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Paper Poster Session
New agents in clinical development against gram-positive bacteria

Ecological effect of solithromycin on the normal human intestinal microbiota

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Background: Macrolides were introduced into antimicrobial therapeutics, beginning with erythromycin A, in the early 1950s. Solithromycin is a fourth generation macrolide, the first fluoroketolide. It is being developed as intravenous and oral formulations for the treatment of patients with community-acquired bacterial pneumonia (CABP). Solithromycin exhibits potent *in vitro* activity against the bacterial pathogens associated with CABP, including macrolide-resistant strains and atypical bacteria. The normal microbiota acts as a barrier against colonization by potentially pathogenic microorganisms and against overgrowth of already present opportunistic microorganisms. Administration of antimicrobial agents, therapeutically or as prophylaxis, causes disturbances in the ecological balance between the host and the normal microbiota. Knowledge about the interaction between antimicrobial agents and the normal microbiota gives the clinician the possibility to choose agents associated with lesser degrees of ecological disturbances. Consequently, the risk of development of resistant strains and transfer of resistance elements between microorganisms is reduced. The objective was to assess the impact of solithromycin on the intestinal microbiota during and after oral administration of solithromycin.

Material/methods: Twelve healthy volunteers received oral capsules of solithromycin 800 mg on Day 1 followed by 400 mg once-daily on Days 2-7. Faecal samples were collected at baseline and on Days 2, 5, 7, 9, 14 and 21 for pharmacokinetic and microbiological analyses.

Results: The number of *Escherichia coli* strains decreased during the study and was normalized on Day 14. The number of other enterobacteria also decreased during the study and the number of enterococci decreased from Day 2 to Day 9 and was normalized on Day 14. The number of *Candida* strains was not changed. The number of lactobacilli decreased from Day 2 to Day 14 and was normalized on Day 21. The number of bifidobacteria decreased on Day 2 and was normalized on Day 21. There was a decrease of *Clostridium* strains on Day 2 and Days 7-14. On Day 21, clostridia were normalized. No *Clostridium difficile s*trains or toxins were detected. The number of *Bacteroides* strains was not significantly changed. Plasma samples were collected predose on Days 2, 5 and 7, and mean solithromycin concentrations were 130 ng/mL, 111 ng/mL, and 98.7 ng/mL, respectively. The solithromycin concentrations in faeces on Days -1, 2, 5, 7, 9, 14 and 21 ranged from 0 mg/kg, 15.8-65.4 mg/kg, 24.5-82.7 mg/kg, 21.4-82.7 mg/kg, 12.1-72.4 mg/kg, 0.2-25.6 mg/kg and 0-0.5 mg/kg, respectively.

Conclusions: The investigation showed the ecological effect of solithromycin on the intestinal microbiota with similar results as reported for other macrolides. *E. coli*, other enterobacteria, enterococci, bifidobacteria, lactobacilli and clostridia decreased while bacteroides and candida were unchanged. No *C. difficile* strains or toxins were detected. The protective role of bacteroides against *C. difficile* in the intestinal microbiota is known and explains this finding.