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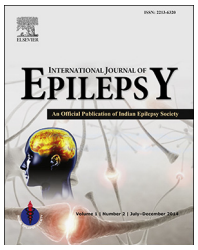

Phenobarbitone: Indian Epilepsy Society-Consensus Document

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Epilepsy is a common neurological disorder affecting 65 million people worldwide and approximately more than 12 million in India. Two-third of the people with epilepsy lives in resource-limited countries. Phenobarbitone was the first anti-epileptic drug (AED) used in 1912 and has been in use for more than 100 years now. Its low cost and favorable cost-efficacy ratio, which is lower than any other AED in current use, makes the drug particularly suitable for use in the low- and middle-income countries. [1] The World Health Organization (WHO) recommends phenobarbitone as a first-line treatment for convulsive seizures in resource-poor countries and includes it in its Essential Drug List. [2] However, the use of phenobarbitone is largely limited owing to the concerns regarding its cognitive and behavioral side effects especially in children. This article summarizes the current role of phenobarbitone in the treatment of epilepsy.

Tables 1-5

1. Recommendations

The Indian Epilepsy Society has the Guidelines in the Management of Epilepsy in India (GEMIND) where phenobarbitone is mentioned as a first-line drug in the management of all types of epilepsy other than absence seizures. The recommendations are based on the information collated from the key studies and systematic reviews related to Phenobarbitone.

2. Mechanism of Action

Phenobarbitone interacts with γ-aminobutyric acid-A (GABAA) receptors and facilitates GABA-mediated inhibition via allosteric modulation of the receptor. It inhibits epileptic activity by other mechanisms such as - increase in chloride-influx leading to hyperpolarization of the postsynaptic neuronal cell membrane [3,4]; blocking high-frequency repetitive firing of neurons; and reduction in glutamate or aspartate-induced depolarization [5].

3. Pharmacokinetics

- Phenobarbitone can be administered by both parenteral (intravenous and intramuscular) and oral routes.
- It is rapidly absorbed and distributed to all tissues and fluids with high concentrations in the liver, kidneys and heart.
- It reaches peak plasma concentration after 0.5–4 h after oral dosing and 2–8 h after intramuscular administration.
- The drug has long half-life, approximately 3-5 days in adults and 1.5 days in children so it is usually given as once daily dose and poses low risk of withdrawal seizures.

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Table 1 – Comparison of various studies listing problems with the use of phenobarbitone.

Study (year)	Subjects	Comments
Mani et al (2001)	135 (phenobarbitone: 55)	4% on phenobarbitone while 43% on PHT had adverse effects
Wang et al (2006)	2455 (phenobarbitone) patients	Phenobarbitone was well tolerated
Satishchandra et al (2014)	75 (63 completed) adult patients with newly diagnosed epilepsy-prospective multi-centric study	No worsening of cognitive or psychological functioning; good seizure control improvement in attention, executive functions, learning, memory, and intelligence. Self-report of cognitive impairment consequent to the epilepsy and its treatment showed a decrease. No deterioration in daily activities and depression.
Meador et al (1995)	59 healthy adults received phenobarbitone, PHT or VPA	Those on phenobarbitone were worse (not significant) than either PHT or VPA, PHT and VPA were comparable.
Tudur Smith et al (2003)	684 patients	Phenobarbitone and CBZ did not differ for the outcomes of 'time to 12 month remission' and 'time to first seizure' phenobarbitone more likely to be withdrawn indicating less tolerance as compared with CBZ.
Feksi et al (1991)	302 (249 completed the study)	53% seizure-free low drop-out rate, low rate of withdrawal due to adverse effects and acceptable compliance.

Adapted with permission from: Satishchandra P, Rao SL, Ravat S, et al. Epilepsy Res 2014; 108:928-36
PHT: phenytoin; VPA: valproate; CBZ: carbamazepine

- Therapeutic drug levels of phenobarbitone = 10 mg/L to 40 mg/L. [6]
- It undergoes auto-induction and increases its own clearance, therefore requires an upward dose adjustment when prescribed as monotherapy.

4. Spectrum

- It is a board spectrum AED used clinically in neonatal seizures, status epilepticus (SE), focal and generalized tonic–clonic seizures, febrile seizure (continuous prophylaxis), and as add-on in refractory epilepsy.
- Absence seizures however do not respond to phenobarbitone and may be aggravated. [7]
- It has also been found useful in the treatment of juvenile myoclonic epilepsy. [8]

Table 2 – Few Examples of Drug Interactions Involving Phenobarbital.

