Therapeutic drug monitoring of selected antibiotics using the volumetric absorptive-microsampling device (VAMS) in the pediatric population with sepsis: bioanalytical and pharmacokinetic aspects of ANTISEPSIS study

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Background: In the effective treatment of infections, it is extremely important to implement the appropriate causal treatment early, in a properly selected dose, taking into account the PK/PD (pharmacokinetic-pharmacodynamic) parameters of the drug. Volumetric Absorptive Microsampling (VAMS) seems to be attractive for targeted determination antimicrobial drugs by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). ANTISEPSIS is a prospective, randomized, single-blind study in a population of antimicrobial-treated children in intensive care units with suspected or confirmed infection (sepsis or septic shock).

Methods: The aim of the study was targeted measurement of the concentrations of antimicrobial drugs in the blood by LC-MS/MS technique using VAMS – Mitra™ device (10µL, Trajan, Australia). In the first stage of the analytical part of the study, the VAMS-LC-MS/MS methods have been developed and validated for several drugs concomitantly: amikacin (AMI), vancomycin (VAN), gentamicin (GEN), linezolid (LZD) and meropenem (MER). Netilmicin, MER-d6 and LZD-d3 were used as internal standards. The specially arranged short- and long-term stability study under different conditions in the climate chamber has been initiated.

Results: The methods were optimized using simple sample precipitation and/or liquid-liquid extraction (LLE). The methods were successfully validated and optimized in calibration, ranging from 1 to 1000 ng/mL (different ranges for each analyte). The validation parameters fulfilled restricted international criteria. The potential hematocrit effect, matrix and carry-over effects were not observed. The first results of the stability examination confirmed the extended stability of analytes in VAMS, especially for MER, which is characterized by limited stability in serum.

Conclusions: The VAMS-LC-MS/MS analytical method was optimized and validated according to international guidelines for bioanalytical method validation. The cross- and clinical validation of the methods (routine in serum versus VAMS) will complement the assay platform in the next step of the analytical part of the ANTISEPSIS study.

Key Words: antivirals, antifungals, sepsis, ANTISEPSIS, VAMS