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Phenobarbitone in Neonatal Seizures: Controversies

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Abstract

Seizures are defined clinically as a paroxysmal alteration in neurologic function, i.e., motor, behaviour and/or autonomic function. Seizures are the most important signal of neurological disease in the neonatal period. They occur in 1-5% of the new-borns. The incidence is higher during this period than in any other period in life. It is important to treat seizures because of the potential adverse effects of seizure on respiratory function, circulation, cerebral metabolism and brain development. If aEEG is being used, termination of all electrical seizure activity should be the goal of therapy. Though mortality due to neonatal seizures has decreased from 40% to about 20% over the years, the prevalence of long term neurodevelopmental sequel has remained almost unchanged at around 30%. This signifies that the treatment of neonatal seizures is still inappropriate and there is a potential for improvement. Current guidelines are based on limited clinical data. The controversies regarding the best first line agent, second line agent, dose and duration, monitoring the drug levels still continue.

Keywords: Depolarisation; EEG; Electrical seizures; GABA; Phenobarbitone; Seizure

Neonatal Seizures

Seizures are defined clinically as a paroxysmal alteration in neurologic function, i.e., motor, behaviour and/or autonomic function [1]. Seizures are the most important signal of neurological disease in the neonatal period. They occur in 1-5% of the new-borns [2]. The incidence is higher during this period than in any other period in life.

Seizures can be classified as [3]:

Epileptic seizures: Phenomenon associated with corresponding EEG seizure activity, e.g. clonic seizures. 2. Non–epileptic seizures: Clinical seizures without corresponding EEG correlate, e.g. subtle and generalised tonic seizures. 3. EEG seizures: Abnormal EEG activity with no clinical correlation (electroclinical dissociation).

Neonatal seizure activity results from an excessive synchronous electrical discharge (i.e., depolarization) of neurons within the central nervous system. The process of depolarization occurs by the inward migration of sodium (Na+), and repolarization by the efflux of potassium (K+) [3].

Certain clinical seizures (e.g. subtle seizures), most generalized tonic seizures and the focal and multifocal types of myoclonic seizures in the new-born originate from electrical seizures in deep cerebral structures (limbic regions), or in diencephalon, or brain stem structures and thereby are either not detected by surface-recorded EEG or inconsistently propagated to the surface. Treating such phenomenon is still a controversial issue. Electroclinical dissociation is the occurrence of only electrographic seizures not accompanied by clinical seizure activity. This dissociation is especially common in the most immature infants and in those treated with anticonvulsant drugs especially phenobarbitone. The main reason behind this is GABA acting as excitatory rather than inhibitory neurotransmitter in the developing brain. And the usual AEDs which are GABA agonist are unable to diminish the electrical seizure activity completely. The common causes of seizures include hypoxic ischemic encephalopathy, metabolic disturbances (hypoglycaemia, hypocalcemia and hypomagnesemia) and meningitis. Table 1 shows the frequency, time of onset of seizures and typical clinical symptoms for each of them [3].

It is important to treat seizures because of the potential adverse effects of seizure on respiratory function, circulation, cerebral metabolism, and brain development. If an EEG is being used, termination of all electrical seizure activity should be the goal of therapy [3]. Though mortality due to neonatal seizures has decreased from 40% to about 20% over the years, the prevalence of long term neurodevelopmental sequel has remained almost unchanged at around 30% [1]. This signifies that the treatment of neonatal seizures is still inappropriate and there is a potential for improvement. Current guidelines are based on limited clinical data. The controversies regarding the best first line agent, second line agent, dose and duration, monitoring the drug levels still continue.

Phenobarbitone has been historically recommended and popularly used as first choice drug for neonatal seizures in loading dose of 20 mg/kg/dose @1 mg/kg/min. Phenobarbitone acts by facilitating GABA mediated inhibition. It increases the mean open duration of the GABAA receptor, thereby increasing Cl- flux, hyperpolarizing the post-synaptic neuronal membrane and interrupting the spread of epileptic activity [3].

Phenobarbitone enters the CSF and most likely brain rapidly and with high efficacy. Also, evidence suggests that entrance of phenobarbitone into brain is increased by the local acidosis associated with seizure. Free levels of the drug are higher in the new-born and infants due to low protein binding [3].

Phenobarbitone induces hepatic metabolism and is therefore associated with large number of drug interactions. It decreases the serum concentration of other concurrently administered anticonvulsants thereby decreasing their efficacy. Valproic acid if administered simultaneously can inhibit the metabolism of phenobarbitone and raise the levels of the drug [4]. Besides this phenobarbitone causes decrease in the effect of paracetamol, increase

in clearance of steroids, rifampicin, theophylline, propranolol and metronidazole [5]. Respiratory effort should be monitored during administration of phenobarbitone.

