Pharmacokinetics of the New Ketolide Telithromycin (HMR 3647) Administered in Ascending Single and Multiple Doses

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Telithromycin (HMR 3647) is the first of a novel family of antimicrobials, the ketolides, developed specifically for the treatment of community-acquired respiratory tract infections. The ketolides are a new addition to the macrolide-lincosamide-streptogramin B (MLS) group of antimicrobials. These agents inhibit bacterial protein synthesis via two mechanisms: first by directly blocking translation of mRNA and second by interfering with the assembly of new ribosomal units (7). Ketolides are characterized by a ketone group, which replaces the cladinose sugar at position 3 of the macrolactone ring. This ketone group not only confers excellent acid stability but also accounts for the fact that, unlike macrolides, telithromycin does not induce MLS resistance in vitro (4, 6, 14). Furthermore, the C11–12 carbamate side chain of telithromycin enhances binding to MLS-resistant ribosomes, and this may explain the activity of telithromycin against MLS-resistant organisms (11).

The global spread of resistance among respiratory tract pathogens is a matter of serious concern. Indeed, a U.S. analysis of Streptococcus pneumoniae isolates from the 1998–1999 respiratory season reported resistance rates of 14, 25, and 22% for penicillin (high-level resistance), cefuroxime, and clarithromycin-azithromycin, respectively (C. Thornsberry, I. A. Critchley, Y. Mauriz, J. Khan, G. Piazza, and D. F. Sahm, Abstr. 39th Intersci. Conf. Antimicrob. Agents, Chemother., abstr. E-133, p. 207, 1998). These properties are generally characteristic of antimicrobials for which, in relation to MIC, the amount of drug delivered rather than the time for which plasma levels are maintained above the MIC is a better predictor of outcome (9). This suggests that a once-daily dosage regimen of telithromycin may be suitable for further evaluation in humans. The present study was conducted to evaluate the single- and multiple-dose pharmacokinetics and dose proportionality of telithromycin given once daily over the dose range of 400 to 1,600 mg/day in healthy human subjects.

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In vitro, telithromycin exhibits concentration-dependent killing and has a significant postantibiotic effect (D. Felmingham, S. Clark, M. J. Robbins, C. Dencer, and A. Bryskier, Abstr. 38th Intersci. Conf. Antimicrob. Agents, Chemother., abstr. E-133, p. 207, 1998). These properties are generally characteristic of antimicrobials for which, in relation to MIC, the amount of drug delivered rather than the time for which plasma levels are maintained above the MIC is a better predictor of outcome (9). This suggests that a once-daily dosage regimen of telithromycin may be suitable for further evaluation in humans. The present study was conducted to evaluate the single- and multiple-dose pharmacokinetics and dose proportionality of telithromycin given once daily over the dose range of 400 to 1,600 mg/day in healthy human subjects.

MATERIALS AND METHODS

This single-center, randomized, open-label, single- and multiple-dose, three-way crossover study was conducted between August 1998 and November 1998 in Bloemfontein, South Africa. The study was performed in accordance with the European Community Good Clinical Practice and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals guidelines, and all subjects were required to provide written, informed consent.

Subjects. This study recruited male subjects aged 18 to 45 years who were judged to be healthy by medical history, physical examination, routine laboratory tests, blood pressure, heart rate, and 12-lead electrocardiogram (ECG).

Subjects were excluded from the study if they were receiving concomitant medication or had received during the preceding 3 months an investigational drug or any drug with a well-defined potential for toxicity to a major organ or a potential to induce liver enzymes or any other medication within the last 2 weeks. Subjects were also excluded if they had any condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs or if they had experienced symptoms of a clinically significant illness in the previous 3 months. Additional exclusion criteria included known long-QT syndrome or a history of allergic disease or of hypersensitivity to drugs with a structure similar to that of...
telithromycin. During the study, subjects were asked to refrain from smoking more than 10 cigarettes per day and to restrict their alcohol intake to no more than 0.5 liters of wine or equivalent per day.

