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# Pharmacokinetics and comparative effects of telithromycin (HMR 3647) and clarithromycin on the oropharyngeal and intestinal microflora

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**The pharmacokinetics in plasma and saliva of a new ketolide, telithromycin (HMR 3647), and the effect on the normal oropharyngeal and intestinal microflora were studied in healthy volunteers and compared with those of clarithromycin. Ten subjects received 800 mg telithromycin perorally once daily and 10 other subjects received 500 mg clarithromycin bid for 10 days. Blood, saliva and faecal specimens were collected at defined intervals before, during and after administration for pharmacokinetic and microbiological analyses. In subjects receiving telithromycin, the mean $C_{max}$, AUC and $C_{24}$ (24 h) in saliva exceeded the values obtained from plasma, while saliva and serum pharmacokinetic parameters were in the same range for the clarithromycin group. The quantitative ecological disturbances in the normal microflora during administration of telithromycin were moderate and comparable to those associated with clarithromycin administration. No overgrowth of yeasts or *Clostridium difficile* occurred. Emergence of resistant strains was seen in both treatment groups. Administration of both telithromycin and clarithromycin was associated with significant increases in MICs for intestinal *Bacteroides* isolates, which persisted 2 weeks after discontinuation of treatment. In addition, a significant emergence of highly clarithromycin-resistant α-haemolytic streptococci, intestinal enterococci and Enterobacteriaceae was detected at day 10 in the clarithromycin group. In conclusion, administration of telithromycin resulted in high drug levels in saliva, which indicates a good therapeutic profile for throat infections. Telithromycin seems to have a more favourable ecological profile compared with clarithromycin in terms of resistance development in the normal microflora.**

## Introduction

Telithromycin (HMR 3647) belongs to the family of ketolides representing a new class of 14-membered ring macrolides.[1] Ketolides are characterized by a keto function in position 3 of the erythronolide A ring, which replaces the cladinose moiety, a sugar long considered to be essential for antibacterial activity.[2] Telithromycin inhibits protein synthesis acting mainly on the 50S ribosomal subunit.

Telithromycin possesses a broad antibacterial spectrum including pathogens involved in respiratory tract infections: Gram-positive cocci, including penicillin- and macrolide-resistant pneumococci, *Haemophilus influenzae* and *Moraxella catarrhalis*, as well as atypical and intracellular bacteria.[3–5] The antibacterial spectrum of telithromycin also covers many anaerobic bacterial groups such as *Bacteroides fragilis*, clostridia and Gram-positive anaerobic cocci.[3,6]

Investigation of the pharmacokinetic profile of telithromycin in saliva is of interest in order to follow the adequacy of treatment and also to explore the feasibility of following kinetics in saliva rather than plasma. Therapeutic concentrations of antibiotic maintained throughout the day would be considered beneficial for the treatment of tonsillitis. Knowledge of the impact of antibiotherapy on the oropharyngeal flora is of importance since it can lead to overgrowth of yeasts, Enterobacteriaceae or streptococcal strains that may cause local or systemic infections in immunosuppressed hosts.[7] Ecological disturbances in the intestinal microflora due to antimicrobial treatment can

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lead to adverse effects such as diarrhoea or pseudomembranous colitis caused by *Clostridium difficile*,[8] or even to systemic infections with yeasts and aerobic Gram-negative rods in immunosuppressed patients. Finally, selection of resistant strains in the normal oropharyngeal and intestinal microflora and possible transfer of resistance genes among various bacterial strains and groups is also a serious consequence of antimicrobial therapy for the patient and for society.[9]

The impact of clarithromycin on the faecal flora is well documented with a decrease in enterococci and *Escherichia coli*, and overgrowth of resistant Enterobacteriaceae during therapy but no emergence of *C. difficile* or yeasts.[10–12]

The purpose of the present study was: (i) to investigate the pharmacokinetic profile of telithromycin and clarithromycin, respectively, in saliva and plasma for therapeutic considerations; and (ii) to assess the impact of antibiotic treatment on the oropharyngeal and intestinal microflora, including potential emergence of resistance before, during and after administration of telithromycin or clarithromycin given to healthy subjects.

