ROLE OF PHENOBARBITONE AS AN ANTIEPILEPTIC DRUG IN 21ST CENTURY

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ABSTRACT

The pharmacotherapy of epilepsy has greatly expanded with the introduction of several anti-convulsants in the last 2-3 decades. Yet phenobarbitone, the first effective anti-convulsant in neurological practice continues to be the most commonly prescribed drug for epilepsy. In spite of a century long experience with phenobarbitone, several controversies exist regarding its efficacy and tolerability. The latter is particularly contributed by declining commercial interest and physician bias. In this chapter we pay tribute to this oldest existing anti-convulsant and review the scientific literature on the existing knowledge of the role of phenobarbitone as an anti-epileptic drug in the 21st century.

INTRODUCTION

Epilepsy is the most common, serious neurological disorder with an annual incidence of 50 per 100,000 population. Pharmacotherapy is the mainstay treatment for most epileptics. The history of anti-epileptic drug development can be traced back to 1857 when potassium bromide was introduced by Sir Charles Locock. The serendipitous discovery of the anticonvulsant properties of phenobarbitone by Alfred Hauptmann in 1912, until then was known for its sedative and hypnotic properties, heralded the modern, effective and relatively less-toxic anti-epileptic drug therapy. More than two decades later, consequent to the screening of several potential therapeutic agents against ‘electrical seizures’ in cats by Merritt and Putnam, a second effective anti-convulsant, namely, phenytoin was introduced. Since then a gamut of anti-epileptic drugs have been introduced following the systematic screening of many thousands of compounds in animal models of epilepsy.1 Although the therapeutic options in pharmacotherapy of epilepsy have significantly broadened, phenobarbitone continues to be the most commonly prescribed anti-epileptic drug in clinical practice, especially in developing/less industrialized countries, notwithstanding the fact that its efficacy and tolerability are shrouded in controversies. In this chapter, we review the evidence available from scientific literature on the role of phenobarbitone in current neurological practice.

MECHANISM OF ACTION AND PHARMACOKINETICS

Phenobarbitone or 5-ethyl-5-phenylbarbituric acid is a substituted barbituric acid, that exerts its anti-epileptic action by facilitating GABA mediated inhibition. It increases the mean open duration of the GABA\textsubscript{A} receptor, thereby increasing Cl\textsuperscript{-} flux, hyperpolarizing the post-synaptic neuronal membrane and interrupting the spread of epileptic activity. There are few studies that have looked into the pharmacokinetic profile of phenobarbitone.2 Phenobarbitone can be administered by oral, intravenous, and intramuscular routes. The oral bioavailability is approximately 95%, and the time taken to peak plasma concentrations is 0.5-4 hours and 2-8 hours respectively when phenobarbitone is given by oral and intramuscular routes. Hence, there is no statistically significant difference in pharmacokinetic profile when phenobarbitone is administered orally or intramuscularly, except, in newborns and premature babies where oral absorption of phenobarbitone is slow and incomplete.3
Following intravenous administration, phenobarbitone is first distributed to the highly perfused organs such as liver, kidney and heart, but not the brain. Subsequently, in the second phase, phenobarbitone is distributed uniformly into all body tissues except fat. This relatively slow entry into the brain is related to the low lipid solubility of phenobarbitone. The pKa of phenobarbitone is similar to the plasma pH, hence the tissue distribution of phenobarbitone is sensitive to variations in plasma pH. Accordingly, in status epilepticus, due to focal acidosis and increased blood flow to the brain, phenobarbitone reaches the brain in a much faster manner. In the CSF concentration of phenobarbitone ranges from 43-60% of the plasma concentration and may be slightly higher in infants. Phenobarbitone crosses the placenta and is excreted in breast milk too. Elimination of phenobarbitone is slow and follows first order kinetics, accounting for its very long half life of 70-130 hours. The half life is the longest in newborns ranging from 59-400 hours. It is metabolized in the liver by cytochrome P450 mediated hydroxylation and excreted in the urine. Alkalinisation of urine promotes phenobarbitone excretion by reducing the passive re-absorption at the renal distal tubules. The plasma concentrations of phenobarbitone that produces a good seizure control ranges from 10-40mg/L; partial seizures require a higher plasma concentration of phenobarbitone as compared to generalized tonic clonic seizures. Estimation of serum concentrations of phenobarbitone is required only when toxicity is suspected and is not recommended as a routine.