**Study design and procedures.** Each of the three treatment periods consisted of a single dose of telithromycin at the theoretical concentration (100 mg per day), followed 4 days later by the same oral dose of telithromycin given once daily for 7 days (days 5 to 11). Each treatment period was separated by a washout period of at least 7 days. The sequence in which subjects received the different dosages of telithromycin was determined by a Williams randomization plan (8). Study medication was administered with 240 ml of water after an overnight fast, and administration was followed by a light breakfast. Telithromycin (400-mg) tablets for oral administration were provided by Hoechst Marion Roussel (Romainville, France).

Subjects were housed for 24 h on the first day (day 1) and the last day (day 11) of each of the three treatment periods and reported to the clinic before breakfast to receive study medication on the other dosing days. Subjects were to abstain from strenuous physical exercise and consumption of tobacco, alcohol, and xanthine derivatives from 48 h before the first dose of telithromycin until 24 h after the last dosing of each treatment period. In addition, grapefruit juice was not permitted from 48 h before the first dose of telithromycin until 96 h after the last dosing of each treatment period.

**Sample collection.** Blood samples (3.5 ml) for pharmacokinetic analysis were taken at the screening visit (2 weeks before study entry), before dosing on all days, and at the following times after dosing on days 1 and 11 of each treatment period: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 h. Urine for determination of telithromycin concentrations was collected at screening and for three consecutive 24-h periods, starting at the time of the last dose on days 1 and 11 of each treatment period. For safety evaluations, blood (30 ml at screening and 20 ml thereafter) was collected at screening, before the first dose of the first treatment period, 24 h after the last dose of each treatment period, and 96 h after the last dose of the third treatment period. Urine was collected at screening, before the first dose of the first treatment period, and 96 h after the last dose of the third treatment period. Plasma and urine samples were stored frozen at −20°C until analysis.

**Analytical methodology.** (i) **Telithromycin.** Telithromycin was assayed in plasma using a validated liquid chromatography/mass spectrometry (LC/MS) method following precipitation of plasma proteins by acetonitrile in a 96-well format. The method has a standard curve range of 0.005 to 3 mg/liter using 100 μl of plasma and a limit of quantification of 0.005 mg/liter. Each run included calibration and quality controls over the standard range. The interbatch percent coefficient of variation (CV) for the quality control samples was between 2.8 and 8%. Te-lithromycin concentration in urine was assayed using a validated reverse-phase high-performance liquid chromatography method. The column eluent was monitored by fluorimetry (excitation at 263 nm and emission at 460 nm), and the detector signal was integrated to produce peak heights. The method has a standard curve range of 0.5 to 100 mg/liter using 50 μl of urine and a limit of quantification of 0.5 mg/liter. Each run included calibration (0.5 to 100 mg/liter) and quality controls (0.5 to 75 mg/liter). The interbatch percent CV for the quality control samples was between 0.8 and 2.9%.

(ii) RU 76363. RU 76363, the main metabolite of telithromycin, was assayed in plasma by liquid chromatography-atmospheric pressure chemical ionization-mass spectrometry using the full-scan MS mode. Samples were deproteinized with acetonitrile, evaporated to dryness, and reconstituted in the analytical mobile phase prior to injection for reversed-phase chromatography. The validated method has a standard curve range of 0.0025 to 0.25 mg of RU 76363/liter (using 100 μl plasma) and a limit of quantification of 0.0025 mg/liter. Each run included calibration (0.0025 to 0.25 mg/liter) and quality controls (0.006 to 0.25 mg/liter). The interbatch percent CV for the quality control samples was between 4.2 and 9.6%.

**Safety.** Safety was evaluated on the basis of ECG, blood pressure, heart rate, and laboratory variables (hematology, blood chemistry, and urinalysis) at screening, before dosing on day 1, 24 h after the last dose of each treatment period, and 96 h after the last dose of the third treatment period. Adverse events were recorded throughout the study. An adverse event, which could be nonserious or serious, was defined as any sign, symptom, syndrome, or illness that appeared or worsened in a subject during the observation period and that could impair the well-being of the subject.

**Pharmacokinetic and statistical analysis.** A sample size of six subjects was calculated to provide 80% power to observe a difference of at least 1 mg/liter in the area under the concentration-time curve (AUC) standardized to the dose, with a risk of 5% and a mean square error of 0.5, based on observations from previous studies. However, since it is common to use 18 subjects for such a pivotal study, this was the number used.