## Materials and methods

### *Subjects*

Twenty subjects (10 women and 10 men; mean age 25.1 years, range 18.0–34.9 years) were enrolled in a randomized double-blind controlled trial. All subjects were considered healthy on the basis of their medical history, none of them had any history of significant cardiovascular, gastrointestinal, hepatic or renal diseases. None of the volunteers had taken any antibiotics during the previous 3 months. No other medication except contraceptives was allowed during the investigation period. The trial was approved by the Ethics Committee of Huddinge University Hospital, Karolinska Institute, Stockholm, Sweden.

### *Drug administration*

The subjects were randomized into two groups. Ten subjects received two 400 mg capsules of telithromycin (Hoechst Marion Roussel, Romainville, France) once daily (a.m.) and two placebo capsules (p.m.) once daily for 10 days. The other 10 subjects were given 500 mg (two 250 mg capsules) of clarithromycin (Sanofi-Winthrop, Paris, France) bid for 10 days.

### *Sampling of blood, saliva and faecal specimens*

A total of 21 plasma samples and 21 saliva samples were collected from each of the 20 patients at defined intervals for pharmacokinetic analyses on days 1, 2, 5, 10, 11 and 12. Faecal samples were collected on days 2, 5, 10, 12 and 15 for assay of the antibacterial agents. Saliva and faecal samples for microbiological analyses were collected before the drug administration (day 0), during administration (days 2, 5 and 10) and after withdrawal of the agents (days 12, 15, 18 and 24). Unstimulated mixed saliva was sampled by spitting into sterile tubes. Faecal samples were collected in sterile plastic containers. All specimens were frozen within 1 h and stored at –70°C until assayed.

### *Assays of telithromycin and clarithromycin concentrations*

The plasma and saliva concentrations of telithromycin and clarithromycin were determined microbiologically using the agar plate diffusion method. Telithromycin and clarithromycin concentrations in plasma and saliva were determined in quadruplicate in Antibiotic Medium Merck A agar and *Bacillus subtilis* ATCC 6633 as the test organism, based in plasma on a lower limit of quantification of 0.025 mg/L. The plates were incubated aerobically for 18 h at 32°C. Concentrations of telithromycin and clarithromycin in faeces were determined by the agar well diffusion method. The test medium was Antibiotic Medium No. 1 (Difco, Detroit, MI, USA) and the indicator strain was *Micrococcus luteus* ATCC 9341. Standards with known concentrations of the two drugs were prepared in a faecal suspension from a healthy volunteer and diluted 1:3 in 0.15 M phosphate buffer pH 7.2. The faecal samples were diluted in phosphate buffer (1:3) and centrifuged at 3000**g** for 10 min. Samples were run in duplicate and on each agar plate a standard series was inoculated. The plates were incubated for 18 h at 37°C. Plasma, saliva and faecal drug concentrations were determined in relation to the diameters of the inhibition zones caused by the known concentrations from the standard series.

### *Processing of saliva and faecal specimens for microbiological analyses*

The microbiological analyses of the specimens were performed as described previously.[12,13] The saliva and faecal specimens were suspended in pre-reduced peptone–yeast extract medium, diluted 10-fold and inoculated on non-selective and selective media. The aerobic agar plates were incubated for 24 h at 37°C and the anaerobic plates for 48 h at 37°C in anaerobic jars (GasPak; BBL, Cockeysville, MD, USA). After incubation, different colony types were counted and isolated in pure culture. All isolates were identified according to Gram's stain and biochemical tests.[14] The anaerobic microorganisms were identified by gas–liquid chromatography of metabolites from glucose.[14,15] The lower limit of detection was $10^2$ microorganisms per millilitre of saliva or per gram of faeces.

### *Antibiotic susceptibility tests*

Three representative colonies of intestinal Enterobacteriaceae, enterococci and *Bacteroides*, and three oral α-haemolytic streptococcal colonies were isolated from each subject on days 0, 10 and 24 in order to study the antimicrobial susceptibility during the investigation period. The MICs for telithromycin and clarithromycin were determined by the agar dilution method using PDM Antibiotics Sensitivity Medium (AB Biodisk, Solna, Sweden). *E. coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212 and *Bacteroides fragilis* NCTC 9343 were used as reference strains. The inoculum was $10^7$ cfu/mL for aerobic strains, and $10^8$ cfu/mL for *Bacteroides* spp. The agar plates were incubated aerobically or anaerobically at 37°C for 24 and 48 h, respectively.