INDICATIONS AND UTILITY OF PHENOBARBITONE

i. Partial and Generalised seizures: Although phenobarbitone is the oldest existing anti-convulsant in clinical practice, its efficacy has not been documented in many rigorously conducted randomized control trials. Evidence for efficacy is mainly the outcome of uncontrolled studies and case series. A landmark randomized double blind controlled trial of anti-convulsant efficacy was the Veterans Administration Cooperative Study, which recruited 622 adults with partial seizures and generalized tonic-clonic seizures. Phenobarbitone was found to be as effective as primidone, phenytoin and carbamazepine in controlling generalized tonic-clonic seizures. Carbamazepine provided a better control of partial seizures. This perceived difference was attributed to higher drop-out rates in the phenobarbitone group due to adverse reactions. This has been replicated in other open labeled studies also.

A decade later, two randomized prospective trials form UK, one in adults and one in children, compared the efficacy of phenobarbitone, phenytoin, carbamazepine and valproic acid in newly diagnosed partial seizures and generalized tonic-clonic seizures. The seizure control rate of phenobarbitone was found to be the same as that of other anti-convulsants. However, the paediatric trial included only 10 children in the phenobarbitone arm; the excessive occurrence of side effects precluded further allocation to this arm. Hence, more trials comparing phenobarbitone with other anti-convulsants in the paediatric age group are required. Trials in developing countries have confirmed the efficacy of phenobarbitone in children and adults.

In summary, phenobarbitone is effective in partial seizures as well as generalized tonic-clonic seizures. There is also evidence from clinical experience, but not from randomized controlled trials, that phenobarbitone is also effective in other generalized seizure types such as myoclonic, clonic, atomic and tonic seizures. Phenobarbitone also has a role in the management of progressive myoclonic epilepsies and tonic spasms in early infantile epileptic encephalopathy. It is not effective in absence seizures. Phenobarbitone is recommended by the World Health Organization as first-line anti-epileptic drug for partial and generalized tonic-clonic seizures for developing countries.

ii. Neonatal Seizures: Phenobarbitone is routinely and empirically used in the management of definite and suspected neonatal seizures, even though this has never been proven, as it is difficult to design an ethically acceptable randomized control trial. Several case series have demonstrated the utility of phenobarbitone in neonatal seizures with a seizure control rate ranging from 36% to 85%. It is difficult to draw any definite conclusion because (i) neonatal seizures consist of heterogeneous paroxysmal events quite different from other seizures; there is a lack of specific seizure definition in most studies; (ii) EEG confirmation is absent in most studies; and (iii) dosages of phenobarbitone in the studies were varied, ranging from 20mg/kg to 40mg/kg.

One randomized trial compared the efficacy of phenobarbitone with phenytoin in neonatal seizures, using EEG criteria for diagnosis. Seizure control rate was similar irrespective of the drug assigned and the severity of seizure was found to be a stronger predictor of outcome. A Cochrane review addressed the benefits and side-effects of various anti-convulsants including phenobarbitone in neonatal seizures. Only two randomized control trials were identified; it was not possible to support any particular anti-convulsant currently in use for neonatal seizures. The role of phenobarbitone as drug of choice in neonatal seizures is the outcome of clinical experience. Its superiority over other anti-convulsants remains to be established.
iii. Status Epilepticus: Phenobarbitone is recommended in the management of refractory generalized status epilepticus that is unresponsive to benzodiazepines and phenytoin. Baring phenobarbitone, the only other drugs available in status are valproic acid, Levetiracetam and the anaesthetic agents. The current treatment guidelines recommend the usage of benzodiazepines-lorazepam/ diazepam- followed by phenytoin in the initial management of status epilepticus. It has been proven in atleast two studies that there is no statistically significant difference in terms of efficacy or tolerability when phenobarbitone initial monotherapy is compared to benzodiazepine-phenytoin combination, benzodiazepine monotherapy and phenytoin monotherapy. The major disadvantage of phenobarbitone usage is the occurrence of respiratory depression necessitating ICU admission and intubation following parenteral administration.

