PHENOBARBITAL SHOULD NOT BE USED AS FIRST-LINE ANTIEPILEPTIC DRUG THERAPY

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The choice of effective therapy fort epilepsy must be based on several considerations. Efficacy usually is considered to be the most important, but antiepileptic drug (AED) toxicity may be just as important a factor in patient evaluation of the benefit of therapy. Other important factors include ease of use, and cost. Ease of use depends mainly on pharmacokinetics, which determine dosing interval. In some patient populations, particularly the elderly, drug interactions can assume greater importance than if patients are not on other drugs for other indications. Sometimes cost becomes the major issue, particularly in resource-poor regions.

Phenobarbital is widely used in the developing world but has fallen out of favor in many countries. It is effective for focal and secondary generalized seizures, but not for primary generalized epilepsy. Bioavailability is excellent. Its long half-life, 72-144 hours depending on a number of factors including age, allow it to be sued once daily, Protein binding is about 50%, leading to a moderate risk for interactions due to binding interactions. In contrast, its hepatic metabolism creates a high likelihood of interactions with a wide range of other AEDs, as well as drugs such as oral contraceptives, anticoagulants, opiates, and others. Concomitant PB therapy can reduce the effectiveness of many agents. It can also lead to altered thyroid function, and adversely affect calcium absorption and vitamin D turnover. Reduced levels of antiretrovirals are a serious potential interaction.

Systemic side effects include skin rashes that may be severe, blood dyscrasias, hepatitis, and connective tissue disorders. IIn addition, PB has several other disadvantages that need to be considered. It has been associated with an increased risk for fetal malformations. Data from the International Registry of Antiepileptic Drugs and Pregnancy (EURAP), which includes 42 countries with more than 700 collaborators showed that, Compared with lamotrigine monotherapy at doses less than 300 mg per day, risks of malformation were significantly higher with valproic acid and phenobarbital at all investigated doses, and with carbamazepine at doses greater than 400 mg per day (Tomson et al. 2011).

Central nervous system toxicity is also prominent in patients taking Phenobarbital. Findings include excessive daytime sleepiness, occurring in up to 60% of patients in some studies, cognitive impairment, and hyperactivity in children. It is interesting that in the Veterans Administration Cooperative Study, the major reason for the advantage of phenytoin and carbamazepine over phenobarbital and primidone was greater toxicity, rather than superior seizure control (Mattson et al 1985).

The adverse cognitive effects of PB, compared to placebo and other AEDS, have been shown in a number of studies (Meador). In addition, the effects of PB may outlast the time when patients are actually taking the drug, Fetal exposure may reduce adult verbal intelligence quotient (Reinisch et al 1995). In children given PB for febrile s seizures, IQ was significantly lower than in un treated siblings both during drug treatment and six months after stopping therapy (Farwell et al 1990). When the same children were retested three years after stopping the drug, scores on the Wide Range Achievement Test (WRAT-R) reading achievement test were still significantly reduced (Sulzbacher et al 1999). One potential mechanism for greater CNS toxicity may be a greater reduction of cerebral glucose metabolism (Theodore).

Another very serious side effect of PB is depression, a major source of disability in both the developed and developing world, estimated to account for at least 11% of the global burden of disease even in low and middle income countries (Patel et al 2007). In the developing world, resources for adequate treatment are very limited. Barbiturares including PB are associated with a greater risk for depression than are other AEDs (Mula and Sander 2007). Given the already high rate of depression in patients with epilepsy, it may be suboptimal to use an AED that increases the risk.

Cost often is cited as the most important reason to use PB as first-line therapy in resource poor regions. However, the cost of PB may not always be lower than othe AEDS. In Zambia, for example, the mean cost to consumers was $US 8.89 for a months supply, compared with $7.51 for carbamazepine (Chomba et al 2010). In general there was a greater markup over the wholesale price for PB, possibly due to increased regulatory requirements; PB is considered a drug of abuse in some jurisdictions. Moreover, due to the risk of withdrawal seizures, sudden loss of supply may be more dangerous than for other AEDs.

The main advantage of PB in epilepsy therapy, in addition to cost, is ease of use and single daily dosing. Its disadvantages include hepatic enzyme induction, teratogenicity, and CNS toxicity. The last of these may be particularly important in developing regions that have serious unmet needs in education and workforce development. There is no reason why AEDs with less toxicity cannot be produced at equivalent prices,

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