DOES USE OF GENERIC MEDICATION POSE RISK WITH REGARD TO SEIZURE CONTROL? NO!

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For a generic product to be considered equivalent, the 90% confidence interval of the log-transformed ratios of area under the plasma concentration-time curve (AUC) and Cmax between brand and generic product fall between goal-posts of 80-125%. This does *not* mean that there can be a 20% to 25% difference between the mean pharmacokinetic parameters of the two products. If ratios were close to 80% or 125%, it is more likely that upper or lower confidence limit will fall outside accepted limits. The actual difference between mean plasma concentrations is considerable smaller, and typically differs between the generic and the brand by no more than 5-7% (Perucca et al., 2006). In fact, on examination of approved generics, the FDA found a mean bioavailability difference between the generic and the brand product of only 3.5% (Bialer, 2007).

These differences should be seen in the context of the overall variability in antiepileptic drug (AED) plasma concentrations in patients on continuous treatment with unchanged brand medication, and this can be substantial. The individual coefficient of variation (CV) of consecutive plasma concentrations was calculated from three or more visits without dose (or brand) change in outpatients from the Comprehensive Epilepsy Program of Minnesota (Leppik, 1988). The mode CV for carbamazepine was 23.3% (n=206), for phenytoin 25.2% (n=192), and for valproate 27.1% (n=181). There are many factors that contribute to this variability in patients with unchanged treatment.

Nevertheless, several reports express a wide-spread concern about the risks with generic substitution among physicians as well as patients (Crawford et al., 2006; Guberman and Corman, 2007). These reports are, however, surveys of opinions rather than of facts and the results could reflect that the regulatory bodies have been less successful in explaining their position than have the marketing activities of stake-holders in brand antiepileptic drugs (AEDs). A recent study analysed switch back rates from generics to brand AEDs in comparison with antihyperlipidemics and antidepressants (Andermann et al., 2007). The switchback rates were substantially higher for AEDs than for non-AEDs. Although the authors interpretation is that the high rates for AEDs may be associated with adverse clinical consequences due to switching from branded to generic AEDs, the reasons for switching back was not investigated. The results may thus just as well reflect expectations and attitudes and differences between epilepsy patients and the other groups in this respect. While there are many uncontrolled case reports and studies reporting increase in seizure frequency or adverse events after switching to a generic AED the causal relationship is unclear. The FDA was unable to document a single example of therapeutic failure when an FDA approved generic product substituted the corresponding brand drug. The so far only randomised study comparing a brand and a generic AED was a small open-label cross-over study of Depakene vs. generic valproic acid (Vadney et al., 1995). This study found no significant differences in seizures between the treatment arms.

Hence, although there is clearly a wide-spread concern about the risks associated with generic substitution, the evidence for adverse clinical consequences are lacking. A recent meta-analysis also suggested that concerns about use of generic substitution may be overemphasized (Kesselheim et al., 2010). It is therefore reasonable to conclude that with the current criteria for bioequivalence the contribution of generic substitution to the overall variation in therapeutic response is negligible.

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