DRUG INTERACTIONS

Phenobarbitone induces the hepatic metabolism of several drugs including (i) anti-convulsants: phenytoin, carbamazepine, valproic acid, lamotrigine, ethosuximide, felbamate, topiramate, zonisamide, tiagabine; (ii) other drugs-oral contraceptive pills, warfarin, steroids and (iii) endogenous hormones: vitamin D. The metabolism of phenobarbitone itself is inhibited by valproic acid, chloramphenicol and dextropropoxyphene.

DRUG OVERDOSE

The clinical features of overdose include excessive drowsiness progressing to stupor and coma, ataxia, dysarthria, and incoordination. Death occurs due to depression of cardiorespiratory function. The severity of CNS depression is higher in drug naïve patients, compared to chronically treated patients for identical serum concentrations of phenobarbitone. Treatment consists of supportive care including mechanical ventilation. There is limited evidence to support the use of enhanced elimination in phenobarbitone overdose. Multiple doses of activated charcoal is useful, while, the role of urine alkalisation is superfluous. Extracorporeal techniques such as haemodialysis and haemoperfusion enhance elimination, but the risk-benefit ratio is quite low; hence they may have a role in life-threatening barbiturate toxicity.

ADVERSE EFFECTS

i. Neurotoxicity: The adverse effects of phenobarbitone on the central nervous system is the most important side effect, responsible for maximum ambiguity, high rates of discontinuation and declining popularity of phenobarbitone. The neurotoxic side effects include sedation, behavioural disturbances including hyperactivity, reduced cognition, and depressed mood. Sedation is the most common side effect, especially at the start of treatment; tolerance to sedation develops if phenobarbitone is initiated at a low dose and up-titrated slowly. In the Veterans Affairs Cooperative Study acute sedation was not more frequent with phenobarbitone when compared to primidone, carbamazepine or phenytoin. The development of tolerance was evidenced by the fact that whereas 33% of patients in the phenobarbitone arm initially reported sedation, only 24% continued to report at 12 weeks.

Contrary to the excessive sedation reported in adults, children experience insomnia and behavioural disturbances as a result of phenobarbitone use, particularly those with pre-existing brain disease. When phenobarbitone was administered to children with febrile seizures, 42% developed hyperactivity, which improved on withdrawing phenobarbitone. Compared to phenytoin, carbamazepine and valproic acid, phenobarbitone was associated with higher rates of discontinuation due to behavioural side effects.

Children with febrile seizures on phenobarbitone prophylaxis scored lower on the Stanford-Binet scales of intelligence compared to placebo. Even after discontinuing phenobarbitone, they had lower reading, spelling and arithmetic scores compared to placebo controls. Adults with antenatal exposure to phenobarbitone have also demonstrated a lower verbal intelligence score compared to controls. An adverse impact on cognition in children using phenobarbitone as evidenced by reduced verbal and performance intelligent quotient, memory and concentration scores, visuomotor performance, spatial memory, short term memory, and vigilance tests has been demonstrated as compared to normal subjects or subjects receiving carbamazepine or valproic acid. Heller et al demonstrated that phenobarbitone is more likely to be discontinued because of adverse effects when compared to phenytoin, carbamazepine and valproic acid. Other neurotoxic effects including depression, apathy, reduced libido and impotence have sometimes been reported in adults.

On the other hand, when phenobarbitone was compared to carbamazepine, no significant difference was noted in cognition or behavior, while, there was a trend for better seizure control and more systemic side effects with carbamazepine. Subsequent trials showed that patients receiving phenobarbitone, phenytoin, carbamazepine and valproic acid have comparable performance on most measures of neuropsychological assessment scales as well as behavioral rating scales.