Despite being most commonly used, various trials have shown limitation of phenobarbitone in control of seizures in neonatal period. Moreover, there are concerns regarding its adverse effects on brain. The Cochrane review [6] found only one RCT that showed comparable seizure control rate with phenobarbital and phenytoin (RR 1.03, 95% CI 0.96 to 1.62), controlling seizures in only half of cases. A recent trial by Pathak et al. demonstrated phenobarbitone to be more effective than phenytoin as first line drug in control of clinical seizures [7]. The study by Perveen et al. demonstrated that phenobarbitone is more efficacious than levetiracetam in treatment of clinically apparent neonatal seizures in term and late preterm neonates with seizures due to perinatal asphyxia [8]. Table 2 summarises the various studies comparing the efficacy of phenobarbitone. Based on available evidence, the WHO guidelines on neonatal seizures currently recommend phenobarbitone as the first line agent for management of neonatal seizures [9].

Cause	Frequency	Typical clinical symptoms	Onset
Hypoxic-ischaemic encephalopathy	30-53%	History of delayed cry, poor Apgar, dull baby	1st 6-12 h
Intracranial haemorrhage (sub arachnoid hemorrhage)	7-17%	Well baby with seizures CT is diagnostic	2-3 days
Cerebral infarction	6-17%	Decrease movement of opposite side but this may not be visible in acute period	Variable
Cerebral malformations	3-17%	Well baby with seizures head size may be abnormal	Variable
Meningitis/septicaemia	2-14%	Associated with fever, bulging fontanelle	After 3 days
Hypoglycaemia Hypocalcaemia, hypomagnesemia Hypo-/hypernatraemia Hyernatremia	0.1-5% 4-22%	IUGR, preterm, infant of diabetic mother. Exclusive breast feed baby with excess weight loss and decrease urine output	1st 48 h
Inborn errors of metabolism	3-4%	Refractory seizures with no often predisposing factor or consanguinity.	Variable
Kernicterus	1%	Severe jaundice	Variable

Table 1: Seizure etiology and their frequency.

Painter et al. showed that the dose of 20 mg/kg is necessary to achieve a blood level of about 20 mcg/ml [14]. Jalling et al. reported that convulsion ceased at serum levels between 12 and 30 mcg/ml, although there was a subgroup of convulsing patients whose seizures could not be controlled despite achievement of therapeutic levels [15]. Ouvrier and Goldsmith have also documented seizure control with phenobarbitone levels in range of 7 to 15 mcg/ml [16]. Wasim et al. performed a prospective observational-study in 99 neonates and reported clinical seizure cessation in 44 neonates (44%) after a single loading dose of 20 mg/kg of phenobarbital. The study demonstrated that more than a third of neonates with sub-therapeutic serum phenobarbital levels also had clinical control of seizures. This finding indicates that the seizure control may be somewhat independent of serum levels of phenobarbitone. However, the minimum serum phenobarbitone level at which seizure was controlled was 6 mcg/ml. Also, the study recommended serum level monitoring in cases of suspected side effects of this drug, or if multiple doses have been given [17].

The data on safety and efficacy of phenobarbitone in relation to its dosage and blood levels is limited. Following the loading dose of phenobarbitone, giving maintenance doses has been a conventional practice. Twenty-four hours after the loading dose, starting maintenance doses at 3-6 mg/kg/day is the most commonly followed practice. Its purpose is to maintain the serum levels built by the loading dose. Also, it has long half-life of about 72-100 h, which covers the period of maximum probability of seizure recurrence in most cases.

Trial	Efficacy and control rate
Gilman et al. [10]	Clinical control=75% with phenobarbitone and 85% when both phenytoin and phenobarbitone were used.
Painter et al. [11]	Electrical control=45% with either phenobarbitone or phenytoin and 60% when both the drugs were used.
Boylan et al. [12]	Electrical control=29% with phenobarbitone
Pathak et al. [7]	Clinical control=72.2% with phenobarbitone and with 14.5% with phenytoin
Pranjali et al. [13]	Clinical control=62% with phenobarbitone
Perveen et al. [8]	Clinical control=86.7% with phenobarbitone and 23.3% with levetiracetam

Table 2: Different trials comparing efficacy and control rate of phenobarbitone.

