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Ecological effect of solithromycin on the normal human intestinal microbiota

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Introduction and Purpose:

Solithromycin is a fourth generation macrolide and the first fluoroketolide. It is being developed as intravenous and oral formulations for the treatment of patients with community-acquired bacterial pneumonia (CABP) (1). Solithromycin exhibits potent *in vitro* activity against the bacterial pathogens associated with CABP, including macrolide-resistant strains and atypical bacteria (2). 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 (3). Consequently, the risk of development of resistant strains and transfer of resistance elements between microorganisms is increased. The objective was to assess the impact of solithromycin on the intestinal microbiota during and after oral administration of solithromycin.

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.
Faecal concentrations of solithromycin were assayed by the agar well diffusion method using antibiotic Medium No. 1 (Difco, Sparks, MD, USA) and *Micrococcus luteus* ATCC 9341 as the indicator strain. The lower limit of sensitivity was 0.064 mg/kg faeces.

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 (Figure 1). The number of *Candida* strains was not changed (Figure 1). The number of lactobacilli decreased from Day 2 to Day 14 and was normalized on Day 21.

Figure 1. Effect of solithromycin oral administration (800 mg on day 1 followed by 400 mg daily on day 2 through day 7) on the intestinal aerobic microbiota of 12 healthy volunteers. The solid line represents the median value of log CFU/g faeces.

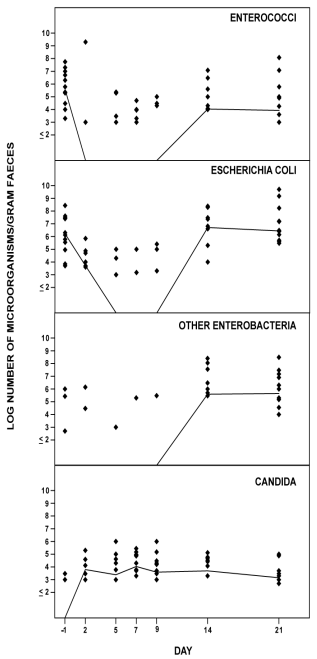
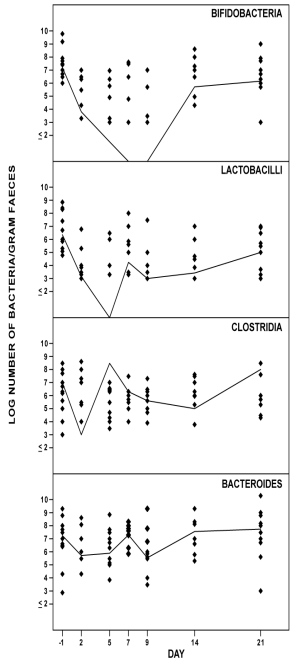


Figure 2. Effect of solithromycin oral administration (800 mg on day 1 followed by 400 mg daily on day 2 through day 7) on the intestinal anaerobic microbiota of 12 healthy volunteers. The solid line represents the median value of log CFU/g faeces.



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* strains or toxins were detected. The number of *Bacteroides* strains was not significantly changed (Figure 2). The solithromycin concentrations in faeces on Days -1, 2, 5, 7, 9, 14 and 21 were 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 ecological effect of solithromycin on the intestinal microbiota was similar 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.

References:

1. Farrell DJ, Castanheira M, Sader HS, Jones RN. 2010. The in vitro evaluation of solithromycin (CEM-101) against pathogens isolated in the United States and Europe (2009). J Infect 61:476-483.
2. Hook EW, 3rd, Golden M, Jamieson BD, Dixon PB, Harbison HS, Lowens S, Fernandes P. 2015. A Phase 2 Trial of Oral Solithromycin 1200 mg or 1000 mg as Single-Dose Oral Therapy for Uncomplicated Gonorrhea. Clin Infect Dis 61:1043-1048.
3. EMEA. 2000. Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products. Committee for Proprietary Medicinal Products (CPMP), The European Agency for the Evaluation of Medicinal Products (EMEA) 2000 CPMP/EWP/2655/99. CPMP/EWP/2655/99.

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