Poster

[P26-1] P26-1: Anticonvulsant drugs

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[P26-1-3] Automated preparation and analysis of a large range of antiepilpetics for therapeutic drug monitoring by LC-MS/MS

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Background

Because of their complicated pharmacokinetics, as well as narrow therapeutic ranges that cause significant differences in individuals' therapeutic dosages, antiepileptic drugs (AEDs) are today among the most common medications for which clinical laboratories perform therapeutic drug monitoring (TDM). In addition, some benzodiazepines (BZDs) are also important drugs used in management of epilepsy. While AEDs are effective within few tens of mg/L, BZDs have a therapeutic range at the g/L level making them challenging to assay simultaneously.

Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) has become a major tool in TDM. It offers high specificity, speed of analysis, multiplexing capabilities and automation associated to a low cost per sample.

Here we present a method to assay a large panel of AEDs and BZDs using a fully automated platform in a single assay without the need for manual pretreatment.

Methods

The system used was comprised of a CLAM-2000 directly coupled to a Nexera X2 UHPLC and a LCMS-8050 triple quadrupole mass spectrometer (Shimadzu Corp., Japan). From the sample tube, 20 L of plasma were aspirated and precipitated with 280 L of methanol containing internal standards. After filtration, extracts were automatically transferred to the autosampler for LC-MS/MS analysis. The overall process time was 3.5 minutes.

Results

Thirteen AEDs and six BZDs were analyzed simultaneously. For each compound, the calibration range was defined using the therapeutic range from 5 times lower than the lowest value of the therapeutic range to 50% over the highest value. For example, the range was 1 –30 mg/L and 0.05 –0.7 mg/L for gabapentin and clobazam, respectively.

Recovery and matrix effects were checked using several individual plasma samples spiked at 4 levels (LLOQ, 3xLLOQ, 0.5xULOQ, 0.9xULOQ).

Intra an inter day precision and accuracy were checked within 5 independent runs. Five individual replicates were analyzed at each level.

No carry-over was measured after injection of the highest calibration standard.

The automated sample preparation was compared to manual one. No difference was statistically significant.

Conclusions

A method for simultaneous measurement of AEDs and BZDs was developed and validated using a fully automated LC-MS/MS platform making it suitable for routine analysis.