Tissue kinetics of telithromycin, the first ketolide antibacterial

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The potential efficacy of an antibacterial depends not only on its spectrum of activity but also on its concentration at the site of infection. The tissue kinetics of telithromycin—the first ketolide antibacterial—are reviewed here. Telithromycin accumulates rapidly in white blood cells, inflammatory fluid, and cells and tissues of the upper and lower respiratory tract, with mean concentrations above the MICs of key respiratory pathogens. Tissue kinetics of telithromycin support facilitated delivery to the site of infection, good efficacy against intracellular respiratory pathogens and respiratory pathogens at extracellular sites in the airways, and effectiveness in the treatment of upper and lower respiratory tract infections (RTIs). The tissue kinetics profile of telithromycin, together with its microbiological profile, makes it a promising new antibacterial for the treatment of community-acquired RTIs.

Keywords: antibacterial, ketolide, telithromycin, tissue kinetics

Introduction

Community-acquired respiratory tract infections (RTIs) are a common cause of morbidity and mortality and pose a significant burden on the healthcare system.1 Bacteria are an important cause of community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), sinusitis and tonsillitis/pharyngitis. The most common bacterial pathogens responsible for CAP, AECB and sinusitis are Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis, and Streptococcus pyogenes is the most common bacterial pathogen in tonsillitis/pharyngitis.2-6 Atypical pathogens such as Mycoplasma pneumoniae and intracellular pathogens such as Legionella pneumophila and Chlamydia pneumoniae also account for a notable proportion of RTIs.4,5,7

Antibacterial therapy of RTIs is usually empirical, either because of the nature of the disease or because of the difficulty in establishing the microbiological aetiology. Treatment is generally a course of a β-lactam or a macrolide.9 However, the effectiveness of this therapeutic approach is threatened by the increasing prevalence of resistance to these agents among common respiratory pathogens.6,10 As a result, there is a need for new antibacterials that retain activity against resistant organisms and have a low potential to select for resistance or induce cross-resistance to other antibacterial agents.11

Telithromycin—the first ketolide antibacterial to be developed for clinical use—has a targeted antibacterial spectrum of activity for community-acquired RTIs. In vitro studies have shown that telithromycin is active against common and atypical/intracellular respiratory tract pathogens, including pneumococcal strains resistant to β-lactams or macrolides12-17 (including those with very high erythromycin MICs).18 Importantly, telithromycin has a low potential to select for resistant strains and does not induce resistance to macrolide, lincosamide or group B streptogramin antibacterials.19,20 Telithromycin is well absorbed with Cmax (2.27 mg/L) reached within 1–3 h post-dose (800 mg once daily for 7 days), and has an elimination half-life of around 12 h allowing a convenient once-daily dosing regimen.21,22

Steady-state is reached within 2–3 days of treatment. Between 60% and 70% of telithromycin is bound to plasma protein (predominantly albumin). Telithromycin displays potent in vitro activity (including bactericidal activity against S. pneumoniae) and has a significant post-antibiotic effect (1.2–8.2 h) against major respiratory pathogens including S. pneumoniae, H. influenzae and M. catarrhalis, irrespective of their susceptibility to β-lactams or macrolides.15,22-26

In most RTIs, the bacteria are localized in the interstitial fluid of the infected tissue or multiply in alveolar macrophages (AM). Thus, the antibacterial concentration achieved at these sites is recognized as an important determinant of clinical efficacy and may vary with each drug.27 Tissue penetration studies have therefore, become an essential part of the assessment of the potential efficacy of new antibacterial agents. The disposition/penetration of telithromycin into target tissues, fluids and cells after single and repeated doses (at steady-state), and the implication of these data for the use of telithromycin in treating RTIs, are reviewed here. Preliminary studies assessed drug penetration into white blood cells (WBCs) and into interstitial fluid and were carried out following a single or repeated 600 mg dose, while further

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Table 1. Summary of clinical studies carried out to determine tissue distributions of telithromycin following oral administration

