Phenobarbitone in Modern India
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Abstract
Phenobarbital has been in use for a century. Because of its low cost and ease of use as a broad spectrum anti-epileptic drug, it is often used in low-cost situations. It has significant adverse effects and can produce learning and behavior problems in children. In addition it is a major inducer of the hepatic Cytochrome P450 system producing many interactions. Because of these issues, the usage of this drug has declined substantially over the past few decades although it remains a therapeutic option in difficult to treat epilepsy patients.

Phenobarbital’s role in the management of epilepsy began a century ago, in 1912. The drug had been synthesized a decade earlier and was in use as a sedative. In 1912 Alfred Hauptmann serendipitously discovered that it controlled seizures in epilepsy patients in whom it was used for sedation. Last year the International League Against Epilepsy (ILAE) marked this centenary with a special symposium and a supplement in the journal Epilepsia. In the introduction to the supplement, Bialer1 noted that PHB was the only synthetic drug to have registered more than a century of continuous and ongoing clinical use. Most current practitioners however do not seem to see it as a prominent part of their armamentarium against epilepsy and hence this review.

Basic Pharmacology
PHB is marketed in India as 15-, 30- and 60-mg tablets of phenylbarbituric acid while the sodium salt is used in the syrup (20 mg/5 ml) and parenteral (200 mg/ml) formulations. The standard 60 mg tablet is marketed at about Rs 1 (range Rs. 0.80-1.70). Drug levels can be reliably measured in various body fluids by both chromatography and immunoassay and the recommended target therapeutic range is 15-45 mg/L. The main mechanism of action as an anti-epileptic is through prolongation of the opening of the chloride channel in the GABA-A receptor in the post-synaptic cell membrane, producing hyperpolarization and limiting spread of seizure activity. PHB is nearly completely and rapidly absorbed after oral administration and this is comparable with the intramuscular route. With a long half-life of 3-5 days (adults) once daily administration is acceptable and ongoing clinical use. Most current practitioners however do not seem to see it as a prominent part of their armamentarium against epilepsy and hence this review.

3-arm controlled study of 95 patients with Alzheimer’s disease who developed epileptic seizures where PHB was at least as efficacious as the other 2 AEDs.3 The general impression is that PHB is at least as effective against both generalized and partial onset seizures as the other standard AEDs and most of the new AEDs. Absences are the only seizure type not amenable to PHB and these can occasionally be aggravated because of drowsiness. Neonatal seizures are the only situation where PHB is practically a drug of choice. It has also been used in refractory status epilepticus. Thus it can be used to treat all the seizure types usually seen in adolescents and adults. Unlike the Na-channel blockers (phenytoin, carbamazepine) PHB does not aggravate primary (genetic) generalized epilepsy and hence may not require EEG confirmation before starting treatment. PHB has also been successfully used in juvenile myoclonic epilepsy.

Adverse Effects
PHB’s notoriety is mainly due to CNS adverse effects. Sedation, cognitive slowing and depressed mood and affect are prominent when the drug is initiated and can be partly mitigated with a slow introduction.

In children this may cause learning difficulties. These effects are not easily picked up on routine follow up and can only be identified on sophisticated neuropsychologic testing. A placebo controlled study of PHB (4-5 mg/kg/day) for febrile seizures showed a mean IQ drop of 8.4 after 2 years of treatment in the treatment. Unfortunately even 6 months after stopping the drug the treatment group was still 5.2 points behind.4 Three to five years later, reading skills were still poorer in the PHB treated group as compared to their peers in the placebo group, leading the authors to conclude that there may be a long term adverse cognitive effect of PHB on developmental skills being acquired during the period of treatment.5 Whether these effects can be mitigated with lower doses (2-3 mg/kg/day) is unknown. Nevertheless these studies were hugely influential in sharply restricting the use of PHB in children in developed countries after the early 1990s. It has been presumed that similar considerations may not apply in developing countries, especially not to adults in cognitively non-demanding occupations. This was confirmed by Ding et al6 who compared 144 patients with epilepsy with matched controls from villages in China where scores actually improved (partly explained by the learning effect) on retesting after treatment.

Behavioral changes can appear at all ages. Adults can occasionally become irritable and aggressive while children have been reported to paradoxically develop hyperexcitability. Two randomized studies from South Asia studied PHB versus carbamazepine7 and PHB versus phenytoin8 but could not confirm any disadvantage for the former.

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Teratogenicity is a major issue impacting AED choice in women of reproductive ages. Since PHB is now hardly used in developed countries, reliable prospective pregnancy registry data is scarce. The best estimate from Tomson suggests a malformation rate of 5.4% with <150 mg/day of PHB monotherapy but 13.7% with higher doses. These figures are higher than the malformation rates with use of carbamazepine, lamotrigine or levetiracetam but still lower than with valproate. PHB usage during pregnancy can cause Vitamin K deficiency (due to hepatic enzyme induction) in the newborn and hence prenatal Vit K1 supplementation (10 mg/day) is mandatory from the 36th week onwards. Symptomatic drug withdrawal (hypotonia, irritability, poor feeding) can also be an issue in infants when the mother is treated with PHB through pregnancy.