In contrast to the high rates of cognitive side effects reported from developed countries, it has been observed that there is no excess neurotoxicity reported from the
developing countries. In a large cohort of children and adults with untreated epilepsy in rural Kenya, there was no difference in seizure outcome or the incidence of side effects when phenobarbイトone was compared with carbamazepine monotherapy. The rates of discontinuation were 3.3% and 5.3% in the phenobarbitone and carbamazepine arms respectively.13 A systematic study by Nimaga et al, in rural Mali demonstrated seizure control in nearly 81% of epileptics treated with phenobarbitone, which translated to a better social functioning in the form of employment and education. None of the patients in this study had side effects severe enough to warrant drug discontinuation.14

In a trial conducted in rural India, there was no significant difference in efficacy or behavior rating scores among children randomized to phenytoin or phenobarbitone.15 A similar observation was reported from a large paediatric cohort from Bangladesh.39 A large multi-centric study from rural China recruited 2455 patients with generalized tonic-clonic seizures; the incidence of mild side effects was 26.1% and phenobarbitone discontinuation-rate was only 1%.40 Phenobarbitone was associated with a significant reduction in treatment related costs while markedly improving seizure control.41

The Yelandur Study by Mani et al in rural South India focused on the treatment of focal and generalized tonic clonic seizures with phenobarbitone or phenytoin and observed a 10-fold higher incidence of side effects in the phenytoin group, with only 11% of patients being lost to follow-up. This study however did not compare the efficacy of treatment on seizure control between the two groups.13

An open-labeled, multicentric, non-comparative study to analyse the risk-benefits of treatment with phenobarbitone in adult patients with generalized tonic clonic seizures and partial seizures with generalization was undertaken by the author.42 Seventy-five subjects were recruited of which 60 patients completed follow up at one year and hence were included in the analysis. The mean age at evaluation was 26.6 + 7.2 years; primary generalized tonic-clonic seizures constituted 92%, while the rest had simple/complex partial seizures with generalization. Seizure freedom was achieved in 74.7% of the patients at one year. The Global Efficacy was rated excellent in 74.7% and 80% by the patient/ carer and investigator respectively. Likewise, Global Assessment of Tolerability was rated excellent in 97.2% and 98.6% by the patient/ carer and investigator respectively. Cognitive functions were assessed by a trained and qualified neuropsychologist in all five centres using a validated questionnaire. At initial evaluation, 7 had frontal executive dysfunction, and 4 had attention deficits. Evaluation at the 6th month and 12th month of follow up demonstrated well-sustained neurocognition in the majority with impairment in only 5 patients. Improvement was noticed in frontal executive function, with control of seizures.42

A Cochrane meta-analysis of four large trials compared the effects of phenobarbitone vs phenytoin monotherapy in children and adults with partial seizures and generalized tonic clonic seizures. There was a statistically significant advantage for phenytoin, as phenobarbイトone was more likely to be withdrawn due to side effects with seizure outcome being identical with either anti-convulsants.43 It is important to note here that there was a significant heterogeneity among the individual trials. Whereas the trials from UK had higher discontinuation rates due to the cognitive side effects, a study from rural India did not find any significant difference in behavioral rating scales.7,9,10,12

Yet another Cochrane meta-analysis compared phenobarbitone vs carbamazepine monotherapy for partial seizures and generalized tonic clonic seizures. Phenobarbitone was more likely to be withdrawn than carbamazepine and there was no statistical heterogeneity. There was no difference in the seizure outcome with either anti-convulsant, although subgroup analysis surprisingly disclosed a favorable trend for phenobarbitone in partial seizures and carbamazepine in generalized seizures.44 These were open labeled trials and hence the role of physician bias could not be ruled out.

