Poster

[P25-2] P25-2: Anti-infective drugs (2): Beta-lactams

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[P25-2-2] Development of novel LCMSMS assay for therapeutic drug monitoring of five beta-lactam antibiotics in human plasma

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Keywords: TDM, LC/MS/MS assay, β-lactam antibiotics, automated sample pretreatment

Background

The β-lactam antibiotics are used in the treatment of bacterial infections in human over decades. One of the consequences of continuous uses of antibiotics is the progressive development of drug resistance. Therapeutic Drug Monitoring (TDM) aims at obtaining pharmacokinetic data of antibiotics for development of personalized medicine treatment. We present here a LC/MS/MS array for five β-lactam antibiotics including meropenem, tazobactam, piperacillin, cefepime and ceftazidime. The assay was evaluated with spiked samples and proven to be sensitive and reliable. The assay is under further evaluation on CLAM-LC-MSMS for fully-automated analysis with on-line sample pre-treatment.

Methods

A LCMS-8060 was employed in this study. A Kinetex C18 column (100 mm x 2.10mm, 1.7m) and a gradient elution of 5.5 minutes were used. Two optimized MRMs were selected foe each compound, one as quantifier and other for confirmation. Pool human plasma was used as matrix to prepare spiked samples. Protein-crash was carried out with organic solvent followed by vortex and centrifugation. The calibration series were prepared for 20~4000 ng/mL with isotope labelled internal standards in plasma.

Results

A MRM-based quantitation method of the antibiotics with four stable isotope-labelled IS was developed. The assay performance was evaluated using spiked plasma samples. A good linearity of R2>0.997 was obtained for the compounds at 20~4000 ng/mL. The accuracy obtained was 87~109% except ceftazidime. Repeatability of the assay was evaluated with spiked samples at low, middle and high concentration and the results was RSD<8%. Recovery of the sample pre-treatment at all levels was 86~113%. The matrix effect was within ±20% except for ceftazidime and tazobactam, for which dilution of the samples could reduce significantly the matrix effect. The LOQ of the method measured are 5.8, 6.0, 1.9, 2.9 and 0.7 ng/mL for tazobactam, cefepime, meropenem, ceftazidime and piperacillin, respectively. This MRM-based assay is under further evaluation on CLAM-LC-MS/MS for accomplishing fully-automated analysis from sample pre-treatment to analysis.

Conclusions

A novel MRM-based assay was established and evaluated for simultaneously TDM of five β-lactam antibiotics. The assay is under testing on CLAM-LC-MSMS platform to carry out fully-automated analysis.