### *Statistical analysis*

Statistical analyses of the pharmacokinetic parameters were mainly descriptive. Quantitative alterations in cultivation were compared statistically within groups between day 0–10 and between day 0–24 using Wilcoxon signed rank test ($P$ values $\leq 0.05$ were considered stastistically significant). The MICs for each species were compared within groups between day 0–10 and between day 0–24 using the Mann–Whitney $U$-test in order to detect significant decreases in susceptibility during and after the administration period ($P$ values $\leq 0.01$ were considered statistically significant). $P$ values were adjusted for multiple analyses.

### *Safety data*

All volunteers had a physical examination before entering the study, at day 11 and after completion of the study (day 24). Vital signs (blood pressure and heart rate) and 12-lead electrocardiogram (ECG) were performed and possible adverse events were followed throughout the investigation period.

## Results

### *Pharmacokinetics of telithromycin and clarithromycin in plasma and saliva*

The plasma and saliva concentrations of telithromycin at day 1 are shown in Figure 1. Telithromycin was eliminated in a one-compartment model in plasma and in a two-compartment model in saliva. Table I shows the pharmacokinetic data for both drugs. In subjects receiving telithromycin the mean $C_{max}$, area under the curve (AUC) and $C_{24}$ in saliva exceeded the values obtained from plasma; $C_{max}$ was *c*. 1.2–1.5 times higher in saliva compared with plasma, AUC (0–24 h) was 1.6–1.7 times higher in saliva compared with plasma and $C_{24}$ was 3–5 times higher in saliva compared with plasma. In the clarithromycin group, values of these parameters in saliva were, generally, slightly lower or equal to the corresponding plasma value. Large variations in $C_{max}$ and AUC were noted in both treatment groups.

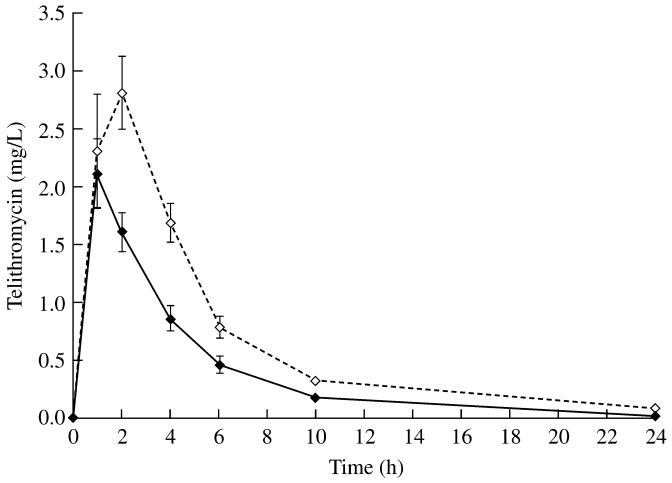


**Figure 1.** Mean concentrations (± S.E.M.) of telithromycin in plasma and saliva on day 1 (◆, day 1 plasma; ◇, day 1 saliva).

### *Faecal concentrations of telithromycin and clarithromycin*

The faecal concentrations of telithromycin and clarithromycin are shown in Table II. The concentrations of telithromycin were high during the administration period, i.e. day 5–10, mean values >500 mg/kg with three subjects having levels >1000 mg/kg. The concentrations of clarithromycin in faeces were lower compared with telithromycin (Table II). One subject had concentrations >500 mg/kg on days 10 and 12. Large variations in drug concentrations were noted in both treatment groups.

### *Effect of telithromycin and clarithromycin on the oropharyngeal microflora*

There were only minor disturbances in the aerobic oropharyngeal microflora owing to the administration of telithromycin and clarithromycin, respectively. No significant alteration in the levels of α-haemolytic streptococci, micrococci, staphylococci, *Haemophilus* or *Neisseria* spp. was noticed in either of the groups during the administration period. The numbers of corynebacteria were reduced at day 10 in both treatment groups, although only significantly in the telithromycin group ($P \leq 0.05$). Six subjects in the telithromycin group and four in the clarithromycin group were colonized by low numbers of *Candida* spp. A transient colonization of the oropharynx with low numbers of Enterobacteriaceae (*Klebsiella* spp., *Enterobacter* spp. or *Citrobacter* spp.) was recorded during or after the administration