<table>
<thead>
<tr>
<th>Target tissue/fluid/cell</th>
<th>No. of subjects</th>
<th>Telithromycin dose regimen</th>
<th>Telithromycin quantification method</th>
<th>Limit of quantification</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>6</td>
<td>600 mg single dose</td>
<td>HPLC</td>
<td>0.46–1.30 mg/L</td>
<td>Pham Gia et al.28</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>600 mg once daily for 10 days</td>
<td>HPLC</td>
<td>0.23–1.36 mg/L</td>
<td>Sultan et al.29</td>
</tr>
<tr>
<td>Blisters</td>
<td>8</td>
<td>600 mg single dose</td>
<td>HPLC</td>
<td>0.03 mg/L</td>
<td>Khair et al.31</td>
</tr>
<tr>
<td>Pulmonary tissue/fluid</td>
<td>23</td>
<td>800 mg once daily for 5 days</td>
<td>validated agar diffusion assay</td>
<td>0.03 mg/L</td>
<td>Muller-Serieys et al.30</td>
</tr>
<tr>
<td>Pulmonary tissue/liquid</td>
<td>19</td>
<td>800 mg once daily for 5 days</td>
<td>validated agar diffusion assay</td>
<td>0.03 mg/L</td>
<td>Gehanno et al.32</td>
</tr>
<tr>
<td>Tonsillar tissue</td>
<td>20</td>
<td>800 mg once daily for 5 days</td>
<td>validated agar diffusion assay</td>
<td>0.025 mg/kg</td>
<td>Edlund et al.33</td>
</tr>
<tr>
<td>Saliva</td>
<td>10</td>
<td>800 mg once daily for 5 days</td>
<td>validated agar diffusion assay</td>
<td>0.025 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

HPLC, high-performance liquid chromatography.
*Alveolar macrophages and epithelial lining fluid.
**Alveolar macrophages, epithelial lining fluid and bronchial mucosa.

The tissue and fluid penetration studies were carried out at the recommended dose, 800 mg once daily for 5 days.

**Description of studies**

Each study was approved by the independent ethics committee of the relevant institution. Written informed consent was obtained from all patients and volunteers before the conduct of study-related procedures. The studies carried out to assess the penetration of telithromycin into target cells and interstitial fluids are briefly described below and summarized in Table 1.

Briefly, the pharmacokinetics of telithromycin in WBCs and plasma were assessed in healthy male volunteers who received either a single 600 mg oral dose of telithromycin or repeated once-daily oral doses of telithromycin 600 mg for 10 days.24 A cantharidin-induced skin blister model was used to assess telithromycin penetration into inflammatory exudate following administration of a single 600 mg oral dose of telithromycin to healthy male volunteers.20 Fibre-optic bronchoscopy together with bronchoalveolar lavage were used in two studies to investigate the penetration of telithromycin into bronchopulmonary tissues and fluids following administration of 800 mg once daily for 5 days.30,31 One of these studies recruited healthy volunteers who were non-smokers,20 whereas the second study recruited patients from a respiratory outpatient clinic who required diagnostic fibre-optic bronchoscopy.31 The majority of patients in the second study were suffering from inflammatory conditions including asthma, chronic bronchitis and persistent cough.31 The penetration of telithromycin into tonsillar tissue was investigated in patients undergoing bilateral tonsillectomy for chronic or recurrent tonsillitis (patients were excluded if they had had an episode of acute tonsillitis within the previous 2 weeks) or as part of a treatment for simple snoring (uvulo-palato-pharyngoplasty with tonsillectomy).32 Each patient received telithromycin (800 mg once daily for 5 days) before bilateral tonsillectomy (3, 12 or 24 h following administration of the fourth dose). Telithromycin levels in saliva were assessed following administration of 800 mg telithromycin once daily for 10 days in 10 healthy volunteers.33

In all studies, blood and tissue/fluid samples were collected at predefined time points following telithromycin administration, telithromycin concentrations were determined by HPLC or a validated agar diffusion method (Table 1), and pharmacokinetic parameters were determined. The collection of tissue/fluid samples at a single time-point in studies involving bronchoscopy or tonsillectomy precluded calculation of telithromycin AUC_{0-24} values; therefore, comparison of telithromycin tissue/fluid penetration versus plasma levels was based on ratios of mean concentrations at specified timepoints.

**Statistics**

Descriptive statistics were used for demographic and ordinal parameters. Effects of site samples and sampling time on telithromycin concentrations were assessed by analysis of variance after log transformation of the telithromycin concentrations. t-Tests were performed for pairwise comparisons of statistically significant effects.

