ANTICONVULSANT TREATMENT IN NEWBORNS

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Abstract: *Neonatal seizures are medical emergencies. Untreated seizures are increasing the risk of secondary brain injury, mortality, epilepsy, abnormal cognitive development and cerebral palsy. Infants with neonatal seizures should be treated in tertiary-level neonatal units, which have continuously available personnel and equipment to provide life support for as long as needed. Seizures lasting longer than 3 minutes, with a greater than 3 per hour, or associating cardio-circulatory and respiratory compromise, require specific anticonvulsant therapy. The first-line anticonvulsant agents are phenobarbital and phenytoin which, in associated are controlling 70% of neonatal seizures. The second and third-line anticonvulsants used if neonatal seizures are refractory to first-line anticonvulsants are: Midazolam, Diazepam, Lorazepam, Lidocaine, Carbamazepine, Primidone, Sodium valproate. Other anticonvulsants are insufficiently tested to be used in the treatment of refractory neonatal seizures. The optimal treatment strategy for neonatal seizures remains controversial.*

Cuvinte cheie: *convulsii neonatale, anticonvulsivante, algoritm*

Rezumat: *Convulsiile neonatale sunt urgenţe medicale. Netratate la timp acestea cresc riscul de leziuni cerebrale secundare, iar pe termen îndelungat cresc riscul de mortalitate, epilepsie, anomalii cognitive, de dezvoltare şi paralizie cerebrală. Nou-născuţii cu convulsii neonatale trebuie îngrijiţi în unităţi de nivel III, care au competenţele necesare îngrijirilor complexe ale acestor copii. Terapia specifică cu anticonvulsivante se iniţiază dacă durata convulsiilor neonatale depăşeşte 3 minute sau convulsiile se repetă de mai mult de 3 ori într-o oră sau determină compromitere cardio-circulatorie şi respiratorie. Tratamentul anticonvulsivant este controversat. Anticonvulsivantele de primă linie utilizate la nou-născut sunt: Fenobarbitalul şi Fenitoina care asociate controlează 70% din convulsiile neonatale. Anticonvulsivantele de linia 2 şi 3 se administrează în cazul în care convulsiile neonatale sunt refractare la administrarea asociată de Fenobarbital şi Fenitoin: Midazolam, Diazepam, Lorazepam, Lidocaina, Carbamazepina, Primidon, Valproat de sodiu. Alte anticonvulsivante sunt insuficient testate pentru a fi utilizate în terapia convulsiilor refractare.*

SCIENTIFICAL ARTICLE PREDOMINANTLY THEORETICAL

Neonatal seizures are the clinical expression of the excessive and synchronous electric activity of a neuronal group occurring in the first 4 weeks of life in a full-term infant and up to 44 weeks from conception for premature infants.(1,2,3,4,5) Neonatal seizures are a medical emergency.(6) On long term, seizures are increasing the risk of mortality, epilepsy, abnormal cognition, development, and cerebral palsy.(7,8,9)

Infants with seizures should be treated in tertiary-level neonatal units, which have continuously available personnel and equipment to provide life support for as long as needed. Newborns with seizures from level 0, I and II units must be rapidly transferred to level III units, after emergency treatment.

Anticonvulsant therapy

Anticonvulsant medication should be started only after adequate ventilation and perfusion have been established. In newborns, anticonvulsants have a long half-life due to low oral absorption, low plasma protein binding, slow hepatic metabolism and delayed renal excretion.(10) This medication is recommended if seizures persist for longer than 3 minutes, or have a frequently greater than 3 per hour, or cause significant deterioration of the vital functions. To establish the maintenance dose serum levels of administered anticonvulsants should to be monitored, ideally. To maximize the efficiency and minimize for the treatment of neonatal seizures are:

