



**Karolinska
Institutet**

Department of Laboratory Medicine

Ecological impact of antibiotic treatment on human normal microflora

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentlig försvaras på det engelska språket i Hörsal 4U
Solen, Tandläkarhögskolan plan 4 (ingång Alfred Nobels Allé 8 eller
Blickargången 7), Karolinska Institutet, Huddinge.

Tisdagen den 11 juni, 2013, klockan 10.00

av

Mamun-Ur Rashid

MD

Huvudhandledare:

Professor Andrej Weintraub
Karolinska Institutet
Department of Laboratory Medicine

Bihandledare:

Professor Carl Erik Nord
Karolinska Institutet
Department of Laboratory Medicine

Fakultetsopponent:

Docent Åsa Ljungh
Department of Laboratory Medicine
Lund University

Betygsnämnd:

Docent Christian Giske
Department of Microbiology, Tumor and Cell
Biology (MTC)
Karolinska Institutet

Docent Lisbeth Barkholt
Medical Products Agency
Uppsala

Docent Volkan Özenci
Department of Laboratory Medicine
Karolinska Institutet

Stockholm 2013

ABSTRACT

The skin and the mucosal surfaces of humans are colonized with microorganisms, which are often referred as the normal microflora. There is a biological balance between the human host and the normal microflora in health. The extensive use of antibiotics in both humans and animals has caused the development of many resistant bacteria. Administration of antibacterial agents can cause disturbances in the ecological balance between the host and microorganisms.

Ceftobiprole is a new broad-spectrum cephalosporin active against methicillin-resistant *Staphylococcus aureus*. Twelve healthy volunteers received ceftobiprole. Plasma and fecal samples were collected according to the study design for analysis. Plasma concentrations of ceftobiprole were 14.7- 24.5 mg/l. No measurable concentrations of ceftobiprole were found in feces. There were minor to moderate changes in the numbers of enteric bacteria, enterococci, *Candida albicans*, bifidobacteria, lactobacilli, clostridia and *Bacteroides* spp. No *Clostridium difficile* strains and no new colonizing bacteria were found.

Ciprofloxacin is a well-known fluoroquinolone active against Gram-negative and Gram-positive bacteria. Thirty-six healthy female volunteers according to the study design received either the extended release formulation of ciprofloxacin or the immediate release formulation. Mean fecal concentrations were 453 mg/kg and 392 mg/kg, respectively. The numbers of *Escherichia coli* were significantly suppressed while the enterococci decreased moderately in both treatment groups. No toxigenic *C. difficile* strains were found.

Telavancin is a new glycopeptide for the treatment of Gram-positive infections. Thirteen healthy volunteers received telavancin. Fecal and urine samples were collected according to the study design. There were no measurable concentrations of telavancin in feces. No significant effects on the number of Enterobacteriaceae, enterococci, *C. albicans*, bifidobacteria, lactobacilli, clostridia and *Bacteroides* spp. were observed in the study. No *C. difficile* strains and no new colonizing Gram-positive bacteria were found.

Thirty-four healthy volunteers were included and received either doxycycline or placebo for 16 weeks. Plasma, saliva and fecal samples were collected according to the study design. The plasma concentrations of doxycycline in the doxycycline group were 0.20-1.49 mg/l. The fecal concentrations of doxycycline in the doxycycline group were 0-4.10 mg/kg. Minor effects on the oropharyngeal microflora were observed in both groups. There were minor changes in the number of enterococci and *E. coli* in both groups. No *C. difficile* strains were isolated.

This thesis shows that intravenous administration of antibiotics (ceftobiprole and telavancin) had less impact on the intestinal microflora. Both antibiotics caused minor disturbance on the normal microflora indicating a low risk to develop *C. difficile* infection. Ciprofloxacin had impact on the microflora regardless of the formulation of the drug. Doxycycline sub-antimicrobial dose had minor effect on the normal microflora and development of resistance.

Keywords: Ceftobiprole, Ciprofloxacin, Telavancin, Doxycycline, Oropharyngeal microflora, Intestinal microflora, Ecological impact, Normal flora, Health, Subantimicrobial dose, Antibiotic resistance.

ISBN 978-91-7549-199-8