**Results from the studies**

**White blood cells**

*Single-dose study.* Telithromycin concentrated rapidly in WBCs, achieving mean concentrations of 25.2 mg/L (range 10.58–49.35 mg/L) 1 h and 52.8 mg/L (range 39.26–73.29 mg/L) 6 h after dosing (Figure 1a). Levels declined thereafter, but were still quantifiable 48 h after a single dose. Telithromycin was quantifiable in plasma in all subjects 30 min after dosing [C_{\text{max}} of 0.90 mg/L (range 0.59–1.29 mg/L) at T_{\text{max}} of 1.50 h (range 1.00–3.00 h), but was no longer quantifiable in plasma in any subjects 48 h after dosing. The geometric mean WBC to plasma concentration ratio was 44 (25.2:0.61 mg/L) 1 h after a single dose of telithromycin and increased to 217 (52.8:0.257 mg/L) and 705 (10.2:0.015 mg/L) 6 and 24 h after dosing, respectively.

*Repeated-dose study.* Telithromycin was quantifiable in WBCs at all timepoints tested. The highest mean concentration of telithromycin in WBCs was 83 mg/L (range 64.6–124.3 mg/L), 2 h after dosing on Day 10 (Figure 1b). WBC concentrations of telithromycin remained high with a mean of 20.9 mg/L (range 17.2–25.4 mg/L) and 8.9 mg/L (range 3.7–17.5 mg/L) 24 and 48 h, respectively, after the last dose on Day 10.

As in the single-dose study, telithromycin was detectable in plasma 30 min after repeat dosing. The C_{\text{max}} was 0.98 mg/L (range 0.74–1.46 mg/L) and 1.31 mg/L (range 0.99–2.04 mg/L) at T_{\text{max}} of 1.25 h (range 1.00–3.00 h) and 1.50 h (range 0.50–2.00 h) on Days 1 and 10 of dosing, respectively. On Day 10 of dosing, the mean WBC to plasma concentration ratio was 101 (83:0.856 mg/L) at 2 h, increasing at each timepoint to 2201 (8.9:0.003 mg/L) at 48 h. The
Tissue kinetics of telithromycin

The ratio of geometric means of AUC$_{0-24}$ for WBCs to plasma was 241 (on Day 10).

These data indicate that telithromycin accumulates rapidly in WBCs, reaching levels 44-fold greater than in plasma 1 h after administration of a single dose. Moreover, telithromycin is retained within WBCs so that the concentration 48 h after repeated once-daily dosing (8.9 mg/L) exceeds the MIC$_{90}$ values for the majority of key respiratory pathogens (Table 2). As these experiments were pilot studies, the WBCs were not fractionated and therefore telithromycin levels in different WBC types were not determined. However, the high concentrations of telithromycin observed in these cells overall may facilitate delivery of telithromycin to the site of infection, and are supportive of good efficacy in treating infections involving intracellular respiratory pathogens such as *C. pneumoniae* and *L. pneumophila*.

Macrolide antibacterials also accumulate in WBCs, whereas the non-lipophilic β-lactams do not. In vitro and in vivo studies indicate relatively poor penetration of erythromycin into WBCs, whereas roxithromycin, clarithromycin and particularly azithromycin give high site-to-serum ratios. Azithromycin, a weak base, is thought to concentrate in the lysosomes of phagocytes and fibroblasts, with accumulation of the protonated drug leading to a slower efflux from the cells. The peak WBC-to-serum ratios observed for telithromycin are of the same magnitude as those for azithromycin. In contrast to azithromycin, however, which can be detected at levels of 18 mg/L in WBCs 10 days after administration of a single dose, telithromycin is rapidly cleared from WBC after treatment discontinuation, with a mean level of 2.93 mg/L 48 h after a single dose.