A Chinese Cochrane meta-analysis of 20 trials concluded that, whereas, phenobarbイトone was not associated with a higher incidence of adverse reactions when compared to phenytoin, carbamazepine and valproic acid, the rate of drug withdrawal was higher with phenobarbitone. This is possibly a reflection of an exaggerated concern for phenobarbitone related side effects.45

ii. Drug withdrawal: Abrupt withdrawal of phenobarbイトone following long-term use is associated with a withdrawal syndrome in the form of hyperexcitability, tremor, irritability, generalized tonic-clonic seizures or even convulsive/ non-convulsive status epilepticus. Phenobarbitone should always be tapered gradually in order to avoid these symptoms.4,31

iii. Vitamin deficiencies: Mild-moderate folate deficiency and macrocytosis occurs with phenobarbitone therapy, but the clinical significance is not known. As mentioned earlier, phenobarbイトone induces the catabolism of vitamin D resulting in low calcium levels, occasionally secondary hyperparathyroidism, rickets, osteomalacia and fractures.46 Periodic assessment of bone density, together with calcium and vitamin D supplementation may be
Table 1: Psychiatric and Cognitive Adverse effects of anticonvulsants

<table>
<thead>
<tr>
<th>Carbamazepine</th>
<th>Irritability, reduced attention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Depression, impaired attention, sedation, delirium, encephalopathy, agitation, psychosis.</td>
</tr>
<tr>
<td>Valproate</td>
<td>Depression, fatigue, cognitive slowing</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Paradoxical disinhibition syndrome – agitation, aggression, irritability, hyperactivity. Psychosis on abrupt withdrawal.</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Depression, anxiety, irritability, psychosis</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Aggression in children</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Insomnia, agitation, emotional lability, psychosis</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Depression, anxiety, irritability, emotional lability</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Depression, irritability, cognitive slowing, psychosis</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Depression, psychomotor slowing, psychosis, impaired cognition</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Depression, aggression, psychosis</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Agitation, depression, psychosis</td>
</tr>
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indicated in high-risk population. Neonatal coagulopathy secondary to antenatal exposure to phenobarbitone is also recognized which responds to prophylactic vitamin K administration.47

iv. Connective tissue disorders: About 5-38% of patients receiving phenobarbitone may develop connective tissue disorders in the form of Dupuytren’s contracture, Peyronie’s disease, plantar fibromatosis, frozen shoulder, generalized joint pain and gum hyperplasia.4,48,49

v. Hypersensitivity reactions: Mild maculopapular or morbilliform skin rashes occur in 1-3% of patients receiving phenobarbitone.4 Severe reactions in the form of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis have only rarely been reported in patients undergoing radiotherapy while receiving phenobarbitone.50,51 Other rare adverse reactions include unmasking of systemic lupus erythematosus/ acute intermittent porphyria, bone marrow aplasia and a barbiturate hypersensitivity syndrome characterized by rash, eosinophilia, fever and hepatic injury.31,52

vi. Teratogenicity: There are mixed reports of teratogenic potential of phenobarbitone compared to other anti-epileptic drugs. Earlier studies have shown that the teratogenic risk with phenobarbitone is similar to or even lower than other anti-convulsants.53 The North American AED Pregnancy Registry on the other hand reported major malformations in 6.5% of children with ante-natal exposure to phenobarbitone including aortic coarctation, Tetralogy of Fallot, pulmonary atresia, and cleft lip/palate, as compared to other anti-convulsants except valproic acid.54

CONTROVERSIES AND DECLINING POPULARITY OF PHENOBARBITONE

The available literature in the form of controlled/uncontrolled trials, case series as well as clinical experience has provided an unequivocal evidence of efficacy of phenobarbitone in the management of generalized epilepsy, neonatal seizures and status epilepticus. The fact that phenobarbitone is the oldest anti-epileptic drug, with nearly one hundred-year-rich experience, and the most commonly prescribed anticonvulsant underscores the fact that it has stood the test of time. The declining popularity and physician bias against phenobarbitone is mainly due to the perceived excessive neurotoxicity. Notwithstanding the fact that significant adverse effect on cognition leads to a high rate of discontinuation among patients from developed countries, it has been observed that there is no such excess neurotoxicity reported from the resource-limited countries, where this drug continues to be used very frequently. There may be several factors responsible for this discrepant observation:

i. Inherent methodological flaws in studies from developing countries - (a) semiology of seizures were not accurately documented; (b) inconstant supply of phenobarbitone; (c) a significant number of patients were lost to follow-up; (d) lack of systematic data for adverse events; and (e) lack of formal testing for cognitive and behavioral side effects. This is particularly the reason why the initial studies in Africa did not lead to any definite conclusions regarding phenobarbitone efficacy.