Acetazolamide	Increase Phenobarbital levels
Phenytoin	Increase Phenobarbital levels by 50-70%
Valproic acid	30-50% increase in Phenobarbital levels
Oxcarbazepine	Increase Phenobarbital levels by 15% at doses > 1200 mg/day
Clobazam	Phenobarbital enhances metabolism of clobazam
Oral contraceptives	Failure of oral contraceptives
Warfarin	Phenobarbital induces metabolism of warfarin
Steroids, antimicrobials, antineoplastic drugs	Decrease levels of drugs by phenobarbital

4.1. *Adverse Effects*

- Like most other AEDs, phenobarbitone is associated with dose-dependent adverse effects.
- Although phenobarbitone demonstrates overall tolerability similar to that of other established AEDs, and serious systemic side effects are uncommon, its potential for neurobehavioral toxicity remains a topic of major concern.
- Sedation and hypnosis are the principal side effects of phenobarbitone.

Table 3 – Pharmacokinetics of Phenobarbital.

Indication	Partial and generalized tonic-clonic seizures neonatal seizures; status epilepticus, febrile seizures
Not useful	Absence seizures
Mechanism of action	Enhance GABA inhibition
Bioavailability	>95%
Time to peak levels after single dose	0.5-4 h
Protein binding	45-60%
Elimination half-life	3-5 days (adults), 1.5 days (children)
Main routes of elimination	Hepatic metabolism; CYP 450 inducer 25% renally excreted unchanged
Maintenance dose	Children: 4-8 mg/kg/day Adults: 60-240 mg/day
Volume of distribution	0.42-0.73 L/kg
Daily doses	1-2
Target plasma concentration	10-40 g/mL
Clearance	Age>40 years, total clearance: 2.5 mL/kg/h Age 15-40 years, total clearance: 4.9 mL/kg/h Age 8 months to 4 years, total clearance: 5.3-14.1 mL/kg/h

Table 4 – Side-effect Profile of Phenobarbitone.

Relatively common	Uncommon
Neurobehavioral	Megaloblastic anemia
Sedation	Osteomalacia
Behavior	Hepatotoxicity
Hyperactivity	
Changes in mood and affect	
Adverse effect on cognition	
Connective tissue disorders	Aggravation of porphyria
Dupuytren's contracture	Hypersensitivity
Frozen shoulder	Teratogenicity

Modified and adapted from: Kwan P, Brodie JM. Epilepsia 2004; 45:1141-9

Table 5 – Phenobarbitone in Status Epilepticus.

Indication	Convulsive SE, nonconvulsive SE in children and adults, refractory SE
Bioavailability	Approximately 95%
Standard dosage in SE	20-40 mg/kg/day
Maintenance dose:	
In children	4-8 mg/kg/day
In adults	60-240 mg/kg/day
Route of elimination	Metabolized in liver; one-fourth excreted unchanged in urine
Advantages of phenobarbitone	Estimated efficacy of 73.6% Broad spectrum of action Affordability Comparative efficiency with other AEDs Neuroprotective effect
Common adverse effects	Respiratory depression, hypotension, severe sedation

SE: status epilepticus; AED: anti-epileptic drug.

- In elderly patients, it may cause excitement and confusion, while in children it may result in paradoxical hyperactivity.
- Careful evaluation of the randomized control trials does not provide convincing evidence for an excess of behavioral adverse effects, compared to other AEDs. [9]

4.2. *Phenobarbitone in Childhood Epilepsy*

- There is not sufficient evidence to establish the use of phenobarbitone in childhood epilepsy. [Based on the level of evidence from The International League Against Epilepsy (ILAE) Task Force 2013]
- Phenobarbitone is considered to be probably effective as initial monotherapy in children with focal onset of seizures, generalized tonic and clonic seizures. [10]
- Phenobarbitone may aggravate or precipitate absence seizures. [11]
- In children with refractory focal epilepsy, phenobarbitone can be considered as an additional therapy by a tertiary epilepsy specialist after use of first-line AEDs and adjunctive AEDs (National Institute for Clinical Excellence [NICE] 2012). [12]
- Phenobarbitone can be used as a second-line agent after benzodiazepines in treatment of convulsive SE in children and after glucose and calcium in neonates.[10,12]
- Several anecdotal case reports demonstrate successful usage of very high dose of phenobarbitone in the management of refractory SE in children.