Pharmacokinetic parameters were calculated using WinNonLin software (version 2.0), and descriptive statistics were performed using SAS software (version 6.12). Concentrations of telithromycin and its major metabolite, RU 76363, in plasma were determined for all sampling times throughout the study. The following pharmacokinetic parameters were calculated for telithromycin and RU 76363 after a single dose (day 1) and multiple doses (day 11): maximal plasma concentration (Cmax), time to reach maximal plasma concentration (tmax), trough plasma concentration 24 h after dosing (C24), AUC over 24 h (AUC0–24), AUC until the last quantifiable measurement (AUC0–2τ), AUC until infinity (AUC0–∞), (when the terminal half-life was available), amount of telithromycin excreted in urine over 24 h (Ae0–24), renal clearance of telithromycin (CLR(0–24)), and elimination half-life (τ). Concentration data were analyzed using noncompartmental methods (9). The mean accuracy of the plasma RU 76363 was 96.8 ± 2.0% (percent CV). The upper limit of quantification of telithromycin was 100 mg/liter.

**RESULTS**

**Subjects.** Eighteen Caucasian, healthy male subjects of mean age 21.3 years (range, 18 to 29 years), mean height 183.2 cm (ranges, 170 to 195 cm) and mean weight 79.2 kg (ranges, 67.8 to 98.4 kg) were recruited. No subjects had concomitant illness, and none were receiving concomitant treatments at the time of inclusion. However, six subjects received concomitant medications for acute minor illnesses during the study, none of which are likely to interfere with the pharmacokinetics or safety of telithromycin. One subject withdrew because of an adverse event during dosing at 1,600 mg/day.

**Telithromycin and RU 76363 assays.** The mean accuracy and precision of the plasma telithromycin assay were 95.7 to 100.7% (percent recovery relative to the theoretical concentration) and 7.5 to 11.7% (percent CV), respectively. For the urine telithromycin assay, the mean accuracy was 100.7% (percent recovery relative to the theoretical concentration), and the precision was 4.6 to 7.1% (percent CV).

**Pharmacokinetics.** Pharmacokinetic analysis was performed on data from 18 subjects for the 400- and 800-mg doses but from only 16 subjects for the 1,600-mg dose: one subject withdrew due to a severe adverse event, and in another subject the trough concentrations suddenly decreased by a factor of 2 between the third and fourth administrations. In the latter subject, the results could be due to a decrease in bioavailability, although no explanation for a potential decrease in bioavailability could be found, e.g. vomiting, concomitant medication,
or compliance. Hence, the data from this subject were rejected from the 1,600-mg multiple-dose pharmacokinetic analysis of telithromycin and RU 76363.

(i) **Telithromycin.** The pharmacokinetics and dose proportionality of single and multiple doses of telithromycin are shown in Tables 1 and 2, respectively. Following a single oral dose of 400, 800, or 1,600 mg, telithromycin was quantifiable in the plasma from the first time point (0.5 h) and reached \( t_{\text{max}} \) after a median of 1 h, irrespective of dose (Fig. 1). Telithromycin was no longer quantifiable in plasma 48, 72, and 96 h after dosing for the 400-, 800-, and 1,600-mg single doses, respectively, and 72 and 96 h after the final dose in the 7-day multiple-dose phase (400- and 800-mg groups). Telithromycin was still quantifiable in 14 out of 16 subjects after the final dose in the 7-day multiple-dose phase in the 1,600-mg group.

Steady state was achieved on the second or third day of multiple dosing, as determined from the trough plasma concentrations. A slight accumulation of telithromycin was observed after 7 days of therapy, with AUC\(_{0–24}\) values 1.37 to 1.49 times higher than those achieved in the single-dose phase. \( R_{\text{ac}} \) was unaffected by the dose.

Overall, there was a modest deviation from dose proportionality for \( C_{\text{max}} \), AUC, and \( C_{24} \) in both the single- and multiple-dose phases (Tables 1 and 2). After single dosing, \( C_{\text{max}} \) was proportional to dose over the 400- to 800-mg and 800- to 1,600-mg intervals, although not over the entire dosage range. After multiple dosing, \( C_{\text{max}} \) was proportional to dose only for the 800- to 1,600-mg interval. AUC deviated from dose proportionality in both the single- and multiple-dose phases; a doubling of the 400- and 800-mg doses, while \( t_{1/2z} \) increased by a factor of 1.8 over the 800- to 1,600-mg dose interval. CL\(_{(0–24)} \) for telithromycin was constant over the dose range after both single and multiple doses.