**Table I.** Pharmacokinetic parameters of telithromycin and clarithromycin in plasma and saliva

| | Telithromycin ($n$ = 10) | | | | Clarithromycin ($n$ = 10) | | | |
|---|---|---|---|---|---|---|---|---|
| | day 1 | | day 10 | | day 1 | | day 10 | |
| Parameter | plasma | saliva | plasma | saliva | plasma | saliva | plasma | saliva |
| $C_{max}$ (mg/L) | | | | | | | | |
| mean | 2.35 | 3.05 | 2.03 | 3.06 | 2.98 | 2.38 | 3.87 | 4.29 |
| (minimum–maximum) | (1.46–3.74) | (1.49–5.39) | (1.01–3.56) | (1.47–5.17) | (1.74–4.94) | (0.78–4.58) | (2.23–7.41) | (2.67–7.39) |
| CV% | 31 | 40 | 42 | 36 | 34 | 46 | 45 | 36 |
| $t_{max}$ (h) | | | | | | | | |
| median | 1.0 | 2.0 | 1.5 | 2.0 | 2.0 | 4.0 | 4.0 | 4.0 |
| (minimum–maximum) | (1.0–2.0) | (1.0–2.0) | (1.0–4.0) | (1.0–4.0) | (1.0–6.0) | (2.0–4.0) | (1.0–6.0) | (2.0–6.0) |
| AUC (0–24 h) (mg•h/L) | | | | | | | | |
| mean | 9.27 | 15.6 | 10.4 | 16.8 | | | | |
| (minimum–maximum) | (5.66–14.03) | (8.4–23.6) | (4.4–20.5) | (7.8–27.9) | | | | |
| CV% | 30 | 31 | 49 | 43 | | | | |
| AUC (0–10 h) (mg•h/L) | | | | | | | | |
| mean | | | | | 18.1 | 13.3 | 27.8 | 27.4 |
| (minimum–maximum) | | | | | (9.8–27.8) | (5.2–28.4) | (18.8–42.8) | (20.2–35.9) |
| CV% | | | | | 32 | 49 | 32 | 20 |
| $C_{24}$ (24 h) (mg/L) | | | | | | | | |
| mean | 0.013 | 0.070 | 0.026 | 0.090 | | | | |
| (minimum–maximum) | (LOQ–0.060) | (0.030–0.094) | (LOQ–0.108) | (0.038–0.172) | | | | |
| CV% | – | 23 | 140 | 51 | | | | |
| $R$[a] | | | | | | | | |
| $G_{mean}$ | 1.7 | | 1.6 | | 0.7 | | 1.0 | |
| CV% | 39 | | 26 | | 47 | | 33 | |

[a]$R$ = AUC (0–24 h) saliva/AUC (0–24 h) plasma and AUC (0–10 h) saliva/AUC (0–10 h) plasma, respectively.
LOQ, limit of quantification.

period in five subjects receiving telithromycin and in four subjects receiving clarithromycin. In the anaerobic oropharyngeal microflora, the numbers of *Actinomyces* and *Prevotella* spp. were moderately suppressed in both groups, while no other bacterial group, such as peptostreptococci, streptococci, bifidobacteria, lactobacilli and *Veillonella* spp., was affected to any major extent. The oropharyngeal microflora was normalized 2 weeks after discontinuation of the administration of telithromycin and clarithromycin, respectively.

### *Effect of telithromycin and clarithromycin on the intestinal microflora*

The administration of telithromycin and clarithromycin caused similar and moderate disturbances in the aerobic intestinal microflora as shown in Figure 2. In both groups, the numbers of *E. coli* were significantly reduced at day 10 ($P \leqslant 0.05$). In the telithromycin group, an overgrowth of staphylococci was recorded at day 10 ($P \leqslant 0.05$), and the levels of enterococci were decreased, although not