Historically, phenobarbitone prophylaxis has been used for weeks to months even after control of neonatal seizures, to minimize the risk of recurrence [18,19]. However, there is accumulating evidence that its long term use may be associated with neuronal apoptosis that can lead to impairment of behaviour, intelligence, cognition, learning and memory [3]. It has also been demonstrated that early phenobarbitone discontinuation in clinically stable neonates does not lead to increase in breakthrough seizures [20]. There is data to suggest that phenobarbitone administration after seizure control does not improve

neurological outcome [21]. Though WHO has recently recommended stoppage of phenobarbitone within 3 days of loading dose [9], timing of phenobarbitone discontinuation after control of seizure is a matter of debate and needs further research. Theodore et al. [22] have reported that little correlation exists between the rate of phenobarbitone withdrawal and seizure control. He observed no significant difference in recurrence of seizures, irrespective of maintenance therapy after discharge. He also reported that abnormal neurological outcome and cerebral palsy were more common in children discharged on phenobarbitone. A recent trial at our institute by Saxena et al. evaluated the withholding of maintenance doses of phenobarbitone altogether, in a RCT in 154 babies. The study demonstrated that the clinical breakthrough seizures till discharge are not likely to increase on withholding phenobarbitone maintenance after the loading dose. It was observed that mortality and abnormal neurodevelopmental outcomes till 3 months were slightly higher in placebo group, though it was not statistically significant [13].

Due to encouraging results of trials on early cessation of phenobarbitone coupled with well documented adverse effects of drug, WHO has recommended reduction in duration of maintenance therapy to three days after seizure control [9].

Considering the magnitude of seizures in the neonatal period, further studies are warranted for studying the side effect profile, serum drug levels of phenobarbitone and other antiepileptics and long term neurodevelopmental outcomes with different AEDs.

References

1. Agarwal R, Deorari A, Paul K Vinod (2015) AIIMS protocols in neonatology. (1stedn), CBS Publishers and Distributors, New Delhi, India.
2. Clancy RR (2006) Summary proceedings from the neurology group on neonatal seizures. Pediatrics 117: S23-27.
3. Volpe JJ (2008) Neonatal seizures. Neurology of the new-born. (5th edn), WB Saunders Philadelphia.
4. Perucca E (2006) Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol 61: 246-255.
5. New-born Drug Protocol - Phenobarbitone Pharmacology.
6. Booth D, Evans DJ (2004) Anticonvulsants for neonates with seizures. Cochrane Database Syst Rev : CD004218.
7. Pathak G, Upadhyay A, Pathak U, Chawla D, Goel SP (2013) Phenobarbitone versus phenytoin for treatment of neonatal seizures: An open-label randomized controlled trial. Indian Pediatr 50: 753-757.
8. Perveen S, Singh A, Upadhyay A, Singh N, Chauhan R (2016) A randomized controlled trial on comparison of phenobarbitone and levetiracetam for the treatment of neonatal seizures: Pilot study. Int J Res Med Sci 2073–2078.
9. WHO (2012) Guidelines on neonatal seizures. Geneva: World Health Organization.
10. Gilman JT, Gal P, Duchowny MS, Weaver RL, Ransom JL (1989) Rapid sequential phenobarbital treatment of neonatal seizures. Pediatrics 83: 674-678.
11. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, et al. (1999) Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med 341: 485-489.
12. Boylan GB, Rennie JM, Pressler RM, Wilson G, Morton M, et al. (2002) Phenobarbitone, neonatal seizures and video-EEG. Arch Dis Child Fetal Neonatal Ed 86: F165-170.
13. Saxena P, Upadhyay A, Singh A, Gupta NK (2014) Effect of withholding phenobarbitone maintenance on treatment of neonatal seizures: A Randomized control trial. Pediatric Academic Societies.
14. Painter MJ, Pippenger C, MacDonald H, Pitlick W (1978) Phenobarbital and diphenylhydantoin levels in neonates with seizures. J Pediatr 92: 315-319.
15. Jalling B (1975) Plasma concentrations of phenobarbital in the treatment of seizures in newborns. Acta Paediatr Scand 64: 514-524.
16. Ouvrier RA, Goldsmith R (1982) Phenobarbitone dosage in neonatal convulsions. Arch Dis Child 57: 653-657.
17. Wasim S, Upadhyay A, Roy M, Saxena P, Chillar N (2016) Serum Phenobarbitone Levels in Term and Near Term Neonates with Seizures. Indian Pediatr 53: 388-390.
18. Boer HR, Gal P (1982) Neonatal seizures: a survey of current practice. Clin Pediatr (Phila) 21: 453-457.
19. Massingale TW, Buttross S (1993) Survey of treatment practices for neonatal seizures. J Perinatol 13: 107-110.
20. Tekgul H, Gauvreau K, Soul J, Murphy L, Robertson R, et al. (2006) The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics 117: 1270-1280.
21. Gal P, Boer HR (1982) Early discontinuation of anticonvulsants after neonatal seizures: A preliminary report. South Med J 75: 298-300.
22. Theodore WH, Porter RJ, Raubertas RF (1987) Seizures during barbiturate withdrawal: Relation to blood level. Ann Neurol 22: 644-647.