P1670
Poster Session VI
New quinolones, oxazolidones, and a chimera of both

ECOLOGICAL AND PHARMACODYNAMIC EFFECTS OF MCB3681 ON SKIN, NASAL, OROPHARYNGEAL AND INTESTINAL MICROBIOTA

M.U. Rashid[1], A. Dalhoff[2], T. Kapsner[3], T. B‰ckstrˆm[1], L. Bjˆrkhem Bergman[1], G. Panagiotidis[1], A. Weintraub[1], **C.E. Nord**[1]

[1]Department of Laboratory Medicine, Karolinska Institutet Karolinska University Hospital, Stockholm, Sweden ; [2]Institute for Infection Medicine, University Medical Center Schleswig-Holstein, Kiel, Germany ; [3]Morphochem Aktiengesellschaft, für kombinatorische Chemie, Munich, Germany

Objectives: MCB3837 is a novel oxazolidinone-quinolone hybrid prodrug rapidly converted in blood to MCB3681 and active against Gram-positive bacteria. Antibacterial agents interact with both the targeted pathogens and the resident human microbiota. The purpose of this study was to evaluate the ecological impact on the skin, nasal, oropharyngeal and intestinal microbiota after the exposure to MCB3681. In addition, pharmacodynamic (PD) effects were studied.

Methods: Twelve healthy male subjects (19-31 years) were infused with 6 mg MCB3837 per kg body weight on 5 consecutive days. Plasma, urine, saliva and faeces were collected for determination of MCB3681 by LC-MS/MS or bioassay. Skin, nasal, saliva, and faecal samples were cultured on non-selective and selective media. Different colony types were counted, isolated in pure culture and identified to genus level. All new colonizing bacteria were tested for MCB3681 susceptibility. Mean viable counts pre-, during and post-exposure were used to evaluate ecological effects. PD effects were analyzed intra-individually comparing viable counts of indicator organisms during and after exposure to baseline.

Results: Mean plasma levels of MCB3681 at the end of infusion on day 5 were 638 ng/mL (495-917 ng/mL) and similar to day 1. While no MCB3681 could be detected in saliva, the mean values were 171 mg/kg (99-226 mg/kg) in faeces. The microbiota of the skin, nose and oropharynx were not affected by the MCB3681. In faeces, *Escherichia coli*, other enterobacteria, bacteroides and candida were not affected while enterococci and Gram-positive anaerobes were significantly reduced. In general, the faecal microbiota was restored at 2 weeks after the end of the administration. No new colonizing aerobic and anaerobic bacteria resistant to MCB3681 (MIC ≥ 4 mg/L) were found. PD effects: The predefined target, i.e., a reduction of population densities of indicator organisms by ≥2 $\log_{10}$, to prove the principle of an in vivo effect of MCB3681 has been met for *Staphylococcus aureus, Lactobacillus* spp., *Clostridium* spp., *Bifidobacterium* spp., and *Enterococcus* spp. Viable counts returned to pre-exposure levels thereafter.

Conclusions: MCB3681 has an ecological impact on the human microbiota and exerts a pharmacodynamic effect on Gram-positive bacteria. The analysis of PD effects of MCB3681 on indicator organisms of the human microbiota and colonizers of all four sites has proven that MCB3681 is active against Gram-positive aerobic and anaerobic bacteria.