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# LEVETIRACETAM FOR THE TREATMENT OF NEONATAL SEIZURES

**Paediatrics**

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## ABSTRACT

Neonatal seizures remain a significant clinical problem and are often refractory to treatment with initial anti-seizure medications. There are only a few treatment options in neonates with seizures because antiepileptic medications such as Phenobarbital, phenytoin and benzodiazepines and are rarely effective in controlling epileptogenesis in neonates. Due to favourable pharmacokinetics and side effects profile and positive efficacy outcomes in neonatal seizures to-date, there is great interest in the use of Levetiracetam in neonates. In this mini review, we discuss the Levetiracetam as an emerging antiepileptic in neonatal seizures.

## KEYWORDS

Levetiracetam, Neonates, Review, Seizures

## INTRODUCTION

Neonatal seizures are one of the most commonly encountered emergencies in paediatrics (1). Neonatal seizures are clinically defined as abnormal, stereotyped and paroxysmal dysfunctions in the central nervous system, occurring within the first 28 days after birth in full term infants or before 44 weeks of gestational age in preterm infants (2). They affect up-to 1.5-3.5/1000 in full term infants and 10-130/1000 in preterm infants (3). Longer seizures and status epilepticus develop more readily at this age, but convulsive neonatal status epilepticus is not as severe as that of older infants and children. Due to maturational differences and adverse complications of the brain, preterm infants of less than 30 weeks of gestation have a higher incidence of seizures compared to neonates older than 30 weeks (4).

Neonatal seizures are rarely idiopathic (5). Hypoxic ischemic encephalopathy ( HIE) due to asphyxia is the most common cause of seizure activity in neonatal population, counts for about two-third of neonatal seizures(6). HIE usually cause seizure within the first 24hours of life (7). Apart from HIE, focal cerebral infarction and intracranial haemorrhage are the most common causes of seizures (8).

| CAUSES OF NEONATAL SEIZURES(7,8) | |
|---|---|
| Hypoxic ischemic brain injury | GLOBAL: hypoxic ischemic encephalopathy<br>FOCAL: cerebral infarction |
| Intracranial haemorrhage | Intra ventricular, Intra cerebral, Subarachnoid |
| CNS Infection | Meningitis, Encephalitis |
| Metabolic | Hypoglycaemia, hypocalcemia, hypomanesemia<br>Inborn errors of metabolism |
| Drug withdrawal or intoxication | Methadone |
| Developmental abnormalities of brain | Migration disorders |
| Epilepsy syndromes | Benign familial neonatal convulsions<br>Early myoclonic encephalopathy<br>Ohtahara syndrome |

Seizures in the neonatal period can be classified into one of three categories, described by Glass et al. As Clinical only, electrographic only and both (9).During development of the neonatal brain, excitatory neurotransmitters (Glutamate) and receptors mature faster than inhibitory gamma-amino butyric acid (GABA) (10). This imbalance, along with the increased concentration of synapses in the neonatal brain, may explain the lower seizure threshold during the neonatal period (10). Potassium chloride receptor 2 is not fully expressed until the end of first year of life; therefore, minimal Chloride is exported which ultimately lead to a high intracellular chloride concentration and it results in synaptic firing (11). The combination of decreased GABA function, increased glutamate function and reversed Chloride gradient potentially decreases the neonatal threshold (12). Generalised seizures are rare in neonates due to immature myelination of the nervous system.

Clonic seizures are more common and will usually begin in one extremity then migrate to opposite extremity (13). Neonatal seizures differ considerably from seizures observed in older children, probably because the immature brain is less capable of propagating electrical seizures (8). Abnormal, repetitive and stereotypic behaviours of neonates should be suspected and evaluated as neonatal seizures. The neonatal electroencephalography (EEG) is probably one of the best and most useful of detecting neonatal seizures . However, neonatal EEG recordings and interpretations require the special skills of well trained physicians and technologists. In addition, video EEG recordings have revealed that up-to 80% of electrographic seizures in neonates lack a clinical correlate. This is particularly likely in encephalopathic newborns. This phenomenon is described as the electro-clinical dissociation or uncoupling (7). It has been found that prolonged seizures may lead to poor neuro-developmental outcome thus appropriate treatment of neonatal seizures is important in reducing long term neurologic disabilities (14).

There are only a few treatment options in neonates with seizures because antiepileptic medications such as Phenobarbital, phenytoin and benzodiazepines are rarely effective in controlling epileptogenesis in neonates, and the known risk of adverse effect on cognition effect of Phenobarbital in infants(15). Efficacy data for Phenobarbital and phenytoin indicate that these medications successfully control neonatal seizures in fewer than 50% of patients when used as monotherapy (16). Good CNS penetration, low protein binding and optimal efficacy make phenobarbitone the drug of choice for the management of neonatal seizures (17). When used in combination, the percentage of seizure resolution rises up-to 60% of all treated cases (18). However , long term use is associated with an impairment of maturation of synapses and enhanced neuronal apoptosis (1).Therefore, a necessity for new efficient and safe AEDs for newborns has emerged. Levetiracetam (LEV) has been suggested that Levetiracetam is commonly recommended by pediatric neurologists managing neonatal seizures (19). Levetiracetam has been emerging as potential therapeutic opinion for refractory neonatal convulsions owing to its safety in liver failure, low protein binding, minimal adverse effects and nearly no drug interactions. In addition, when looking at long term effects in neonates treated for seizures, Phenobarbital exposure was associated with worsening

neurodevelopmental outcomes, which were not seen when compared to results obtained with Levetiracetam at 2 years in a study conducted by Maitre N et al (20). Instead of favourable pharmacokinetic and safety profile, use of levetiracetam as a first line agent is low and current guidelines for neonatal seizures management list levetiracetam as only second line therapy. In the study by Han et al LEV use has demonstrated seizure cessation within 24h in 57% (21/37) of patients (2). In a study conducted by Falsaperla R et al has demonstrated that that all patients included in their study has esponded to LEV, with a variety range of seizure resolution period (from 24h to 15days) and no patents required a second anticonvulsant therapy(21).