In the 72-h period following administration of a single dose of telithromycin, 400, 800, or 1,600 mg, 7.64, 13.0, and 19.0%, respectively, of the dose was eliminated unchanged in the urine. Corresponding values for the 72-h period following the final dose of the 7-day treatment period were 9.93, 18.4, and 25.8%. Approximately 96% of urinary excretion took place within 24 h of the final dose.

(ii) **RU 76363.** RU 76363, an alcohol resulting from loss of aryl rings, is the major hepatic metabolite of telithromycin. Following single doses of telithromycin at 400, 800, or 1,600 mg, RU 76363 was quantifiable in plasma at the same time points as telithromycin. The levels of RU 76363 peaked after those of the parent compound. The AUC\(_{0–24}\) of this metabolite was 10 to 12% that of the parent compound, a figure that was constant across the dose range.

The pharmacokinetics and dose proportionality for single and multiple doses of RU 76363 are shown in Tables 3 and 4. RU 76363 deviated moderately from dose proportionality in a manner similar to that for telithromycin, with a doubling of dose resulting in a 2.5- to 3.7-fold increase in AUC. For both \( C_{\text{max}} \) and \( C_{24} \), RU 76363 deviated significantly from dose pro-

### TABLE 1. Pharmacokinetics and dose proportionality of telithromycin following a single oral dose

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>( C_{\text{max}} ) (mg/liter)</th>
<th>( t_{\text{max}} ) (h)</th>
<th>( C_{24} ) (mg/liter)</th>
<th>AUC(_{0–24}) (mg • h/liter)</th>
<th>AUC(_{0–24}) (mg • h/liter)</th>
<th>CL(_{(0–24)}) (liters/h)</th>
<th>( t_{1/2z} ) (h)</th>
<th>( t_{1/2z} ) (h)</th>
<th>( A_{\text{UC}} ) (24%)</th>
<th>( C_{\text{max/dose}} ) (mg/liter)</th>
<th>AUC(_{0–24/dose}) (mg • h/liter)</th>
<th>( C_{24/dose} ) (mg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>0.80 (57)</td>
<td>1.0 (0.5–4.0)</td>
<td>0.0069 (72)</td>
<td>2.57 (40)</td>
<td>3.09 (35)</td>
<td>12.17 (26)</td>
<td>2.13 (37)</td>
<td>6.68 (24)</td>
<td>7.42 (32)</td>
<td>1.59 (42)</td>
<td>1.90 (42)</td>
<td>8.40 (32)</td>
</tr>
<tr>
<td>800</td>
<td>1.90 (42)</td>
<td>1.0 (0.5–4.0)</td>
<td>0.0296 (45)</td>
<td>8.25 (31)</td>
<td>8.96 (32)</td>
<td>12.32 (17)</td>
<td>2.43 (41)</td>
<td>10.13 (27)</td>
<td>18.4 (27)</td>
<td>2.04 (30)</td>
<td>2.19 (42)</td>
<td>8.40 (32)</td>
</tr>
<tr>
<td>1,600</td>
<td>4.07 (30)</td>
<td>1.0 (0.5–4.0)</td>
<td>0.103 (53)</td>
<td>23.1 (34)</td>
<td>25.4 (35)</td>
<td>13.28 (23)</td>
<td>2.81 (31)</td>
<td>10.13 (27)</td>
<td>18.4 (27)</td>
<td>2.04 (30)</td>
<td>2.19 (42)</td>
<td>8.40 (32)</td>
</tr>
</tbody>
</table>

\* Data are means, with percent CV in parentheses, except where indicated otherwise. Statistical significance was determined by ANOVA and Tukey’s test. Elimination half-lives were calculated by a compartmental analysis.