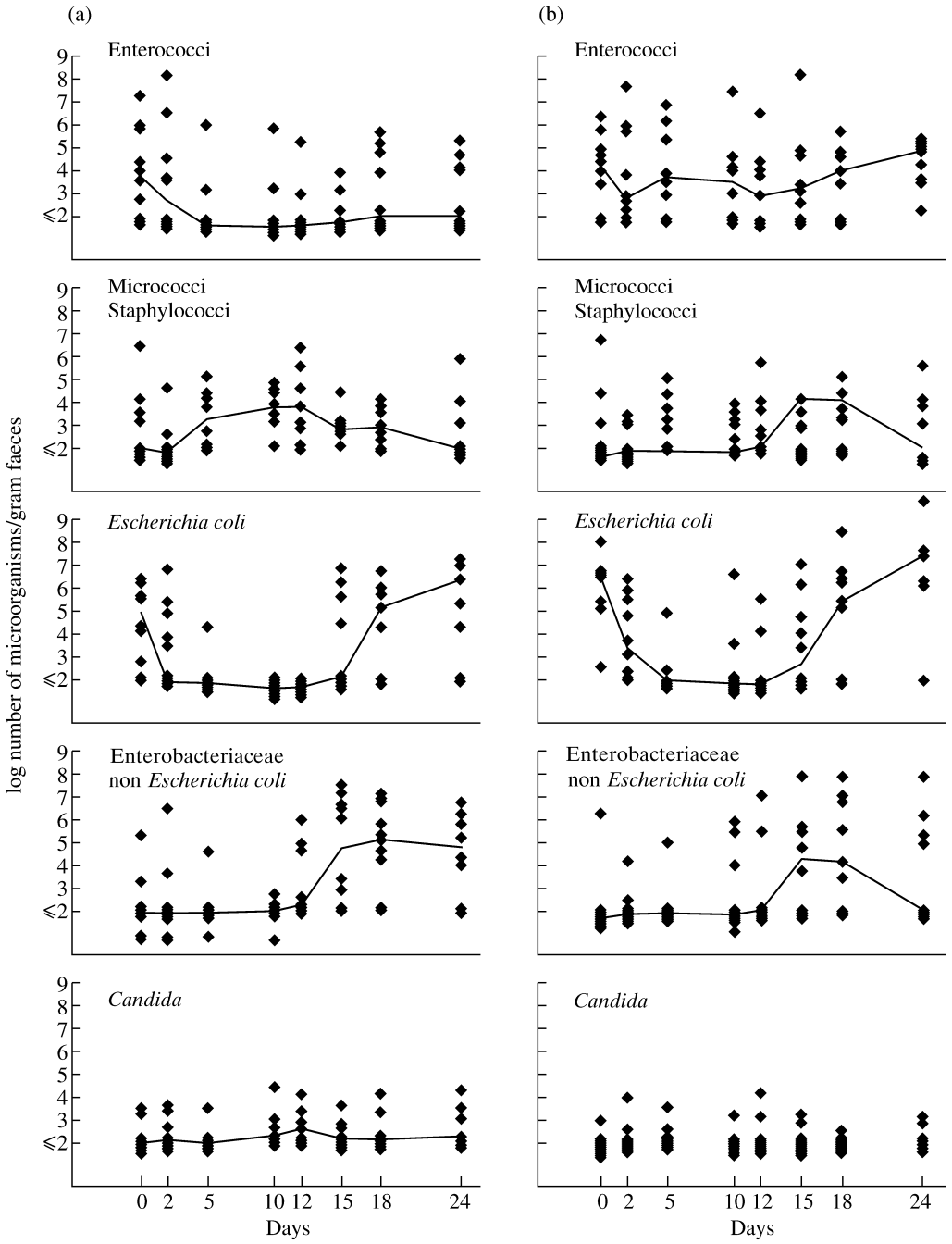


**Figure 2.** Impact of (a) telithromycin and (b) clarithromycin administration on the intestinal aerobic microflora of 10 subjects. —, median value of the logarithmic number of microorganisms/g faeces.