4.3. *Phenobarbitone in Neonatal Seizures*

- Phenobarbital should be used as the first-line agent for treatment of neonatal seizures.
- In neonates with birth asphyxia, prophylactic usage of phenobarbitone is not recommended.
- Phenobarbitone in Febrile Seizures
- Prophylactic treatment with intermittent antipyretics, intermittent anticonvulsant (diazepam or clobazam), or continuous anticonvulsant (phenobarbitone or valproic acid) should not be considered for simple febrile seizures.
- Phenobarbitone may be effective at reducing febrile seizure recurrence in children with a history of simple or complex febrile seizures with risk of behavioral problems such as hyperactivity, irritability, aggression, and cognitive impairment. [13,14]
- Intermittent diazepam or continuous phenobarbitone may be no more effective at reducing the risk of subsequent epilepsy in children with febrile seizures.[13,14]
- The evidence is inconclusive whether phenobarbitone is more effective than sodium valproate (VPA) at reducing the proportion of children with febrile seizure recurrence.7

4.4. *Phenobarbitone in Status Epilepticus (SE)*

- A substantial number of physicians prescribe phenobarbitone as the initial line of treatment for generalized convulsive status epilepticus (GCSE). [15]
- In a study evaluating the treatment efficacy of initial management of GCSE by phenobarbitone, diazepam plus phenytoin, phenytoin, and lorazepam, it was found that phenobarbitone was no less effective than lorazepam (the best AED) in control of overt GCSE. [16] The same study also observed that phenobarbitone is similar to other AEDs in protecting against recurrence of GCSE over 12 h time period. Moreover, in the study population, the risk of AED-related adverse events was similar across all the four drug groups. Furthermore, in nearly half of the patients, phenobarbitone was successful as the first-line therapy.
- The loading dose of phenobarbitone in SE is 20–40 mg/kg and the maintenance dose is 4–8 mg/kg/day in children and is 60–240 mg/day in adults given at 1–2 daily doses with a target plasma concentration of 10–40 μg/mL.6
- In patients where the SE is resistant to first-line administration of benzodiazepines, phenobarbitone has been extensively used effectively as the next line of therapy. A study of meta-analysis of literature has recently suggested that phenobarbitone has an estimated efficacy of 73.6% (95% CI: 58.3–84.8%). [17] Significant advantage of phenobarbitone in addition to this efficacy is its potential neuroprotective effect.

- The efficacy of levetiracetam was reported to be lower than the efficacy of phenobarbitone.
- There is no sufficient evidence to demonstrate the superiority of VPA over phenobarbitone in the management of convulsive SE. [18] Phenobarbitone is one of the second-line AED in the management of convulsive SE.

4.5. *Phenobarbitone in Refractory Status Epilepticus*

- Refractory SE is associated with high morbidity and mortality.
- Phenobarbitone has been reported to be highly effective in the management of refractory SE.
- Very high dose of phenobarbitone is effective in the management of adult and elderly patients with RSE. [19]
- Very high dose of phenobarbitone (30-120 mg/kg) is effective in seizure control with milder side effects than thiopental infusion in childhood RSE. [20,21]

4.6. *Effect of Phenobarbitone in Pregnancy*

- Phenobarbital readily crosses the placenta and plasma concentrations in neonates are similar to those in the mother.
- Data from the European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) registry shows occurrence of congenital malformations. [22]
- Phenobarbital is associated with congenital anomalies such as dysmorphic face, Fallot tetralogy in heart, hydronephrosis, inguinal hernia with umbilical hernia, and congenial dislocation of the hip when exposed during the first trimester of pregnancy.
- Use of Phenobarbitone in Developing Countries
- The studies conducted in developed countries show neurobehavioral toxicity caused by phenobarbitone leads to high discontinuation rates of the drug, whereas when the drug is used in developing world no such neurobehavioral toxicity is reported. [23]
- In India, the treatment gap in epilepsy varies from 40% in Kerala to 90% in West Bengal. [24] There is a need for an effective, affordable, and acceptable AED to reduce this treatment gap. Phenobarbitone is most suited for this role due to its good efficacy, broad spectrum of action, unique mechanism of action, and recent evidence has demonstrated a favorable cognitive-behavioral profile. [25]
- The negative reputation of phenobarbitone regarding tolerability comes more from its lack of a commercial sponsor than from a critical analysis of the available literature. [26]

5. Conclusion

With epilepsy affecting more than 60 million people worldwide and over 80% of them living in resource-limited countries, a low-cost AED such as Phenobarbitone can play a significant role as the most cost-effective treatment. Though the adverse effect profile is controversial but recent evidence suggests it may be better tolerated thansuggested by the earlier studies.

6. National Advisory Board

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