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>( C_{\text{max}} ) (mg/liter)</th>
<th>( t_{\text{max}} ) (h)</th>
<th>( C_{24} ) (mg/liter)</th>
<th>AUC(_{0–24}) (mg • h/liter)</th>
<th>AUC(_{0–24}) (mg • h/liter)</th>
<th>CL(_{(0–24)}) (liters/h)</th>
<th>( t_{1/2z} ) (h)</th>
<th>( t_{1/2z} ) (h)</th>
<th>( A_{\text{UC}} ) (24%)</th>
<th>( C_{\text{max/dose}} ) (mg/liter)</th>
<th>AUC(_{0–24/dose}) (mg • h/liter)</th>
<th>( C_{24/dose} ) (mg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>0.829 (42)</td>
<td>1.0 (0.5–6.0)</td>
<td>0.0172 (56)</td>
<td>3.50 (31)</td>
<td>4.01 (39)</td>
<td>11.21 (28)</td>
<td>2.62 (49)</td>
<td>7.70 (21)</td>
<td>9.57 (35)</td>
<td>1.66 (42)</td>
<td>7.00 (31)</td>
<td>0.0343 (56)</td>
</tr>
<tr>
<td>800</td>
<td>2.27 (31)</td>
<td>1.0 (0.5–3.0)</td>
<td>0.070 (72)</td>
<td>12.5 (43)</td>
<td>12.59 (22)</td>
<td>12.5 (34)</td>
<td>2.87 (50)</td>
<td>9.81 (20)</td>
<td>17.7 (27)</td>
<td>2.27 (31)</td>
<td>12.5 (43)</td>
<td>0.070 (72)</td>
</tr>
<tr>
<td>1,600</td>
<td>4.48 (35)</td>
<td>1.0 (0.5–3.0)</td>
<td>0.217 (40)</td>
<td>30.2 (22)</td>
<td>35.9 (17)</td>
<td>13.1 (31)</td>
<td>3.76 (31)</td>
<td>18.7 (31)</td>
<td>24.4 (29)</td>
<td>2.24 (33)</td>
<td>15.11 (22)</td>
<td>0.108 (40)</td>
</tr>
</tbody>
</table>

\* Data are means, with percent CV in parentheses, unless otherwise indicated. Statistical significance was determined by ANOVA and Tukey’s test. Elimination half-lives were calculated by a compartmental analysis.

\* Values are medians with ranges in parentheses.

\* None of the values are significantly different from each other.

\* For 400-, 800-, and 1,600-mg doses, \( n = 10, 15, \) and 12, respectively.

\* Significantly different from the values for other doses (\( P < 0.001 \)).

\* Significantly different from the values at 400 and 800 mg (\( P < 0.001 \)).

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half-lives were calculated by compartmental analysis. Adverse events most commonly affected the digestive tract and were manifest as diarrhea, nausea, and gastrointestinal pain and disorder. All were mild or moderate in intensity, except for one case of vomiting and diarrhea, which was of severe intensity and which occurred during the multiple-dose 1,600-mg phase. This patient was withdrawn from the study.

Telithromycin had no clinically significant effect on clinical laboratory assessments, vital signs (blood pressure, heart rate, and ECG), or physical examination. In addition, no QTc values above 450 ms were observed throughout the study.

**DISCUSSION**

Telithromycin (HMR 3647) is an innovative new ketolide antimicrobial, which has been specifically designed for the treatment of community-acquired respiratory tract infections. The pharmacokinetic profile and dose proportionality of telithromycin and its major circulating metabolite, RU 76363, have been established when the drugs are given as single and as multiple once-daily doses to healthy subjects. RU 76363, an alcohol formed from loss of aryl rings during hepatic metabolism, is 4- to 16-fold less active than telithromycin in vitro.

Following oral administration telithromycin was rapidly absorbed, reaching \( C_{\text{max}} \) within 1 h of dosing. Steady state plasma concentrations of both telithromycin and its major metabolite, RU 76363, were reached within 2 to 3 days of multiple dosing, regardless of the dose. After 7 days of dosing, there was moderate accumulation of both telithromycin and RU 76363, with AUC values approximately 1.5-fold higher than those attained following a single dose. \( R_{\text{ac}} \) was relatively constant over the dosage range. This moderate accumulation might be explained by a slight decrease in nonrenal clearance with multiple dosing, since the main (initial) elimination half-life increased by 20 to 30\% while CL\(_{\text{R}(0-24)}\) remained unchanged.