Inflammatory fluid

Although antibacterial sequestration into WBCs is important for efficacy against intracellular pathogens, many respiratory tract pathogens are located at extracellular sites within the airways. In particular, the concentration of an antibacterial in interstitial fluid is of importance when considering RTIs involving *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Telithromycin was quantifiable in blister fluid at the first time-point (2 h after dosing) in seven of the eight volunteers, and the mean maximum concentration in blister fluid, reached 6 h after dosing, was 0.373 mg/L (range 0.154–0.741 mg/L), compared with a mean plasma concentration of 0.261 mg/L (range 0.107–0.462 mg/L) at this timepoint. Concentrations of telithromycin plateaued up to 16 h after dosing and declined thereafter, but were still quantifiable in the blister fluid of all subjects 24 h after dosing (Figure 2). At this time, the mean concentration in blister fluid (0.08 mg/L, range 0.042–0.155 mg/L) remained seven-times higher than in plasma (0.012 mg/L, range 0.007–0.023 mg/L). The geometric mean of the AUC$_{0-24}$ ratio of telithromycin in blister fluid over plasma was 1.38, indicating that telithromycin was well distributed in blister fluid. The mean residence time (from 0 to 24 h) in blister fluid was more than twice that in plasma (11.06 h versus 4.85 h).

These results indicate that after a single 600 mg dose, telithromycin penetrates well into inflammatory extracellular fluid, with concentrations above the MIC$_{50}$ values for most key respiratory pathogens (Table 2). Macrolide antibacterials also penetrate well into inflammatory fluid. Clarithromycin and azithromycin exhibit significantly greater penetration than erythromycin. Blister fluid-to-plasma AUC ratios of 0.38–3.00 and 1.09 have been reported for...
azithromycin (single dose) and clarithromycin (multiple doses), respectively.49,50 The ratio of 1.38 for a single 600 mg dose of telithromycin therefore compares favourably with those of these compounds.

Bronchopulmonary tissues and fluids

Healthy volunteers. In the study involving healthy volunteers, four parallel groups underwent bronchoscopy and bronchoalveolar lavage 2, 8, 24 and 48 h, respectively, after administration of the last dose of telithromycin on Day 5.30 The mean concentration of telithromycin in AM was 65 mg/L (range 16–168 mg/L) 2 h after dosing, and peaked at 100 mg/L (range 56–166 mg/L) 8 h after the last dose. At the last timepoint (48 h), the telithromycin level in AM was 2.15 mg/L (range 0.7–11.7 mg/L) and declined smoothly thereafter. At the last timepoint (48 h), telithromycin was still quantifiable at a mean concentration of 0.30 mg/L (range 0.17–0.55 mg/L) (Figure 3a and b). Telithromycin levels in AM and ELF remained above the MIC90 values for key respiratory pathogens for up to 24 and 8 h, respectively.

Mean plasma levels of telithromycin reached 1.07 mg/L (range 0.53–1.85 mg/L) 2 h post-dose. However, the mean concentrations of telithromycin in AM and ELF were significantly higher than those in plasma at each timepoint (P < 0.05). Telithromycin concentrations also declined more slowly in AM and ELF than in plasma (Figure 3a and b). As a result, the AM- and ELF-to-plasma ratios increased over time. Two hours after dosing, mean telithromycin concentrations in AM and ELF were 55-fold and 4.8-fold higher, respectively, than the corresponding plasma concentrations.

Table 2. Minimum inhibitory concentrations (MICs) of telithromycin for key respiratory pathogens34–38

