Antibacterial activity of telithromycin (HMR 3647) in relation to 
in vitro simulated human plasma kinetics

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Telithromycin (HMR 3647) is a ketolide suitable for the treatment of respiratory infections. The aim of this study was to demonstrate its antibacterial efficacy against an erythromycin-susceptible Staphylococcus aureus, an erythromycin-resistant Streptococcus pneumoniae and Haemophilus influenzae. The free serum concentrations of telithromycin, produced by repeated oral administration of 800 mg to adults for 10 days, was simulated in an \textit{in vitro} system. The ketolide displayed bacteriostatic activity against all three strains tested. This study supported the observation that an 800 mg po dose of telithromycin demonstrated antibacterial efficacy against respiratory tract pathogens.

Introduction

Telithromycin (HMR 3647) is the first antibiotic belonging to a new class of 14-membered ring macrolides named ketolides. Telithromycin exhibits marked \textit{in vitro} activity against a large bacterial spectrum, including multidrug-resistant pneumococci, staphylococci, \textit{Haemophilus influenzae, Moraxella catarrhalis} and intracellular respiratory pathogens such as \textit{Chlamydia pneumoniae}.\textsuperscript{1}

Telithromycin is expected to be administered od, based on its increased pharmacodynamic efficiency and a favourable kinetic profile.\textsuperscript{2}

Kinetic models for evaluation of antibiotic activity permit the production of \textit{in vitro} drug levels of similar pharmacokinetics to those found \textit{in vivo} during therapy.\textsuperscript{3} The aim of this study was to explore the antibacterial efficacy of telithromycin modelled in an \textit{in vitro} system simulating the free serum concentrations produced by repeated administration of a po dose of 800 mg od to adults for 10 days.

Materials and methods

Antimicrobial agent and bacterial strains

Telithromycin was prepared at Hoechst-Marion-Roussel (Romainville, France).

The clinical isolates tested were an erythromycin-susceptible \textit{Staphylococcus aureus} (011UC4), an erythromycin-resistant \textit{Streptococcus pneumoniae} (030MV2) and a \textit{\beta}-lactamase-producing \textit{H. influenzae} (350RD7). The MICs of telithromycin for these organisms, as measured by a two-fold agar dilution method,\textsuperscript{4} were 0.04, 0.15 and 0.6 mg/L, respectively.

\textit{In vitro} kinetic model

The \textit{in vitro} model, designed to prevent dilution of the bacterial inoculum, has been described previously.\textsuperscript{5} The system consists of a reservoir containing brain–heart infusion (BHI, Diagnostic Pasteur, Marnes la Coquette, France), a second reservoir containing the antibiotic in BHI and a 2 L laboratory bioreactor (Applikon, Les Mureaux, France) that represents the peripheral compartment containing the bacteria in the test medium. BHI was supplemented with 4\% red cell extract (Diagnostic Pasteur), allowing the growth of \textit{S. pneumoniae} and \textit{H. influenzae}. Preliminary studies showed that the best growth in the bioreactor was obtained by preparing initial inocula as follows. The inoculum was an overnight culture [optical density at 600 nm (OD\textsubscript{600}) of c. 1], an exponential phase growth culture (OD\textsubscript{600} 0.3) or a bacterial suspension (OD\textsubscript{600} 1) in the case of \textit{S. aureus, S. pneumoniae} and \textit{H. influenzae}, respectively. The antibiotic was added after 1 h incubation. Samples (1 mL) were removed from the fermenter over a 6 h period at regular intervals for determination of both viable counts and antibiotic concentrations. Viability was determined by spiral plating on to Mueller–Hinton agar plates (Diagnostic Pasteur), supplemented according to the strain tested.\textsuperscript{4}

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with incubation overnight at 37°C, in a 5% CO₂ enriched atmosphere in the case of S. pneumoniae and H. influenzae. Carry-over of antibiotic was avoided by using adequate dilutions of samples. The lower limit of detection was 400 cfu/mL. Antibiotic concentrations were measured by microbiological assay with Bacillus subtilis ATCC 6633 spore suspensions as indicator strain in agar test Medium A (Merck, Nogent sur Marne, France). Each experiment was performed in duplicate.

The human pharmacokinetic profile has been simulated in accordance with data obtained in 12 volunteers having received telithromycin 800 mg po od for 10 days. Protein binding was estimated to be close to 70%. Only free concentrations were taken into account.

Results and discussion

Pharmacokinetic analysis

The validity of our in vitro infection model was established by measuring telithromycin concentrations at various times. After 10 days administration of 800 mg telithromycin po in healthy volunteers, previously reported maximal plasma concentration and the area under the concentration–time curve (AUC), expressed as total concentrations, were 1.84 ± 1.14 mg/L and 8.49 ± 2.59 mg·h/L, respectively. Protein binding being 70%, the free targeted peak and AUC were calculated as 0.55 ± 0.34 mg/L and 2.55 ± 0.78 mg·h/L, respectively. The Table shows that the experimental data were similar to the pharmacokinetic parameters observed, with a peak of 0.7 mg/L and AUC of 3 mg·h/L.

Antibacterial activity

The Figure summarizes the resultant killing curves. Against susceptible S. aureus, telithromycin led to a decrease in log₁₀ cfu/mL from 7.4 to 6.3 after 6 h, while the untreated inoculum reached 8.7. In the case of erythromycin-resistant S. pneumoniae, only a 0.5 log₁₀ decrease was observed. Against H. influenzae, telithromycin was clearly bacteriostatic, maintaining the inoculum at a level of 8.7 log₁₀ cfu/mL. In the same time, the untreated control increased from 8.3 to 9 log₁₀ cfu/mL.

Table. Pharmacokinetic analysis of telithromycin (free concentrations, represented as mean ± s.d.)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Telithromycin concentrations (mg/L)</th>
<th>Target (800 mg)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.05 ± 0.029</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>0.53 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.69 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>0.68 ± 0.091</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.66 ± 0.091</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>0.65 ± 0.064</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.56 ± 0.096</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.47 ± 0.059</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.39 ± 0.061</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.32 ± 0.039</td>
<td></td>
</tr>
</tbody>
</table>

Cₘₐₓ (mg/L) 0.71 ± 0.09 0.55 ± 0.34
Tₘₐₓ (range, h) 1–1.5 0.5–3.0
AUC (mg·h/L) 3.02 ± 0.39 2.55 ± 0.78

*aPharmacokinetic parameters observed in healthy volunteers. Cₘₐₓ, maximum mean plasma concentration; Tₘₐₓ, time corresponding to Cₘₐₓ.

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Telithromycin in an in vitro model

These results are in accordance with those usually obtained by classical time–kill assays at a constant MIC multiple concentration.8,9 Our data support the choice of 800 mg telithromycin po as an od dose, since this regimen retains plasma concentrations consistently higher than, or at least equal to, MICs, whatever the bacterium tested. These results are in agreement with those obtained in a murine thigh-infection model, in which it was reported that the AUC/MIC was the major determinant of in vivo activity for telithromycin, and that od dosing would be appropriate for this ketolide.10 However, in vivo conditions at the site of infection often being more unreliable than those in a controlled in vitro model, this dosing deserves confirmation in a clinical setting.

References


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