1. Phenobarbital is the first choice drug to treat neonatal seizures. It is relatively effective and the side effects are reduced in term and preterm infants.(11,12,13,14) It can be used as maintenance therapy, it quickly penetrates the cerebrospinal fluid and has rapid effect.(11,15) An intravenous (i.v.) loading dose of 20 mg/kg of phenobarbital will achieve the therapeutic level of approximately 20 µg/ml with minimal side effects.(16,11,15,17,18) Intramuscular administration (i.m.) leads to a slower and unequal absortion, a later effect, so the dose should be 10-15% higher.(11,17,19,,20,21,22) If seizures persist it is recommended to increase the dose (5 mg/kg every 5 minutes) to a maximum of 40 mg/kg, providing ventilatory support as needed. The loading dose controls around 25% of seizures. Doses higher than 40 mg/kg don't achieve a better therapeutic effect, produce sedation for several days, and the risk for respiratory and cardiac depression is increasing progressively.(11,16) The maintenance dose: is 3-5 mg/kg/day (i.v., i.m., orally) in 1-2 divided doses, started 12 hours after the loading dose.

2. **Phenytoin** is also a first choice drug in the treatment of neonatal seizures if i.v. phenobarbital is not available. It is often the second drug of choice to be added when seizures are not

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controlled by phenobarbital alone. Phenytoin blocks voltage-sensitive sodium channels in neurons.(23) Phenytoin administration has been associated with cardiac toxicity. An i.v. loading dose of 20 mg/kg, infusion with a maximum rhythm of 50 mg?minute (0,5 mg/kg/minute) will achieve therapeutic blood levels of 15-20 µg/ml.(11,17) The i.m. administration leads to eratic absortion and muscular necrosis.(24) The maintenance dose is 4-8 mg/kg/day i.v. (30 min infusion) started 12 hours after the loading dose. The association of Phenobarbital and Phenytoin controls 70% of neonatal seizures.(2,9)

3. Midazolam - is a second-line anticonvulsant. This medication is loaded at 0,05-0,15 mg/kg (i.v.), every 2-4 hours or as needed. Midazolam has a short half-life, is well tolerated but has variable efficacy.(14,18,25) The maintenance dose is 0,01-0,06 mg/kg/hour in continuous infusion.

4. **Diazepam -** is a second-line anticonvulsant. The loading dose is 0,1-0,3 mg/kg i.v. or 0,5-1 mg/kg rectally. Diazepam is cleared from the brain within minutes, so it can not be used as a maintenance therapy. Administered after barbiturates, increases the risk for the respiratory failure and circulatory colapse. Sodium benzoate, the vechicle for i.v. diazepam, uncouples bilirubin from albumin, increasing the risk for kernicterus.(10,11,14)

5. Lorazepam - is a second or third-line anticonvulsant. The loading dose is 0,05-0,1 mg/kg i.v. in 5 minutes. Lorazepam has a long half-life (40 hours), long time of action (6-24 hours), and reduced side effects.(10,11,14) The dose may be increased by 0.05 mg/kg i.v. slowly every 10-15 minutes to a maximum dose of 4 mg. The maintenance dose: 0,05 mg/kg/dose i.v., i.m., orally or rectally every 6-24 hours.

6. **Lidocaine -** is a second or third-line anticonvulsant. The loading dose is 2 mg/kg i.v. over 10 minutes, followed by a continuous infusion of 6 mg/kg/hour for 12 hours, then 4 mg/kg/hour for 12 hours and 2 mg/kg/hour for another 12 hours. Then dose will be reduced with 1 mg/kg/hour every day until discontinuation (5 to 6 days) or the maintenance dose can be administered.(26) Sometimes after drug discontinuation, seizures reappear.(27) The maintenance dose: 6 mg/kg/h.

7. **Carbamazepine -** is a third-line anticonvulsant. The loading dose is 10 mg/kg via nasogastric tube. The late onset of action - 2-4 hours after administration - question the use this drug for the treatment of neonatal seizures. The maintenance dose: 10-15 mg/kg orally in 3-4 divided doses.

