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Therapeutic Drug Monitoring by Dried Blood Spot and LC-MS/MS: Novel Application to Carbamazepine and Its Metabolite in Paediatric Population

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Abstract : Epilepsy is one of the most common neurological disorders, with an estimated prevalence of 50 million people worldwide. Twenty five percent of the epilepsy population is represented in children under the age of 15 years. For antiepileptic drugs (AED), there is a poor correlation between plasma concentration and dose especially in children. This was attributed to greater pharmacokinetic variability than adults. Hence, therapeutic drug monitoring (TDM) is recommended in controlling toxicity while drug exposure is maintained. Carbamazepine (CBZ) is a first-line AED and the drug of first choice in trigeminal neuralgia. CBZ is metabolised in the liver into carbamazepine-10,11-epoxide (CBZE), its major metabolite which is equipotent. This develops the need for an assay able to monitor the levels of both CBZ and CBZE. The aim of the present study was to develop and validate a LC-MS/MS method for simultaneous quantification of CBZ and CBZE in dried blood spots (DBS). DBS technique overcomes many logistical problems, ethical issues and technical challenges faced by classical plasma sampling. LC-MS/MS has been regarded as superior technique over immunoassays and HPLC/UV methods owing to its better specificity and sensitivity, lack of interference or matrix effects. Our method combines advantages of DBS technique and LC-MS/MS in clinical practice. The extraction process was done using methanol-water-formic acid (80:20:0.1, v/v/v). The chromatographic elution was achieved by using a linear gradient with a mobile phase consisting of acetonitrile-water-0.1% formic acid at a flow rate of 0.50 mL/min. The method was linear over the range 1-40 mg/L and 0.25-20 mg/L for CBZ and CBZE respectively. The limit of quantification was 1.00 mg/L and 0.25 mg/L for CBZ and CBZE, respectively. Intra-day and inter-day assay precisions were found to be less than 6.5% and 11.8%. An evaluation of DBS technique was performed, including effect of extraction solvent, spot homogeneity and stability in DBS. Results from a comparison with the plasma assay are also presented. The novelty of the present work lies in being the first to quantify CBZ and its metabolite from only one 3.2 mm DBS disc finger-prick sample (3.3-3.4 µl blood) by LC-MS/MS in a 10 min. chromatographic run.

Keywords : carbamazepine, carbamazepine-10,11-epoxide, dried blood spots, LC-MS/MS, therapeutic drug monitoring
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