ii. Lower doses used in resource-limited countries control seizures effectively without adversely affecting cognition;

iii. Patients from low and middle income countries may have a higher ‘tolerance threshold’ as treatment options for uncontrolled seizures are few;

iv. Last but not the least, pharmacogenetics may contribute to the differential cognitive side effects across different ethnic groups.29

The reported efficacy and tolerability in poor nations is in contradiction to high drop-out rate in developed countries. Besides, psychopathology and cognitive deficits in epileptic patients are known to be multifactorial, and anticonvulsants are only one of the contributing factors. Sedating drugs such as valproate, gabapentin, tiagabine and vigabatrin cause fatigue and cognitive slowing. Activating drugs such as felbamate and lamotrigine cause anxiety and aggression.55,56 The reported efficacy and lower side effect profile makes newer antiepileptic drugs quite popular. But it has to be borne in mind that the clinical experience is still limited. The occurrence of neurotoxicity is one of the most important reasons why phenobarbitone has been side-lined in the developed countries.
where a whole gamut of newer anti-convulsants are available. The excessive preoccupation with cognitive side effects of phenobarbitone may not be completely justified as most of the antiepileptic drugs have one form of cognitive/behavioral side effect or the other (Table 1).

ECONOMIC FACTORS

The greatest advantage of phenobarbitone apart from the broad-spectrum anti-epileptic action is the low cost. In fact, the expenditure per year for a patient using phenobarbitone is even lesser than the transport costs for physician visits.14 A recent study from an epilepsy clinic in North India analysed the direct and indirect cost of epilepsy treatment, including cost of travel and loss of productivity. The annual cost of treatment with phenobarbitone amounted to US$ 11. The cost of treatment with phenytoin, carbamezepine and valproic acid were 2, 3 and 4 times respectively greater than that of phenobarbitone.57 The newer anti-epileptic drugs are obviously much more expensive. Phenobarbitone is a boon for patients from resource-poor countries, where the choice has to be made between phenobarbitone vs ‘no-treatment’ rather than between phenobarbitone and ‘newer anti-epileptic drugs’.14

Low cost is not just phenobarbitone’s greatest asset but also greatest liability having led the drug into commercial neglect. Phenobarbitone may be allowed to fade from use at least in affluent societies, not so much because of its limitations but because its virtues are no longer promoted, as evidenced by the fact that the last major study in the developed world on phenobarbitone was conducted in 1987. Most of the recent trials are from the resource-poor settings developed countries where there is strong drive to establish phenobarbitone as an effective anti-convulsant.

CONCLUSION

Epilepsy is a heterogenous disorder in terms of semiology, aetiology and outcome. The most important consideration in epilepsy management is the classification into focal or generalized seizures because clinical experience dictates that different anti-epileptic drugs have different efficacy against different seizure types. In this context, phenobarbitone with its broad spectrum of antiepileptic action, coupled with low cost can be considered an ideal drug in a resource constrained country such as India, particularly among the general masses. Treatment with phenobarbitone will increase coverage while reducing the treatment related costs simultaneously. Despite the fact that it is the oldest anti-convulsant in clinical practice, there is a relative paucity of objective and systematic analysis of its efficacy, mainly due to lack of commercial interest; besides, phenobarbitone is perceived to be a highly neurotoxic drug in the developed countries.

With the data obtained from the recently conducted multi-centric trial across five centres in India, one could confidently conclude that phenobarbitone still has definite place in the management of adult primary/secondary generalized epilepsy as monotherapy in the 21st century. Neurocognitive deficits which have been feared, are far and few and outweigh its efficacy.

REFERENCES

Role of Phenobarbitone as an Antiepileptic Drug in 21st Century


42. Satishchandra P, Rao SL, Rawat S et al. Multicentric open label study prospective study of Phenobarbitone in drug naive newly diagnosed epilepsy subjects. Project funded by M/S Nicholas Piramal India Ltd, Mumbai (under preparation)


50. Role of Phenobarbitone as an Antiepileptic Drug in 21st Century