**Table II.** Faecal concentrations of telithromycin and clarithromycin in 10 subjects receiving 800 mg telithromycin once daily for 10 days or 500 mg clarithromycin bid for 10 days, respectively

| | Faecal concentrations of telithromycin (mg/kg) | | | | | Faecal concentrations of clarithromycin (mg/kg) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | day 2 | day 5 | day 10 | day 12 | day 15 | day 2 | day 5 | day 10 | day 12 | day 15 |
| No. of samples | 10 | 8 | 10 | 9 | 10 | 10 | 8 | 10 | 9 | 9 |
| Mean | 200.68 | 513.51 | 506.63 | 192.51 | 0.94 | 112.18 | 272.39 | 234.90 | 186.14 | 13.31 |
| S.D. | 167.21 | 316.86 | 407.40 | 226.44 | 0.71 | 114.81 | 137.62 | 128.32 | 144.85 | 21.05 |
| Range | 1.2–502.0 | 138.3–1150.6 | 13.2–1329.9 | LOQ–687.5 | LOQ–2.4 | 0.0–276.8 | 134.6–410.2 | 58.1–502.0 | 52.7–512.8 | 0.9–67.1 |

LOQ, limit of quantification.

significantly, during the administration period. Overgrowth of non-*E. coli* Enterobacteriaceae, such as *Klebsiella*, *Citrobacter* and *Enterobacter* spp., occurred in five volunteers receiving telithromycin and in six subjects receiving clarithromycin during or after the administration period. No significant overgrowth of *Candida* spp. occurred in any of the groups.

Figure 3 shows the effect of telithromycin and clarithromycin on the anaerobic intestinal microflora. There was a marked reduction of lactobacilli and bifidobacteria on day 10 in the telithromycin group ($P \leqslant 0.05$) and in the clarithromycin group ($P \leqslant 0.01$), which persisted at day 24 in both groups ($P \leqslant 0.05$). The numbers of peptostreptococci, streptococci, clostridia, *Veillonella* and *Bacteroides* spp., or the total number of anaerobic bacteria was not significantly affected by any of the administration regimens. None of the subjects were colonized by *C. difficile* during the administration period.

### *Antibiotic susceptibility tests*

The antibiotic susceptibility of isolated oral α-haemolytic streptococci and intestinal enterococci, Enterobacteriaceae and *Bacteroides* spp. for telithromycin and clarithromycin, respectively, are shown in Table III. A minor increase in MICs occurred among salivary streptococci from the telithromycin group, although all isolates remained susceptible to telithromycin throughout the study period (MIC $\leqslant$ 1.0 mg/L). In the clarithromycin group a significant decrease in susceptibility was noted, $MIC_{90}$ increased from 0.032 mg/L pretreatment to >128 mg/L at day 10 and 24 ($P \leqslant 0.001$, Mann–Whitney *U*-test). In the telithromycin group, MICs of telithromycin against enterococci and Enterobacteriaceae at day 10 and 24 were not significantly altered compared with pretreatment values. Isolates with MIC $\geq$ 16.0 mg/L were mostly non-*E. coli* Enterobacteriaceae (e.g. *Klebsiella* and *Citrobacter* spp.). In the clarithromycin group, MICs against enterococci and Enterobacteriaceae (mostly *E. coli*, *Klebsiella*, *Citrobacter* and *Enterobacter* spp.) were significantly increased at day 10 ($P \leqslant 0.001$) but not at day 24 compared with pre-treatment values. A selection of highly resistant *Bacteroides* isolates was recorded during and after treatment in both treatment groups ($P \leqslant 0.001$).

### *Adverse events*

Thirty-one mild to moderate adverse events considered possibly related to study medication were reported during the investigation period. With telithromycin, the most frequently reported adverse events were taste perversion and diarrhoea (three subjects each). In the clarithromycin group, the most frequently reported adverse events were taste perversion (10 subjects), abdominal pain (three subjects) and diarrhoea (two subjects). Telithromycin or clarithro-

mycin had no clinically noteworthy effect on vital signs or ECG parameters. The duration of the QTc interval was not increased for any of the subjects.

