ISSUES IN MEDICINE

Use of phenobarbitone for treating childhood epilepsy in resource-poor countries

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Should the continued use of phenobarbitone for childhood epilepsy in resource-poor countries be considered a form of discrimination? Phenobarbitone was recommended by the World Health Organization (WHO) as the first-line agent for the control of seizures,[1] but this has been contested on the grounds that it is biased against resource-poor countries.[2] It was first used as an anticonvulsant in 1912, but now has little role to play in First-World countries where the newer-generation agents are readily accessible.

Phenobarbitone monotherapy has equivalent efficacy to the newer anticonvulsants (phenytoin, sodium valproate and carbamazepine) in children with partial-onset and generalised tonic-clonic seizures.[3]

Phenobarbitone is cheap, readily available, and easy to use and store. However, it has definite cognitive and behavioural side-effects in many children. It can exacerbate seizures in about 35% of children, and extreme caution should be taken with children who have a pre-morbid state of behavioural problems or attention deficit hyperactivity disorder (ADHD).

Cognitive and behavioural concerns

All anticonvulsants have absolute cognitive side-effects.[4] Generally the severity of cognitive side-effects is mild, allowing continuation of therapy, especially where there is a favourable risk-benefit ratio. However, when critical learning functions are affected the impact may be substantial. Routine clinical follow-up of children with epilepsy is reported to be insufficiently sensitive to evaluate cognitive functioning.[5] Neuropsychological intelligence screens are required.

The majority of studies[6-9] on phenobarbitone found significant adverse effects on cognition. One study[6] identified an intelligence quotient drop of 8.4 points after 2 years on the medication. Another study[7] found that there was a reduction in reading skills after 3 - 5 years on medication. Significant improvements in divided attention abilities were reported on cessation of phenobarbitone.[9]

Unfortunately, most studies assessing cognitive function in relation to phenobarbitone have been deemed methodologically inadequate.[4] A database of 1 357 articles assessing the cognitive effects of anti-epileptic drugs published in peer-reviewed journals between 1970 and 1998 identified only 1 phenobarbitone absolute side-effect study and 4 relative comparison studies. However, the review concluded that phenobarbitone had definite impact on higher functions.[4]

Studies have failed to appreciate dose-related effects. The cognitive and side-effect profile of low-dose phenobarbitone (3 mg/kg/day) may differ from a 5 - 10 mg/kg/day dosage regimen. Little is known about how tolerance to the cognitive effects of anti-epileptic drugs develops; failure to take this factor into account may lead to false-positives in the evaluation of cognitive side-effects of anti-epileptic drugs.[10]

Adverse behavioural effects

Studies[8,11] on phenobarbitone, especially in children, have demonstrated irritability, hyperactivity, aggression, inattentiveness, sleep disturbances and increased depression. One study[11] reported that 76% of the children treated with phenobarbitone experienced 1 or more behavioural side-effects compared with 31% of children receiving other anti-epileptics.

Pal *et al.*[12] performed a controlled trial comparing the side-effect profiles of phenobarbitone and phenytoin in rural Indian children. They found that the side-effect profile was similar in both groups, with 17% of the children in the phenobarbitone group experiencing behavioural complications and sleep disturbances. The study concluded that phenobarbitone was an effective anticonvulsant with an acceptable side-effect profile.

The co-morbidity of disorders associated with epilepsy is well described.[13] Of children attending Red Cross Children's Hospital epilepsy clinic, 60% have associated learning and behavioural disabilities. A proportion of children with epilepsy have a predisposition to these disabilities as part of their underlying neurological condition, and phenobarbitone can 'expose' them or exacerbate this tendency.[14]

However, conflicting results are found when comparing data from developed and resource-poor countries. Phenobarbitone's side-effect profile is reported to be less of an issue in resource-poor countries, with figures in the region of 3.1 - 4%.[15,16]

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Seizure aggravation and drug tolerance

At low dosage range phenobarbitone has an anti-absence effect, while higher dosages may paradoxically result in absence aggravation.[17]

In addition, phenobarbitone exacerbates severe myoclonic epilepsy of infancy (Dravet syndrome), infantile spasms, Lennox-Gastaut syndrome and continuous spike and wave in sleep (CSWS).[17] Although in isolation these syndromes are relatively rare, when combined the potential impact is significant. If one considers children with absence epilepsy and children with these syndromes together, up to 35% will have seizures potentially exacerbated.[18] Most published studies have been limited to the 'safe' epilepsies, viz. generalised tonic-clonic seizures and partial seizures, while patients with myoclonic epilepsy, drop attacks, and neurodegenerative syndromes were excluded.

