Poster

[P27-1] P27-1: Anti-infective drugs (6): Anti-MRSA and antifungals

Chair: Yasuhiro Tsuji, Japan

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[P27-1-9] Development of novel LCMSMS assay for therapeutic drug monitoring of eight antifungal drugs in human serum

Jie Xing[1], Shaohua Chia[2], Cao Yuan[3], Edwin Zhi Wei Ting[4], TzePeng Lim[5], SiXuan Tan[6], Zhaoqi Zhan[7]

(1.Shimadzu (Asia Pacific) Pte Ltd., 2.Shimadzu (Asia Pacific) Pte Ltd., 3.Shimadzu (Asia Pacific) Pte Ltd., 4.Shimadzu (Asia Pacific) Pte Ltd., 5.Pharmacy,Singapore General Hospital, 6.Pharmacy,Singapore General Hospital, 7.Shimadzu (Asia Pacific) Pte Ltd.)

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Background

Systemic antifungal chemotherapy is used to treat invasive fungal infections. However, the drug concentrations may vary in patients mainly due to fluctuating pharmacokinetics. Therapeutic drug monitoring of antifungals is demanded for optimizing the efficacy and minimise drug overdose risk. In this study, we developed a LCMSMS assay for simultaneous determination of two classes of antifungal drugs, five triazoles and three echinocandins in human serum. The performance of the assay is evaluated with spiked samples thoroughly and it is under further testing on a system coupled with CLAM-2000 to accomplish fully-automated analysis with on-line sample pre-treatment.

Method

Human serum was pre-treated with methanol-acetonitrile to precipitate proteins. A LCMS-8060 triple quadrupole with ESI interface coupling with UHPLC was used to develop MRM-based assay for quantitative analysis of eight antifungal drugs: fluconazole, posaconazole, voriconazole, hydroxyitraconazole, itraconazole, anidulafungin, micafungin and caspofungin. A Kinetex C18 column (100 x 2.1 mm, 1.7 m) was used for the separation of the compounds with a gradient elution of 9 mins. The CLAM-2000 coupling with the system is used for testing of a fully-automated assay.

Results

Optimisation of MRM parameters of the eight antifungal drugs was performed on the LCMS-8060. Three MRM transitions were selected for each compound with one as quantifier ion while the other two as confirmation ion. A quantitation method was established and evaluated: linear calibration curves with r^2 >0.997 were obtained using mixed standards spiked in human serum. It was found that out of the eight drugs, two drugs (anidulafungin and micafungin) showed relatively low sensitivity. The linear ranges established are: 5~5000 pg-mL for fluconazole and voriconazole; 20~5000 pg-mL for posaconazole, itraconazole and hydroxy-itraconazole and caspofungin; 100~5000 pg-mL for anidulafungin; 200~5000 pg-mL for micafungin. The LOQ obtained is in the range of 5~200 pg-mL. This MRM-based assay is under further evaluation on CLAM-LC-MSMS for accomplishing fully-automated analysis including serum sample de-proteinization and quantitation.

Conclusions

A novel MRM-based assay was established and evaluated for simultaneously TDM of eight antifungal drugs. The assay is under further testing on CLAM-LC-MSMS to accomplish fully-automated TDM from sample pre-treatment to analysis.