

Phenobarbital for Neonatal Seizures: A Time for Perusal

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The neonatal period is the highest risk period for seizures during the lifespan of humans, with seizures occurring in 1-5% of the neonates [1]. Despite the magnitude of the problem, the current treatment paradigms are based on limited clinical evidence; the debate concerning the best drug or drugs, their dose and duration still continues. Phenobarbital is the most commonly prescribed anticonvulsant worldwide for treatment of neonatal seizures. There are limited studies exploring the effectiveness of phenobarbital. The reported seizure cessation rates vary between 33% to 40% after a single loading dose of 15-20 mg/kg [2]. In a study by Gilman, *et al.* [3], rapid sequential loading with phenobarbital (up to 40 mg/kg) could improve the clinical response rate in neonates with seizures ($n=120$) till a cumulative response rate of 77%. However, the therapeutic effect plateaued after serum levels of 40 $\mu\text{g}/\text{mL}$ [3]. Furthermore, there is limited data on efficacy and safety of phenobarbital in relation to its dosage and blood levels [4]. The study by Wasim, *et al.* [5] in this issue of *Indian Pediatrics* addresses this critical issue of drug efficacy and serum drug levels. The authors performed a prospective observational-study in 99 neonates. They reported clinical seizure cessation in 44 neonates (44%) after a single loading dose of 20 mg/kg of phenobarbital. Interestingly, more than a third of neonates with sub-therapeutic serum phenobarbital levels had clinical seizure cessation. This finding could indicate that either the seizure control is independent of serum levels or the current cut-off values of therapeutic drug levels need to be revisited.

Rapid achievement of therapeutic levels (through intravenous or intramuscular routes) has been reported to result in earlier control of serial seizures in neonates [6]. However, neonates with adequate serum phenobarbital levels may still not achieve seizure control [6-8]. There may be several reasons for this observation; the underlying etiology, altered drug pharmacokinetics, and altered blood-brain barrier properties. Additionally, greater serum phenobarbital levels may be required for

seizure control in preterms as they have a lower brain to plasma ratio of phenobarbital [9]. There is also a wide variability in the pharmacokinetic parameters in neonates; like the volume of distribution, fraction unbound in plasma, and the elimination half-life [10]. Additional factors influencing drug pharmacokinetics include frequent use of hypothermia and other drugs used to treat the sick neonate. Given the multitude of factors, therapeutic drug monitoring for phenobarbital should be encouraged for optimal care of neonates with seizures.

The work by Wasim, *et al.* [5] has certain limitations which can be avoided in future studies. The foremost limitation was the lack of use of video EEG as a diagnostic tool and for defining endpoints. Neonatal seizures are difficult to recognize clinically, and both over- and under-diagnosis are common. Electrical seizures (as confirmed by EEG) have been shown to persist in 53% neonates treated with phenobarbital/phenytoin [11]. Phenobarbital has also been reported to increase electro-clinical dissociation in neonatal seizures [12]. Therefore, the clinical assessment alone should not be used for evaluating the efficacy of phenobarbital in controlling the seizure activity. Any research in the field of neonatal seizures should preferably use multichannel video-EEG to define and monitor seizure activity. While using the EEG, the degree to which electrical seizures need to be suppressed, is again an unresolved issue. The pharmacodynamic curves for clinical and EEG seizure control with phenobarbital have been suggested [3,12,13]. The ideal goal may be a total suppression of electrographic seizures. However, such suppression will require intensive monitoring, use of drugs in high doses, and a possibility of drug-related toxicities. An integral part of intensive monitoring should be therapeutic drug monitoring.

Phenobarbital may have a role in the prevention of seizures as well. Phenobarbital (20 mg/kg IV) given within 6 hours of life to term and near-term neonates with hypoxic ischemic encephalopathy, significantly decreased the incidence of neonatal seizures as compared

to placebo (8% vs. 40%; $P=0.01$) in one randomized trial with small sample size [14]. When used as a preventive drug, the target should be to achieve seizure prevention with no drug-related toxicity. In this context, therapeutic drug monitoring can help to titrate the serum levels in the therapeutic range.

There has been a concern of long-term neurodevelopmental adverse effects of drugs used during the neonatal period. Phenobarbital enhances chloride flux through the GABA-A receptor and may cause neuronal apoptosis; an observation demonstrated in the immature rat brain at plasma concentrations relevant for seizure control in humans [15]. In the study by Wasim, *et al.* [5], repeated loading doses of phenobarbitone resulted in significant increase in the number of neonates attaining toxic levels (4/6 neonates loaded with 40 mg/kg phenobarbital had toxic levels after 12 hours). The study raises a question over the practice of repeated loading with phenobarbital in neonates who do not respond to the initial dose or who have recurrences while on maintenance doses.

The study by Wasim, *et al.* [5] has not addressed many factors (like hepatic, renal functions, serum proteins, co-medications), which may have potentially influenced the serum phenobarbital levels. Any future studies on therapeutic drug monitoring should also consider these and other factors that can potentially influence drug levels. Despite this, findings of the study by Wasim, *et al.* [5] are significant, and should stimulate further scientific exploration of therapeutic monitoring of phenobarbital and other drugs in neonates. Neonates are a special and vulnerable research group among an already vulnerable group of children; and therefore, drugs in wide use like phenobarbital need to be evaluated with rigor. The reports of long-term adverse effects of antiepileptics and other drugs used in neonates should serve as the basis for more rigorous study of pharmacokinetics and pharmacodynamics of these drugs in neonates.

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