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>n</th>
<th>MIC50 (mg/L)</th>
<th>MIC90 (mg/L)</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin-susceptible</td>
<td>2142</td>
<td>0.008</td>
<td>0.03</td>
<td>0.002–0.5</td>
</tr>
<tr>
<td>Penicillin-intermediate</td>
<td>476</td>
<td>0.015</td>
<td>0.12</td>
<td>0.004–1.0</td>
</tr>
<tr>
<td>Penicillin-resistant*</td>
<td>744</td>
<td>0.06</td>
<td>0.5</td>
<td>0.004–8.0</td>
</tr>
<tr>
<td>Erythromycin-susceptible</td>
<td>2312</td>
<td>0.008</td>
<td>0.015</td>
<td>0.002–0.12</td>
</tr>
<tr>
<td>Erythromycin-resistant*</td>
<td>1043</td>
<td>0.06</td>
<td>0.5</td>
<td>0.008–8.0</td>
</tr>
<tr>
<td>erm(B)</td>
<td>586</td>
<td>0.03</td>
<td>0.5</td>
<td>0.008–8.0</td>
</tr>
<tr>
<td>mef(A)</td>
<td>368</td>
<td>0.12</td>
<td>0.25</td>
<td>0.008–1.0</td>
</tr>
<tr>
<td>erm(B) + mef(A)</td>
<td>71</td>
<td>0.5</td>
<td>0.5</td>
<td>0.06–1.0</td>
</tr>
<tr>
<td>Quinolone-resistant*</td>
<td>35</td>
<td>0.03</td>
<td>0.12</td>
<td>0.008–0.5</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>2948</td>
<td>1.0</td>
<td>2.0</td>
<td>≤0.002–8.0</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>1131</td>
<td>0.06</td>
<td>0.12</td>
<td>0.004–0.5</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>1485</td>
<td>0.015</td>
<td>0.015</td>
<td>0.004–64</td>
</tr>
<tr>
<td>Erythromycin-resistant*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erm(B)</td>
<td>44</td>
<td>8</td>
<td>32</td>
<td>0.008–32</td>
</tr>
<tr>
<td>mef(A)</td>
<td>66</td>
<td>0.25</td>
<td>0.5</td>
<td>0.008–0.5</td>
</tr>
<tr>
<td>erm(TR)</td>
<td>33</td>
<td>0.015</td>
<td>0.03</td>
<td>0.008–0.5</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>1547</td>
<td>0.06</td>
<td>64</td>
<td>0.015–264</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>19</td>
<td>0.0625</td>
<td>0.25</td>
<td>0.031–2.0</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td>26</td>
<td>0.008</td>
<td>0.015</td>
<td>≤0.004–0.015</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>47</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008–0.06</td>
</tr>
</tbody>
</table>

*Includes macrolide-resistant strains.

Figure 2. Mean telithromycin concentrations (mg/L) in blister fluid (filled circles) and plasma (open circles) after a single 600 mg dose in healthy volunteers. Limit of quantification for blister fluid 0.03 mg/L.

Table 2. Minimum inhibitory concentrations (MICs) of telithromycin for key respiratory pathogens34–38
Tissue kinetics of telithromycin

A second study assessed the penetration of telithromycin into AM, ELF and bronchial mucosa (BM) in patients requiring diagnostic fibre-optic bronchoscopy.31 Patients received telithromycin 800 mg once daily for 5 days and then underwent bronchoalveolar lavage and bronchial biopsy either 2, 12 or 24 h after the last dose of telithromycin. High telithromycin concentrations in AM (69.32 mg/L, range 21.7–125.7 mg/L), ELF (14.89 mg/L, range 5.2–36.5 mg/L) and BM (3.88 mg/kg, range 1.8–6.9 mg/kg) were achieved 2 h after the last dose (Figure 4a and b). Mean plasma concentrations of telithromycin reached 1.86 mg/L (range 0.88–3.73 mg/L) at this sampling time. However, mean telithromycin concentrations in AM, ELF and BM were 2159.6-fold, 14.4-fold and 12.1-fold higher, respectively, than those in plasma 24 h after the last dose (Figure 4a and b), and concentrations of telithromycin in AM and ELF were above the MIC90 values for most key respiratory pathogens for 24 and 12 h after dosing, respectively.

Patients undergoing bronchoscopy for diagnostic purposes

These findings show that telithromycin penetrated well into all potential sites of lower RTI following a repeated oral dose of 800 mg in patients undergoing bronchoscopy. Telithromycin concentrations in ELF 2 h post-dose showed a trend towards higher values in patients compared with healthy volunteers. Overall, however, ELF and AM concentrations in patients and healthy volunteers did not differ markedly between 2 and 24 h. It is expected that telithromycin would penetrate equally well in patients with RTIs and be effective in the treatment of lower RTIs, such as CAP and AECB. Furthermore, the high concentrations of telithromycin attained in AM, and their slow decline over 48 h, indicate that this agent will be of value in treating facultative or obligate intracellular pathogens, such as Legionella and Chlamydia spp., making it a good candidate for therapy of ‘atypical’ pneumonia. ELF represents a major site of infection in pneumonia caused by extracellular pathogens.31 The telithromycin concentration in ELF was sustained above the MIC90 values of key respiratory pathogens for between 8 and 12 h after the last dose. These data are again supportive of good efficacy in the treatment of CAP.