Increased Vitamin D catabolism is of particular significance in the Indian context where patients are often deficient even before starting AED therapy. Folate depletion is a less well known adverse effect. In patients on very long term treatment, PHB has produced Dupuytren’s contracture and ‘shoulder-hand’ syndrome by unknown mechanisms. Idiosyncratic skin reactions are rare but have a 50% chance of cross reactivity with phenytoin and carbamazepine.

Zhang et al attempted to address all these concerns in a systematic review. These authors could not find any convincing evidence that PHB caused more adverse events than carbamazepine, phenytoin or valproate but they did note that PHB was associated with a higher rate of drug withdrawal. An accompanying editorial questioned the power of this analysis to address concerns about PHB’s safety. It was also pointed out that there was no scope for comparing PHB with the whole gamut of modern AEDs! The whole argument reflects the differing perspectives of developing versus developed countries.

**Phenobarbitone and the Treatment Gap in Epilepsy**

A large number of patients with epilepsy in India do not come to medical attention or do not receive treatment for various causes: this is the treatment gap. It has been measured to be just under 40% in the literate and relatively well served population of Kerala while it reaches an alarming 90% in some parts of West Bengal. On an average more than 50% of Indian patients with epilepsy receive no treatment and the situation is similar in most developing countries. PHB has been the mainstay of most systematic attempts to address this treatment gap.

The Yellandur study in Karnataka by Mani et al recruited 135 patients in a non-randomized trial of phenytoin and/or PHB and followed them up for 5 years. Sixty-eight patients with generalized tonic-clonic seizures received PHB monotherapy, 60 were on phenytoin and another 7 received duotherapy. All management was entirely clinical by trained primary-care physicians. Only 3 (4%) of PHB treated patients developed adverse effects. Terminal remission (seizure freedom for 2 years) was analyzed at the end of each of 4 years and ranged from 58-66% for those patients who were compliant and who had a lifetime total of less than 30 seizures. In the words of the authors: ‘In rural areas of less developed countries, epilepsy control in its early stages can be practical and effective with existing resources. The key to success is a combination of trained primary-care physicians, health workers, inexpensive phenobarbital, drug compliance, health education, and follow-up.’ Similar studies and results have been obtained from Cameroon, Nigeria, Mali and Laos.

The most elaborate of these has been a demonstration project set up between the WHO, the ILAE and the International Bureau for Epilepsy in Hunan province in China which started with a door-to-door survey in 2000. This estimated a treatment gap of 93.4% and was followed by a pragmatic intervention study using PHB monotherapy as the first treatment option. Of 2455 patients recruited, 2-year follow-up was available for 1324 patients with 26% of patients seizure free. Another 45% had a greater than 50% reduction of seizure frequency. The estimated probability of patients remaining on treatment with PHB at 6 years was 0.53 and this is comparable to the retention rate of modern AEDs.

**Using Phenobarbitone in Modern India : An Argument for Pragmatism**

PHB’s adverse effects are probably more comprehensively documented than that for any other AED. This leads one to wonder whether this is purely due to its prolonged stay in active service. Personal experience can however be more compelling than any published evidence for the individual physician. In 1987, a close friend failed his undergraduate exams in the MBBS course. He had been started on PHB for seizures secondary to neurocysticercosis. He was changed over to carbamazepine and he passed his remaining exams comfortably. Today he is a respected practicing surgical pathologist with an enviable CV. Was the earlier failure due to PHB?

Public spending on healthcare in India at 1.4% of GDP is abysmally low as compared not only to developed countries (6.5-8%) but also compared to China (2.3%) or Thailand (3.3%). Per capita, the Indian government spends just $43 as compared to $87 in Sri Lanka, $155 in China and $261 in Thailand. Thus expecting adequate epilepsy treatment as part of comprehensive public health care is a distant dream. The only way forward is to tackle epilepsy in mission mode as has been proposed by Tripathi et al and this will most likely have to be a public-private partnership operating at the lowest possible cost.

Epilepsy is a major and often correctable component of overall neurologic disability. If well controlled and in the absence of behavioral, cognitive or other neurologic problems, it is compatible with a completely normal and fulfilling life. About 50% of patients with new onset epilepsy will become seizure free with a modest dose of an appropriate AED. PHB is the least expensive AED, widely available in government and private pharmacies, easy to store and easy to use with once daily dosing. With a broad spectrum of action, it is not known to exacerbate primary generalized epilepsy: a major concern with phenytoin and carbamazepine, which are the next in order of cost. This is important since initial diagnosis and treatment at the primary level has to be entirely clinical, with no scope for any sophisticated investigations. Vitamin D and folate supplementation are easy to add in vulnerable individuals. Thus there is a compelling argument to make PHB the first monotherapy for epilepsy in all public and charitable health services.

As a personal statement, I find it difficult to justify prescribing PHB to anyone who can afford Valproate or any of the modern AEDs. Is it then either ethical or appropriate for me to recommend this drug to school age children just because their parents cannot afford treatment with any of the alternatives? This dilemma cannot be resolved individually and it is my hope that in the future AED choices will be determined by clinical and not economic compulsions.
References