## MECHANISM OF ACTION

LEV a second generation anti-epileptic is approved by Central Drug Standard Control Organization (CDSCO) and Food Drug Administration (FDA) as an adjunctive therapy for partial onset seizure in infants beyond one month of age. However, the drug has been used off-label in the management of neonatal seizures (22). Levetiracetam, a novel agent, provides a new target, the synaptic vesicle protein SV2a, which avoids challenging characteristics in the neonatal brain that other antiepileptics encounter (23). Levetiracetam a pyrrolidine derivative antiepileptic having novel mechanism of action as it acts by binding to the synaptic vesicle protein SV2a, which is expressed throughout the brain. LEV binding to SV2a impedes glutamate release in presynaptic neurons and then regulating regulating the intracellular calcium of postsynaptic neurons through NMDA and AMPA receptors (24). Because SV2a is found in all areas of the brain, it can treat partial seizures that arise in various regions of the brain, as seen in neonates.

### Pharmacokinetics

There are limited studies on the pharmacokinetics of LEV in the neonatal age group. In adults, LEV exhibits high bioavailability>95%, quickly reaches peak and steady state concentration in 1.3hours, displays linear time dependent kinetics (25). Levetiracetam has median half life of 8.9hours, as expected on the basis of the lower clearance of levetiracetam in neonates. The half life is 6-8hours in adults and 5-7hours in older children. Merhar et al observed that the clearance of LEV in premature infants receiving 14.4 to 39.9mg/kg of LEV was reduced compared to that in children and adults(half life of approximately 9 hours compared to 5-7 hours and 7-8 hours respectively (26). In a study by Mehar et al the median volume of distribution was 0.89L/kg in neonates (26). Levetiracetam has lower protein binding (about 10%) than medications such as phenytoin (90%), resulting in less serum drug variability in neonates (27).The Vd is 0.5 to 0.7L/kg in adults and 0.6-0.7L/kg in older children (28). The drug is metabolised by type B esterases in whole blood to inactive metabolite, thus undergoes minimal hepatic metabolism, resulting in fewer drug –drug interactions. Approximately 66% of the drug is eliminated in the urine, and clearance is dependent on renal function.

### Dose

The use of levetiracetam in neonatal seizures continue to increase. Its Intravenous (IV) formulations, limited interactions and benign side effect profile make it an attractive treatment option. Reported loading doses vary from 10-20 mg/kg to as high as 40-50 mg/kg. The maximal amount of LEV infused in a newborn was 150mg/kg within a 24 hours period (29). Maintenance doses described also vary from 10-80 mg/kg/day with most providers starting at 20 mg/kg/day, whereas others suggest 40 mg/kg/day. Although twice daily dosing is usual, three times a day dose has been suggested (7). In a study by Ramantani G et al, Intravenous LEV was used as first line therapy with more effectiveness than Phenobarbital, without any side effects (30). But we eagerly look forward to the results of phase II trial planned to determine the optimal dosing of levetiracetam as the first line drug for the management of neonatal seizures (31). The study by Gowda et al, provides evidence to support the use of LEV in neonatal seizures (32).

### Side effects

Anti-seizure medications such as NMDA (N-methyl D- aspartate) receptor antagonists, GABA agonists and Sodium channel blockers have been considered to potentiate neuro-degeneration in the developing brain of animal models. In contrast, LEV has shown a favourable neurodevelopment outcomes and lack of neurodegenerative effects in early animal studies, making LEV a fair treatment option in neonatal seizures (2). In a study by Ji Yon Han et al, the vital signs and laboratory findings have not revealed any adverse effects following administration of LEV (2). In a study no major side effects were observed, nearly 50% of the cases presented lethargy and feeding difficulty, which were found to be resolved after reduction adjustments of doses (21). One of the uncommon side effects described in therapy with LEV was increased irritability and tiredness (33).

### Future

Two large multicentric studies of intravenous LEV use are currently under way. The first LEVNEONAT , is a multicentre French clinical trial with the aim to develop new treatment strategies for the treatment of neonatal seizures using LEV with the purpose to determine the correct dosing,safety and efficacy of the intravenous LEV as a first line treatment in term newborns with seizures secondary to HIE (34,35). The aim of the second study is to determine the efficacy of intravenous LEV as a first line anticonvulsant for the treatment of neonatal seizures, compared to Phenobarbital (36).

LEV in the rat model has demonstrated to lack any neurotoxic effects at all therapeutic doses (37). Levetiracetam has been found to not increase apoptosis in a developing rodent brain or interfere with neuroprotective up-regulation of hypoxia inducible transcription factor 1(HIF-1a)(38). It can also decrease neurodegeneration in rodent models of hypoxic ischemia or epilepsy. LEV has been demonstrated to increase expression of gamma glutamate transporters (GLTs) excitatory amino acid transporter 1/glutamate-aspartate transporter (EAAT1/GLAST) and EAAT2/GLT1, which mechanism has been proposed one of the most important effects of LEV in neuro-protection (39,40). In this context, LEV has also been demonstrated to decrease the expression of pro oxidant protein inducible nitric oxide synthase and increase the expression of the antioxidant protein cysteine/glutamate exchanger in the hippocampus(41), diminishing those damages caused by seizure induced oxidative stress(42).

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