Cost and availability

Phenobarbitone is the most cost-effective of all anticonvulsants currently in use. Alternatives such as phenytoin, carbamazepine and sodium valproate are 5, 15 and 20 times more expensive. Cost of therapy is of the utmost importance as poverty is considered the root cause of the large treatment gap that currently exists in most resource-poor countries.19

The non-availability of anti-epileptic drugs is considered one of the most important obstacles to the care of children with epilepsy. Phenobarbitone is currently the only anticonvulsant uniformly available throughout rural South Africa and most of the rest of Africa. The simplicity of its use (i.e. long half-life, once-daily administration, stability, and room temperature storage) facilitates its use by poor uneducated households.

It is the only anticonvulsant 'tried and tested' in the rural regions of resource-poor developing countries. Simple community-based treatment protocols using phenobarbitone as a first-line agent have been implemented successfully in countries such as Malawi, Kenya, Mali and India.[12,15,20]

A phenobarbitone treatment protocol is currently also being implemented in 7 counties of 5 provinces in Northern and Eastern China.[21]

Phenobarbitone has also been selected for its simplicity; primary health care workers can be trained to administer it. The relevance of this becomes apparent when one considers that some African countries have 1 doctor or less per 50 000 people.

Conclusion

Phenobarbitone is cheap, readily available, and easy to use and store. It is effective against partial and generalised seizure disorders. However, it has definite cognitive and behavioural side-effects in many children. It can exacerbate seizures in approximately 35% of children with epilepsy, and extreme caution should be taken when using this drug in children with a pre-morbid state of behavioural problems or ADHD. In other words, used wisely and carefully at the lowest effective dosage (3 mg/kg/day) this would be an excellent drug whose role in the resource-poor countries has not expired.

Access to health care services is not just a basic need of children, but also a fundamental human right. Ideally, the choice of anti-epileptic drug for each child should be based on seizure type and/or syndrome and the individual child's needs. The brutal reality is that in developing countries both choice and supply of drugs are limited. Economic restraints often require that a compromise be reached between individual welfare and limited resources. Phenobarbitone currently has by far the most favourable cost-efficacy ratio of all anticonvulsants in use. As a result the WHO continues to advocate its use as first-line anti-epileptic agent in developing countries. In both China and India, the world's two most populous nations, phenobarbitone is used as the front-line anticonvulsant through community-based health worker-driven projects, in an attempt to reduce the treatment gap.

Typical absences would be the commonest form of epilepsy in childhood potentially exacerbated by phenobarbitone use. Health care workers can be trained to recognise simple absences and thereby lessen the risk of aggravation with high-dose phenobarbitone.

A study by Aldenkamp and Vermeulen[4] concluded that all established anti-epileptic drugs have reported absolute cognitive side-effects, but that the effects are definitely greater for phenobarbitone. Phenobarbitone was furthermore the only anti-epileptic drug with absolute effects that concerned specific higher-order cognitive memory function when compared with no treatment.

The conflicting side-effect profiles found in reports from developed versus resource-poor countries supports the notion that research findings cannot be extrapolated from First-World to Third-World children. One reason for the discrepancy in side-effects reported in resource-poor countries could be that parental demands and expectations are different, i.e. expectations are higher in developed countries. Studies examining phenobarbitone dose-related effects in children in resource-poor countries are lacking.[4] Disappointingly few studies allow valid inferences to be drawn.[4] Unfortunately, with the reduction of phenobarbitone use in developed countries and the lack of readily available neuropsychological testing in resource-poor countries, the likelihood of a definitive study to assess the drug's cognitive and behavioural impact is low.

In the meantime the continued use of phenobarbitone in childhood epilepsy should be advocated (as it is currently by

the WHO) until the huge treatment gap between the rich and poor nations is significantly lessened. Only once the gap disappears would it be justified to shout 'discrimination'. The replacing anticonvulsant should ideally be as cost-effective as phenobarbitone, but with a superior cognitive profile. Sodium valproate currently qualifies as the most likely replacing agent, with carbamazepine as an alternative.

Lastly, in a situation where phenobarbitone is the only option it is important to maintain therapy at the lowest effective level to minimise impact (3 mg/kg/day).[19] Childhood is a precious time and a few years of cognitive disruption can be severely detrimental to a child's education and future. Parents and carers must be fully informed of the potential side-effects of all medications and have the right to demand the best care for their children.

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