Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol11Issue3abst223P.pdf

Bioequivalence Study and Intra-individual variability of Carbamazepine

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Background and purpose: High performance liquid chromatography (HPLC) method was developed, validated and applied for the determination of carbamazepine in human plasma using diclofenac as internal standard (IS).

Methods: Extraction procedure involved protein precipitation followed by liquid-liquid extraction with dichloromethane. The mobile phase consisted of acetonitrile : isopropanol : pH 3 phosphate buffer (36:15:49, v/v/v). The flow rate was 1.2 ml/min. The eluent was monitored at 220 nm. This method has been used successfully to study bioequivalence of carbamazepine.

Two way cross-over study on 24 healthy male volunteers to assess the bioequivalence of two products of carbamazepine tablets (generic vs innovator) was carried out according to Food and Drug Administration (FDA) Guidelines. Both products were administered orally as a single dose (200 mg) separated by a two-week wash-out period. Following drug administration, blood samples were collected over 72 hour, and plasma harvested from the blood was analyzed for carbamazepine concentration by high-performance liquid chromatography assay.

Results: The ratios of geometric mean of test/reference tablets were 109.691% for C_{max}, 104.67% for AUC_{0-72} and 90.56% for AUC_{0-inf}. The 90% confidence intervals of these parameters were 1.024 – 1.210, 0.941 - 1.249, and 0.844 – 1.138 respectively. These ratios were found to be within FDA bioequivalence acceptable range. However intra-individual variability between these two formulations regarding pharmacokinetic parameters revealed that there was wide intra-individuals variation.

Conclusions and implications: The clinical significant of the present work concerning the intra-individual variability due to switchability between generic and reference drug should be stressed. Therapeutic drug monitoring may be useful in the case of change from innovator or generic or vice versa during carbamazepine therapy