Macrolide antibacterials have also been shown to penetrate and accumulate in tissues, cells and fluids of the lower respiratory tract,51,52 whereas β-lactam antibacterial penetration is poor, with concentrations reaching only 20–40% of those achieved in plasma.53 Site-to-serum ratios at 24 and 48 h indicate that telithromycin penetration into lung tissue is far superior to that of erythromycin and comparable to that of clarithromycin.54,55 Although site-to-serum ratios of telithromycin are somewhat lower than those of azithromycin (determined in patients undergoing bronchoscopy for diagnostic purposes),56 this is because azithromycin achieves very low serum concentrations: the peak concentrations of telithromycin achieved in AM and ELF were in fact higher than those of azithromycin in this study. Whereas peak azithromycin concentrations in AM and ELF were achieved more than 48 h after dose administration, maximum levels of telithromycin in AM and ELF were achieved by 12 and 2 h post-dose, respectively. Telithromycin was also more rapidly cleared from AM following treatment discontinuation (levels had begun declining by 24 h), whereas high levels of azithromycin persisted in AM up to 96 h after the final dose.56

Tonsillar tissue and saliva

Of the Group A β-haemolytic streptococci (GABHS), S. pyogenes is the primary bacterial cause of tonsillitis/pharyngitis. Penicillin is the current antibacterial of choice, although macrolides are prescribed to
patients who are intolerant of β-lactams. However, macrolide-resistant strains of GABHS are becoming prevalent in some countries.57

Telithromycin rapidly penetrated tonsillar tissue, achieving a mean concentration in tonsillar homogenates of 3.95 mg/kg (range 3.37–4.60 mg/kg) within 3 h of dosing (Figure 5). This was 3.38-times greater than the corresponding plasma concentration. Telithromycin was also eliminated more slowly from tonsils than plasma. This was reflected in the tonsil-to-plasma concentration ratio, which increased to 7.1 and 13.1 at 12 and 24 h after dosing, respectively. Telithromycin levels in both tonsils and plasma were maintained above the MIC90 for GABHS (0.015 mg/L) at all timepoints examined throughout the 24 h dosing period (Figure 5; Table 2). Indeed, up to 24 h, the average tonsillar concentrations of telithromycin (0.72 mg/kg) were 48-fold higher than the MIC90 of GABHS. The sustained high concentrations of telithromycin in tonsillar tissue suggest that this antibacterial agent will be effective in the treatment of GABHS tonsillitis/pharyngitis. It should be noted that the study design precluded assessment of telithromycin concentrations based on degree of tonsillar inflammation, therefore these results are only suggestive of the levels that may be achieved in patients with tonsillitis/pharyngitis.

Although tonsillar concentrations of β-lactams, such as penicillin V, amoxicillin, cefprozil and cefuroxime, exceed their MIC90 for GABHS, the tonsil-to-plasma ratios of these antibacterials are lower than those of telithromycin, reflecting the relatively poor tissue penetration of β-lactams.58–60 It should, however, be noted that tissue homogenate methodologies used in the studies assessing the tissue penetration of β-lactam antibacterials may underestimate levels of non-lipophilic β-lactams in extracellular fluid,61 where many of the bacteria causing RTIs are localized. In addition, the tonsillar penetration of telithromycin compares favourably to that of the macrolides erythromycin and dirithromycin.62–64 Although azithromycin

<table>
<thead>
<tr>
<th>Time after dosing:</th>
<th>AM (2h)</th>
<th>AM (12h)</th>
<th>AM (24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean concentration</td>
<td>69.32</td>
<td>318.10</td>
<td>161.57</td>
</tr>
<tr>
<td>Range</td>
<td>21.7–125.7</td>
<td>36.8–569.9</td>
<td>25.4–292.7</td>
</tr>
<tr>
<td>Mean plasma concentration</td>
<td>1.86</td>
<td>0.23</td>
<td>0.08</td>
</tr>
<tr>
<td>Range</td>
<td>0.88–3.73</td>
<td>0.18–0.28</td>
<td>0.046–0.11</td>
</tr>
<tr>
<td>Tissue to plasma ratio</td>
<td>40.9</td>
<td>1203.7</td>
<td>2159.6</td>
</tr>
</tbody>
</table>

