Poster

[P26-1] P26-1: Anticonvulsant drugs

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[P26-1-1] Volumetric absorptive microsampling as an alternative tool for therapeutic drug monitoring of first-generation anti-epileptic drugs

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Background

Dosage adjustment of anti-epileptic drugs (AEDs) by therapeutic drug monitoring (TDM) is very useful, especially for children. Microsampling -the collection of small volumes of blood- is increasingly considered a valuable alternative to conventional venous sampling for TDM. Volumetric absorptive microsampling (VAMS) allows accurate and precise collection of a fixed volume of blood, eliminating the volumetric blood hematocrit bias coupled to conventional dried blood spot collection.

Methods

A method for quantifying five AEDs and one active metabolite was developed, including carbamazepine, oxcarbazepine, valproic acid, phenytoin, phenobarbital and carbamazepine-10,11-epoxide. VAMS tips, separated from the plastic handler, were extracted with 100 L of an acetonitrile/water mixture (80/20), containing 6 deuterated internal standards. Following shaking for 10’ at 60˚C and centrifugation, samples were diluted 1:1 with H_2O prior to injection of 10 l onto a Chromolith® reversed phase-18e column and MS/MS analysis using a SCIEX API 4000, operated in positive and negative ionization mode.
Method validation was based on European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) guidelines for bioanalytical method validation and included evaluation of selectivity, carry-over, linearity, precision, accuracy, matrix effect, recovery, hematocrit effect and stability.

Results

No unacceptable interferences were observed in VAMS prepared from blank blood from 6 different donors. No carry-over was found in blank samples injected after the highest calibrator. Calibration data for all of the compounds, with exception of oxcarbazepine, was found to be heteroscedastic. Intra- and interbatch precision and accuracy values met the acceptance criteria (i.e. <15% CV and bias). Internal standard-compensated matrix effects did not exceed ±10%. While for all compounds a high recovery (81%) was obtained using blood samples with deviating hematocrit values (0.21-0.62), the recovery was somewhat hematocrit-dependent (lower hematocrit samples yielding higher results than high hematocrit samples). All compounds, except oxcarbazepine, were found stable in VAMS for at least 1 month when stored at room temperature, 4˚C and -20˚C and for at least 1 week when stored at 60˚C.

Conclusions

An LC-MS/MS method was optimized for the quantification of five AEDs and one active metabolite in VAMS. This method will be applied on patient samples.