## Discussion

Careful investigation of the impact of antibiotic treatment on the endogenous microflora is of importance since alteration in the balance of the flora, qualitatively and/or quantitatively, may facilitate colonization by new potentially pathogenic strains or enable overgrowth of resistant microorganisms already present in the normal flora.[16,17] Treatment with clarithromycin has been associated with suppression of intestinal enterococci, Enterobacteriaceae and certain anaerobic bacteria.[10–12] The effect of ketolides like telithromycin on the normal microflora has not been studied before. In the present study, the mean concentra-

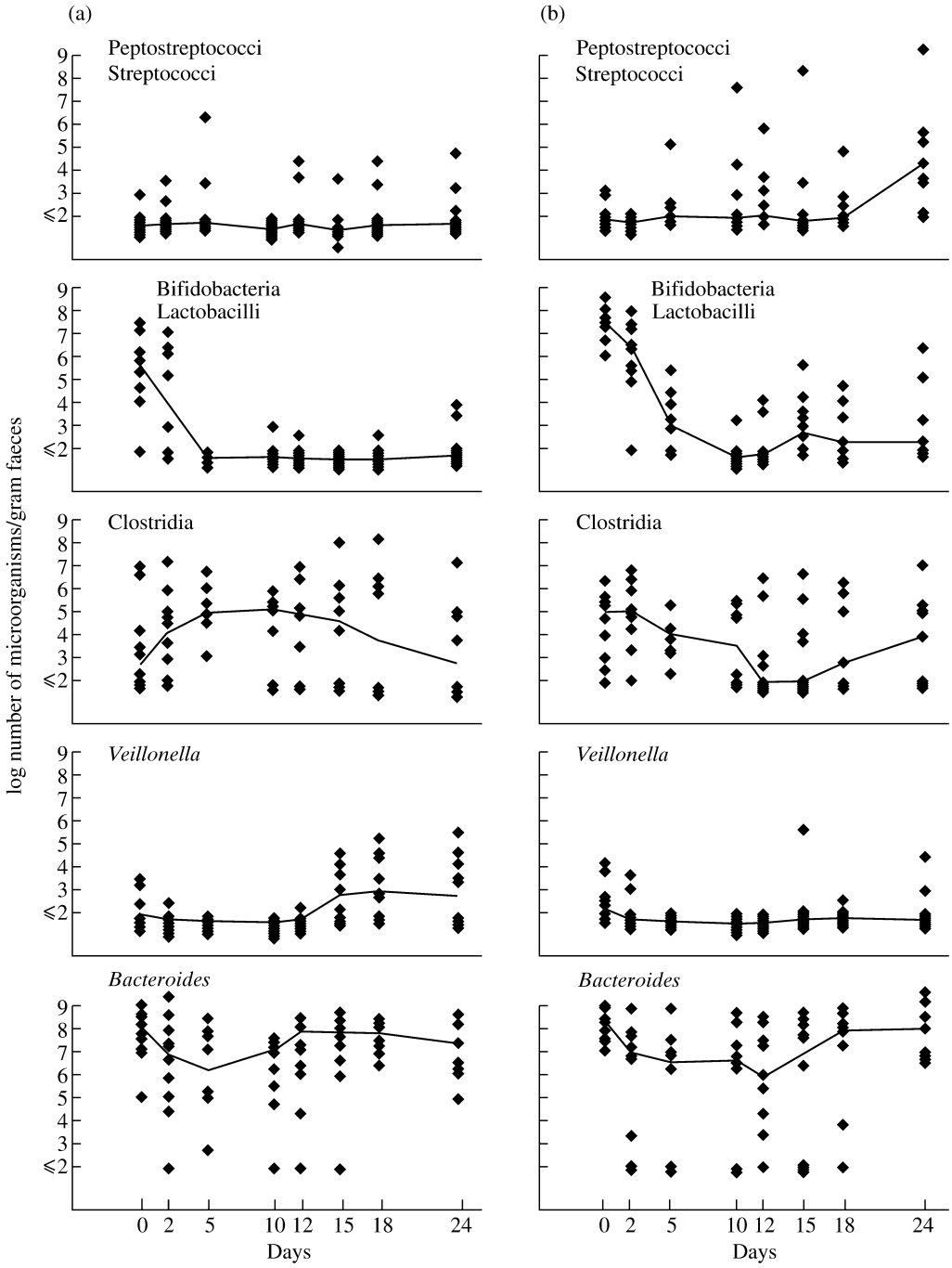


**Figure 3.** Impact of (a) telithromycin and (b) clarithromycin administration on the intestinal anaerobic microflora of 10 subjects. —, median value of the logarithmic number of microorganisms/g faeces.

