated with therapeutic hypothermia are lacking, it is possible that phenytoin has prolonged clearance associated with higher serum levels. Careful monitoring of serum phenytoin levels and its rational dosing is required for neonates receiving therapeutic hypothermia for treatment of HIE (7,44).

Carbamazepine

Carbamazepine is ASM which blocks voltage-dependent sodium channels. This ASM is preferred for neonates with characteristics suggesting channelopathy (developmental and epileptic encephalopathies due to KCNQ2, KCNQ3, or SCN2A mutations) include no other seizures etiology, with or without encephalopathy, normal brain imaging and certain EEG findings, or have positive family history of a channelopathy. The daily dose of carbamazepine is 10 mg/kg orally divided into two doses. In neonatal case reports and/or case series, significant adverse effects are not reported, but transient somnolence, gastrointestinal symptoms, skin reactions and hyponatremia may occur (5,6,45).

Pyridoxine

Due to possible neonatal onset of vitamin B6-dependent epilepsy, pyridoxine is recommended in neonates with seizures unresponsive to second-line ASM and with unknown seizures etiology. The loading dose of pyridoxine is 100 mg intravenously or orally by simultaneous monitoring of the EEG pattern, followed by 30 mg/kg/day intravenously or orally in two divided doses for 3–5 days. If seizures stop after receiving pyridoxine, it's recommended to continue until the aldehyde dehydrogenase deficiency is excluded by negative genetic testing. The adverse effects of pyridoxines are respiratory depression and hypotension. Prolonged treatment with high dosages of pyridoxine may cause peripheral neuropathy (5,6).

Conclusion

Neonatal seizures are a significant risk factor associated with poor neurodevelopmental outcome, epilepsy and death. Treatment of neonatal seizures is highly variable, largely because of insufficient evidence-based data to guide medication choice in neonates. In accordance with the current recommendations, phenobarbital is the first-line therapy for neonatal seizures cessation, while phenytoin, levetiracetam and midazolam are second-line ASM. In neonates with refractory seizures, it is recommended to receive pyridoxine, and if suspected channelopathies, carbamazepine and phenytoin.

Conflict of Interest

The author declare no conflict of interest.

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