The pharmacokinetics of telithromycin deviated moderately from dose proportionality after single and multiple oral administration: a doubling of the dose resulted in an increase of approximately threefold in AUC. \( C_{\text{max}} \) deviated only slightly from dose proportionality. \( t_{1/2z} \) and \( t_{1/2\alpha} \) also increased significantly with dose in the multiple-dose phase: over the 800- to 1,600-mg dosage interval \( t_{1/2z} \) increased by a factor of 1.5, while \( t_{1/2\alpha} \) increased 1.8-fold. CL\(_{\text{R}(0-24)}\) remained constant over the 400- to 1,600-mg dose range. Consequently, the per-

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>( C_{\text{max}} ) (mg/liter)</th>
<th>( t_{\text{max}} ) (h)(^b)</th>
<th>( C_{24} ) (mg/liter)</th>
<th>( \text{AUC}_{\text{0-24}} ) (mg • h/liter)</th>
<th>( \text{AUC}_{\text{0-24}} ) (mg • h/liter)</th>
<th>( C_{24} ) (mg/liter)</th>
<th>( \text{AUC}_{\text{0-24}} ) (mg • h/liter)</th>
<th>( t_{1/2z} ) (h)(^f)</th>
<th>( t_{1/2\alpha} ) (h)(^f)</th>
<th>( C_{24} ) (mg/liter)</th>
<th>( \text{AUC}_{\text{0-24}} ) (mg • h/liter)</th>
<th>( C_{24} ) (mg/liter)</th>
<th>( \text{AUC}_{\text{0-24}} ) (mg • h/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>0.0512 (46)</td>
<td>1.5 (1.0–4.0)</td>
<td>0.00076</td>
<td>0.277 (47)</td>
<td>0.277 (47)</td>
<td>0.0102 (46)</td>
<td>0.054 (47)</td>
<td>0.102 (46)</td>
<td>0.0045 (47)</td>
<td>0.0102 (46)</td>
<td>0.054 (47)</td>
<td>0.102 (46)</td>
<td>0.0045 (47)</td>
</tr>
<tr>
<td>800</td>
<td>0.1286 (23)</td>
<td>2.0 (1.0–4.0)</td>
<td>0.00546 (48)</td>
<td>0.974 (29)</td>
<td>0.983 (31)</td>
<td>0.1286 (23)</td>
<td>0.983 (31)</td>
<td>0.1286 (23)</td>
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<td>0.1286 (23)</td>
<td>0.983 (31)</td>
<td>0.1286 (23)</td>
<td>0.1286 (23)</td>
</tr>
<tr>
<td>1,600</td>
<td>0.238 (19)</td>
<td>3.0 (1.5–4.0)</td>
<td>0.0181 (50)</td>
<td>2.37 (24)</td>
<td>2.61 (28)</td>
<td>0.1190 (19)</td>
<td>1.306 (28)</td>
<td>0.01190 (19)</td>
<td>1.306 (28)</td>
<td>0.01190 (19)</td>
<td>1.306 (28)</td>
<td>0.01190 (19)</td>
<td>1.306 (28)</td>
</tr>
</tbody>
</table>

\(^a\) Values are means, with percent CV in parentheses, unless otherwise indicated. Statistical significance was determined by ANOVA and Tukey’s test. Elimination half-lives were calculated by compartmental analysis.

\(^b\) Values are medians with ranges in parentheses. \( P < 0.001. \)

\(^c\) For values at 800 and 1,600 mg, \( n = 17. \)

\(^d\) Significantly different from the values for the 400-mg dose \( (P < 0.05). \)

\(^e\) Significantly different from the values for the 800- and 1,600-mg doses \( (P < 0.01). \)

\(^f\) Significantly different from the values for other doses \( (P < 0.001). \)

\(^g\) Significantly different from the values for the 800- and 1,600-mg doses \( (P < 0.001). \)
percentage of telithromycin eliminated unchanged in the urine increased with dose with a magnitude similar to that of the AUC.

The moderate deviation from dose proportionality observed in this study may reflect a decrease in the metabolic clearance of the drug and a slight increase in the bioavailability of telithromycin with increasing dose. As the amount of telithromycin eliminated in the initial phase represents the major fraction, it may be assumed that the 30% increase in the t1/2C1 for a doubling of dose corresponds to a 30% decrease in plasma clearance. As CLR(0–24) was unchanged in this study, this suggests that nonrenal clearance (i.e., hepatic metabolic clearance) decreases with increasing dose.

