Invited editorial comment

Epileptic Disord 2011; 13 (4): 366-7

Safety profile of phenobarbital: can meta-analyses tell us the truth?

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Phenobarbital (PB) is the oldest antiepileptic drug (AED) currently licensed for the treatment of seizure disorders and it has retained a unique position in the therapeutic armamentarium. Thus, PB remains the most widely used AED in the developing world (Baldy-Moulinier *et al*., 1998; Kwan and Brodie, 2004). The main advantages of PB are reliability of supply, affordable cost and ease of use (Kwan and Brodie, 2004). For instance, in India in 2002 the per-diem cost of PB was shown to be more than four fold lower than that of carbamazepine and more than five fold lower than that of sodium valproate (Mani *et al*., 2001). However, for the 2006 recommendations on initial monotherapy for epileptic seizures, the International League against Epilepsy did not recommend PB as first line monotherapy (Glauser *et al*., 2006). This recommendation was based on several studies which suggested that PB is less efficacious and less tolerated than a number of other AEDs. Specifically, these studies had pointed out frequent and disabling side effects, and particularly sedation and other cognitive and behavioural adverse events (Taylor *et al*., 2001; Tudur Smith *et al*., 2003). However, recent studies performed in the developing world have challenged these conclusions (Kwan and Brodie, 2004). In this context, re-evaluating the precise placement of PB within the panel of AEDs, and specifically PB tolerability, is important.

In the current issue of Epileptic Disorders, Zhang and colleagues report a systematic review of side effects of PB in epilepsy (Zhang *et al*., 2011). In this work, the authors pooled the safety data of 20 studies which evaluated PB efficacy and tolerability in adults and children during the last 20 years. Several sets of analyses were performed including the analysis of the total withdrawal rate, the withdrawal rate for adverse events and the relative risk of the occurrence of some specific adverse events including nervous system side effects and congenital malformations.

Based on their results, the authors suggest that "PB should not be cited as an AED with a high risk of side effects". However, it could be argued that several methodological issues temper this optimistic conclusion:

(i) Although 20 studies were retrieved from the literature, PB was only compared to classic AEDs, namely sodium valproate, carbamazepine and phenytoin. According to the panel of AEDs currently licensed, as well as the safety profile relative to classic AEDs, the impact of these comparisons might be limited.

(ii) Both double-blind and open-label trials were included in the analyses. However, whether open-label studies fulfil the minimum methodological requirements to be fully informative in a meta-analysis aiming at evaluating the safety profile of an AED remains is disputable. As acknowledged by the authors in the discussion section, the frequency of occurrence of adverse events can be highly biased by non-blinded procedures.

(iii) As previously discussed (Rheims *et al*., 2011), the influence of AED dosage is a key issue for meta-analyses of AEDs. Thus, it has been previously suggested that RCTs performed in industrialised countries may differ from those performed in the developing world with regards to the dose of PB, with a lower dose in the developing world (Kwan and Brodie, 2004). In this context, it would have been appropriate to examine how the results presented here were influenced by PB daily dosage.

(iv) There was significant heterogeneity of data in the study, an issue which questions the "strength of evidence". As discussed by the authors, several factors might have lead to this situation. Among them, the issue of the comparability of specific safety outcomes is important. Indeed, the authors analysed in detail the occurrence of some specific adverse events. Specifically, they separated "nervous system" and

doi:10.1684/epd.2011.0467

"psychological and psychiatric" side effects. Despite the importance of such dichotomy in clinical practice, the reliability of the published data to address this issue is disputable. In a recently published study (Shukralla *et al*., 2011), it was suggested that the reporting of adverse events in AED randomised controlled trials is poor and has not improved over the years. In addition, this lack of uniformity across studies is particularly pronounced in paediatric studies (Shukralla *et al*., 2011).

(v) Despite the concerns regarding the reliability of retrieval of adverse events across studies, the main conclusion formulated by Zhang and colleagues, that there is no difference in terms of tolerability between PB and VPA, CBZ or PHT, was mostly based on the lack of difference in terms of frequency of adverse events. However, the risk ratio for withdrawal rate for adverse events was significantly greater for PB than for sodium valproate (RR [95% CI]: 7.64 [3.17, 18.42], $p<0.0001$). In addition, despite significant statistical heterogeneity, there was a trend towards a greater risk ratio of withdrawal rate for adverse events for PB than for carbamazepine (RR [95% CI]: 1.50 [0.72, 3.10], p=0.28) or for phenytoin (RR [95% CI]: 2.75 [0.94, 8.09], p=0.07). In this context, it could be argued that sodium valproate is better tolerated than PB.

Overall, this analysis does not seem to be powerful enough to alter the concerns about PB safety. Furthermore, it is important to remember that in previous PB trials, not only the safety profile but also the efficacy of PB was questioned, which has been suggested to be less than that of other classic AEDs (Mattson *et al*., 1985). In this context, the overuse of PB in developing countries, especially for children, may be one of the main aspects associated with the epilepsy treatment gap, and efforts to overcome this issue should be continued (De Boer, 2002). □

Disclosure.
Speaker fees were received from Pfizer and UCB.

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