8. **Primidone -** is a third-line anticonvulsant. The loading dose is 15-25 mg/kg orally. Levels of 6 mcg/ml are therapeutic. The maintenance dose: 10-20 mg/kg orally divided in 3 doses.

9. Thiopental - is a third-line anticonvulsant. The loading dose is 10 mg/kg, administered slowly i.v. in 2 minutes, followed by a continous infusion of 1-6 mg/kg/hour. The drug has proved to be very effective seizures associated with perinatal asphyxia.(11)\

10. Sodium valproate - is a third-line anticonvulsant. The loading dose is 30-50 mg/kg orally or rectally. The maintenance dose is 5-10 mg/kg orally every 12 hours. It should, however, be used with caution in newborns given the uncertain risk of hepatotoxicity.(11,14)

11. Another anticonvulsants. There are some drugs insufficiently tested in the newborn**: Lamotrigin, Topiramat, Felbamat, Zonisamid, Vigabatrin.** Insufficient existing data don't allow pertinent dosing recommendations for the treatment of refractory neonatal seizures, but they are "promising" future drugs.

12. A therapeutic trial of **pyridoxine** (B6), under EEG or aEGG monitoring is the last resort therapy in refractory seizures. The dose is 50-100 mg i.v. (preferred) or i.m. In idiopathic seizures, refractory to all unspecific and specific therapies **folinic acid,** is recommended.(28)

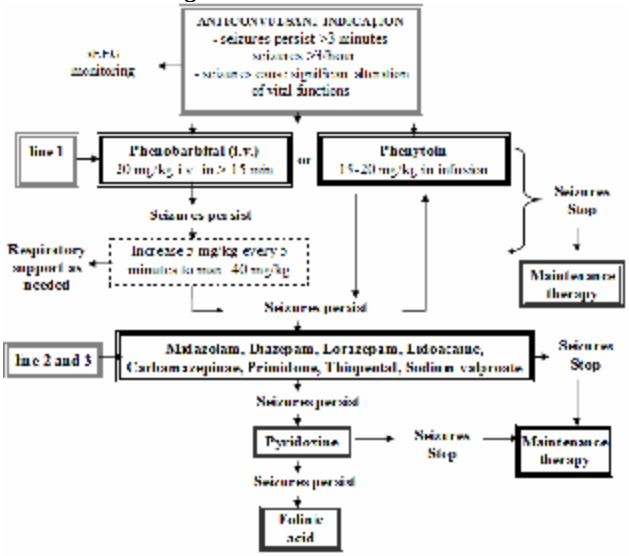
Duration of anticonvulsant therapy

The duration of the therapy has to be decied on individual basis considering the gestational age, history, etiology, type of the seizures, baseline EEG aspect, the response to the therapy and the persistence of the abnormal neurological signs.

The discontinuation of the anticonvulsants is recommended before discharging the newborn if the seizures are controlled and neurological exam of the baby is normal (risk of recurrence is < 8% during the first year of life). The anticonvulsant therapy may be stopped in a newborn with normal neurological examination 2 weeks after the last clinical seizure even if the EEG route shows minimal abnormalities, or EEG is normal but the neurological examination remains abnormal. If EEG is normal the anticonvulsant therapy is no longer justified. (11,18,24)

If the EEG pattern is paroxysmal in the absence of clinical manifestations, the anticonvulsant therapy should be continued at maximal dosage, due to the high risk of seizures recurrence.(11,15)

Anticonvulsant algorithm in neonatal seizures



Follow-up

Newborns with neonatal seizures that required anticonvulsant have to be periodically monitored, since seizures and anticonvulsant therapy are predisposing risk factors for cognitive, neurological, developmental abnormalities and epilepsy.(10,24) This patients should be guided to the pediatric neurologist. The monitoring of therapy, dosage adjustment of anticonvulsant after the neonatal period, and EEG monitoring should be done by a pediatric neurologist. Pediatric neurologist will also decide discontinuation of anticonvulsant therapy.

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