**Table III.** Minimum inhibitory concentrations of telithromycin and clarithromycin against oral α-streptococci, intestinal enterococci, enterobacteria and *Bacteroides*

| Antimicrobial agent/ treatment group | Sampling day | MIC (mg/L) | | |
|---|---|---|---|---|
| | | $MIC_{50}$ | $MIC_{90}$ | range |
| α-Haemolytic streptococci | | | | |
| telithromycin | 0 | 0.016 | 0.032 | 0.016–0.25 |
| | 10 | 0.125 | 0.25 | 0.032–1.0 |
| | 24 | 0.125 | 0.50 | 0.016–1.0 |
| clarithromycin | 0 | 0.016 | 0.032 | 0.016–64 |
| | 10 | 64 | >128.0 | 0.016–>128 |
| | 24 | 128 | >128.0 | 0.5–>128 |
| Enterococci | | | | |
| telithromycin | 0 | 0.016 | 8.0 | 0.016–8.0 |
| | 10 | 0.25 | 16.0 | 0.25–16.0 |
| | 24 | 0.25 | 32 | 0.016–32 |
| clarithromycin | 0 | 0.5 | 1.0 | 0.016–1.0 |
| | 10 | >128 | >128 | >128.0–>128 |
| | 24 | 1.0 | >128 | 0.016–>128 |
| Enterobacteria | | | | |
| telithromycin | 0 | 4.0 | 8.0 | 2.0–8.0 |
| | 10 | 16 | 16.0 | 4.0–16 |
| | 24 | 8.0 | 64.0 | 4.0–64 |
| clarithromycin | 0 | 32 | 64.0 | 16.0–>128 |
| | 10 | >128 | >128 | 16.0–>128 |
| | 24 | 32.0 | 128.0 | 16.0–>128.0 |
| *Bacteroides* | | | | |
| telithromycin | 0 | 2 | >128 | 0.25–>128 |
| | 10 | >128 | >128 | >128–>128 |
| | 24 | >128 | >128 | 0.125–>128 |
| clarithromycin | 0 | 1.0 | >128 | 0.125–>128 |
| | 10 | >128 | >128 | 32–>128 |
| | 24 | 64 | >128 | 0.016–>128 |

tion of telithromycin in saliva was higher on average than that in plasma and was above the $MIC_{50}$ (≤0.06 mg/L) for most respiratory pathogens, such as β-haemolytic streptococci, *Streptococcus pneumoniae* and *M. catarrhalis*, up to 24 h post-dose.[3,4,18] This indicates a good therapeutic profile for throat infections. The retention of α-haemolytic streptococci is favourable from an ecological point of view, since these microorganisms are known to produce bacteriocins which protect against colonization with Enterobacteriaceae and other potentially pathogenic microorganisms.[19,20] The high faecal concentrations of telithromycin during the administration period, which is a direct consequence of faecal elimination of this drug, are in accordance with the alterations seen in the intestinal microflora mainly affecting enterococci and *E. coli*. The quantitative ecological disturbances in the normal oral and intestinal microflora during administration of telithromycin were considered moderate and comparable to those of clarithromycin administration in the present study as well as in earlier studies.[10–12] However, in both treatment groups qualitative alterations in terms of emergence of resistant strains occurred, which were most pronounced in the clarithromycin group. In both treatment groups, there was an increase in MICs against oral streptococci, mostly represented by *Streptococcus salivarius*. In the telithromycin group, virtually all α-haemolytic streptococci were considered susceptible to telithromycin (preliminary breakpoint $R \geq 4.0$ mg/L, according to the manufacturer) throughout the study period, while in the clarithromycin group, a shift from susceptiblity to resistance was seen during and after treatment (breakpoint $R \geq 1.0$ mg/L).[21] In the clarithromycin group, a significant selection of highly clarithromycin-resistant intestinal enterococci and Enterobacteriaceae was seen at day 10, while MICs of these bacterial groups did not increase significantly during the administration period in the telithromycin group. The results of emergence of clarithromycin resistance are in agreement with those observed in a previous study.[12]

In conclusion, administration of telithromycin resulted in saliva concentrations that exceeded the MICs for common respiratory pathogens, and caused moderate ecological disturbance in the normal oral and intestinal microflora comparable with that associated with clarithromycin. In terms of resistance development in the normal microflora, telithromycin appears to have a more favourable ecological profile than clarithromycin.

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