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MEETING ABSTRACT

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Pharmacokinetics and pharmacodynamics of echinocandins in ascites

René WELTE[1], Tiziana GASPERETTI[1], Sandra LEITNER-RUPPRICH[2], Caroline HÖRTNAGL[2], Maria AIGNER[2], Cornelia LASS-FLÖRL[2], Herbert OBERACHER[3] and Romuald BELLMANN[1,*]

[1]*Clinical Pharmacokinetics Unit, Inflammation Research Laboratory, Division of Medical Emergency and Intensive Care Medicine, Department of Internal Medicine I, Medical University of Innsbruck, Austria;* [2]*Department of Hygiene, Microbiology and Public Health, Division of Hygiene and Medical Microbiology, Medical University of Innsbruck, Austria;* [3]*Institute of Legal Medicine and Core Facility Metabolomics, Medical University of Innsbruck, Austria*

Background: The echinocandin antifungals anidulafungin (ANI) and micafungin (MICA) are recommended for treatment of candidemia. Their efficacy in peritonitis and thoracic empyema caused by *Candida* is less clear. Target-site concentrations, however, might be crucial for eradication of pathogens. Therefore, we refined an established method [1] for quantification of ANI and MICA in ascites and in pleural effusion in order to assess target-site pharmacokinetics. In addition, pharmacodynamics of ANI and MICA in ascites were assessed by *in vitro* simulation of fungal growth.

Methods: ANI and MICA were measured by high-pressure liquid chromatography (HPLC) and UV detection. Sample preparation was performed by protein precipitation with acetonitrile (ACN) and supernatant purification by solid phase extraction (SPE). Quantification was validated according to the bioanalytical method validation guidelines. Simulation of *C. glabrata* and *C. albicans* growth was performed in RPMI media and ascites spiked with ANI or MICA over a period of 144 h at 37°C. Numbers of fungal colony-forming units (CFU) were counted and assessed, considering the duplicity and the dilution.

Results: The lower limit of quantification (LLOQ) could be reduced from 0.1 to 0.05 µg/ml for ANI and MICA in ascites. Intra- and interday variability and reproducibility was within the required range (<15%). Accuracy of linearity was within 85–115%. Extraction recovery could be doubled for ANI in ascites. Simulation of fungal growth in RPMI and ascites showed differences for *C. glabrata* and *C. albicans* proliferation. In untreated ascites, an increase in CFU by 10^2 within 144 h was observed for *C. albicans*, whereas no significant proliferation was seen for *C. glabrata*. An ANI concentration of 1 mg/l in ascites caused complete eradication of *C. albicans*. However, neither ANI nor MICA affected CFU numbers of *C. glabrata* in ascites.

Discussion: Implementation of SPE and a modified ACN precipitation technique lead to significant improvement in LLOQ and extraction rates for ANI and MIC. Due to higher accuracy and reproducibility, this method appears to be suitable for quantification of ANI and MICA in pharmacokinetic studies, particularly, when low echinocandin concentrations are anticipated. Results of fungal growth simulations suggest that antifungal efficacy in ascites may depend on the *Candida* species and on the applied echinocandin.

Corresponding author e-mail: romuald.bellmann@i-med.ac.at

Reference

1. Welte R, Bellmann R: **A method for quantification of echinocandins in body fluids.** *Intrinsic Act,* 2015; 3(Suppl. 2):A7.7. doi:10.25006/IA.3.S2-A7.7