RU 76363, the main circulating metabolite of telithromycin, is formed by hydrolysis of the aryl rings of the carbamate side chain of telithromycin; its AUC represents about 10 to 12% that of telithromycin. The decrease of telithromycin clearance cannot be attributed to a decrease in the formation of the RU 76363 metabolite, since the pharmacokinetics of this metabolite also deviated from dose proportionality in a manner similar to that observed for telithromycin. The dose proportionality of other circulating metabolites of telithromycin was not assessed since their AUC values represent only 1 to 2% of that of telithromycin (15).

In the present study, the Cmax and C24 values after 7 days of dosing with 800 mg telithromycin were 2.27 and 0.070 mg/liter, respectively. The telithromycin MICs at which 90% of the isolates are inhibited values for S. pneumoniae (including MLS-resistant strains) and Haemophilus influenzae are ≤0.06 and 2 mg/liter, respectively (1, 5). These data therefore suggest that telithromycin given at a daily dose of 800 mg will provide adequate plasma levels to maintain activity against respiratory pathogens, irrespective of macrolide susceptibility.

Telithromycin was generally well tolerated at all doses, though the incidence of adverse events tended to be higher at the 1,600-mg dose. These data, taken together with the pharmacokinetic profile of the compound, suggest that a once-daily 800-mg oral dose of telithromycin maintains an effective concentration in plasma and is suitable for evaluation in further pharmacokinetic and clinical trials for the treatment of community-acquired respiratory tract infections.

ACKNOWLEDGMENT

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REFERENCES


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**TABLE 4. Pharmacokinetics and dose proportionality of RU 76363 following 7 days of once-daily oral dosing with telithromycin**

<table>
<thead>
<tr>
<th>Dose</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mg/liter)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>C&lt;sub&gt;24&lt;/sub&gt; (mg/liter)</th>
<th>AUC&lt;sub&gt;0–24&lt;/sub&gt; (mg × h/liter)</th>
<th>AUC&lt;sub&gt;0–24&lt;/sub&gt;/dose (mg × h/liter)</th>
<th>t&lt;sub&gt;1/2C1&lt;/sub&gt; (h)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;/dose (mg × h/liter)</th>
<th>AUC&lt;sub&gt;0–24&lt;/sub&gt;/dose (mg × h/liter)</th>
<th>C&lt;sub&gt;24&lt;/sub&gt;/dose (mg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>0.0601 (33)</td>
<td>1.5 (1.0–6.0)</td>
<td>0.00328 (95)</td>
<td>0.430 (36)</td>
<td>0.430 (36)</td>
<td>3.70 (39)</td>
<td>0.1201 (33)</td>
<td>0.860 (36)</td>
<td>0.0137 (64)</td>
</tr>
<tr>
<td>800</td>
<td>0.1505 (26)</td>
<td>2.0 (1.0–4.0)</td>
<td>0.0137 (64)</td>
<td>1.48 (38)</td>
<td>1.60 (45)</td>
<td>4.67 (15)</td>
<td>0.1505 (26)</td>
<td>1.48 (38)</td>
<td>0.137 (64)</td>
</tr>
<tr>
<td>1,600</td>
<td>0.271 (19)</td>
<td>4.0 (1.5–6.0)</td>
<td>0.0415 (29)</td>
<td>3.38 (18)</td>
<td>4.04 (21)</td>
<td>6.06 (40)</td>
<td>0.1355 (19)</td>
<td>1.688 (19)</td>
<td>0.0208 (29)</td>
</tr>
</tbody>
</table>

Data are means, with percent CV in parentheses, unless otherwise noted. Statistical significance was determined by ANOVA and Tukey’s test. Elimination half-lives were calculated by compartmental analysis.

a Values are medians with ranges in parentheses. P < 0.01.

b Significantly different from the value for 1,600 mg (P < 0.05).
c Significantly different from the value for 800 mg (P < 0.01).
d c Significantly different from the values for the other doses (P < 0.001).

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**FIG. 2. Mean concentration-time curves for RU 76363 following oral administration of telithromycin at 400, 800, and 1,600 mg once daily to 18 healthy volunteers for 1 day (top) or 7 days (bottom). Error bars, ±SEM.**