Figure 4. Mean concentrations of telithromycin (mg/L or mg/kg) in (a) plasma (black bars) versus alveolar macrophages (AM, hatched bars) and (b) plasma (black bars) versus epithelial lining fluid (ELF, hatched bars) and bronchial mucosa (BM, white bars) following 5 days oral administration of 800 mg once daily in patients requiring bronchoscopy.
and clarithromycin achieve higher tonsillar concentrations than telithromycin, their concentrations do not exceed their MIC values for any macrolide-resistant strains of GABHS at any point during the dosing period. Telithromycin concentrations however peaked at levels in excess of the MIC90 values for macrolide-resistant [mef(A)]- or erm(TR)-positive] GABHS.

It should also be noted that all studies of drug penetration in tonsillar tissue used homogenized tissue for analysis, thus preventing the differentiation of intracellular and extracellular drug concentrations in study samples. Therefore, data may not accurately reflect the actual concentration of drug to which the pathogen is exposed in the tissue.

In a further study involving 10 healthy subjects who received telithromycin 800 mg once daily for 10 days, telithromycin achieved high concentrations in saliva (Cmax 3.06 mg/L, range 1.47–5.17). These concentrations were on average higher than those in plasma (2.03 mg/L, range 1.01–3.56 mg/L). The geometric mean of the AUC0–24 saliva/AUC0–24 plasma ratio was 1.6 at steady-state. The salivary concentrations of telithromycin exceeded its MIC90 for GABHS for up to 24 h after dosing, further supporting the use of this antibacterial agent in the treatment of tonsillitis/pharyngitis.

Conclusions

Studies in recent years have suggested a correlation between antibacterial concentration at the site of infection and clinical efficacy. Therefore, in RTIs, antibacterial penetration into respiratory tissues and fluids is an important determinant of clinical outcome. Telithromycin shows excellent penetration into WBCs, indicating effective delivery to sites of infection and potential efficacy against intracellular respiratory pathogens. Good extracellular tissue penetration of telithromycin is predicted from the levels reached in inflammatory blister fluid following a single 600 mg dose and is confirmed in disposition studies in bronchopulmonary tissues and fluids following multiple dosing at the recommended dose of 800 mg once daily. The concentrations of telithromycin in respiratory tissues and fluids suggest that it will offer an effective treatment for lower RTIs caused by common (including resistant) and atypical/intracellular pathogens. Telithromycin also rapidly achieves high concentrations in tonsillar tissue and is maintained at levels above its MIC90 for GABHS throughout the 24 h dosing period. The concentration of telithromycin in both tonsils and saliva indicates good therapeutic potential for GABHS tonsillitis/pharyngitis.

The distribution, penetration and retention profile of telithromycin in lung and tonsillar tissues suggest that it can be taken reliably in a convenient once-daily dosing regimen. Importantly, this has the potential to improve patient adherence to antibacterial therapy and reduce the likelihood of development of resistance resulting from missed doses. Similarly, achieving high and maintained concentrations of telithromycin in respiratory tissues above the MICs of key pathogens may facilitate eradication of the infecting organism and prevent the selection and emergence of resistance. Telithromycin has a well-balanced intracellular/extracellular concentration ratio that results in bactericidal quantities necessary to eliminate the extracellular as well as the intracellular organisms. The tissue penetration of telithromycin is superior to that of β-lactams and compares very favourably to that of macrolides. Telithromycin also reaches high concentrations in plasma (Cmax up to 2.03 mg/L). This has important implications for the successful treatment of RTIs accompanied by bacteriaemia and thus associated with a greater risk of mortality.

Pharmacokinetic–pharmacodynamic modelling suggests that the parameter predictive of clinical outcome for β-lactams, erythromycin and clarithromycin—which display time-dependent activity—is the time above the MIC, whereas the parameter predictive of efficacy for fluoroquinolones, aminoglycosides and telithromycin—which display concentration-dependent activity—is the AUC or Cmax to MIC ratio. The high and sustained levels of telithromycin in WBCs and respiratory tissues and fluids, together with its MIC values for key respiratory pathogens, should ensure adequate efficacy at the site of infection.

In summary, telithromycin achieves high concentrations in respiratory and inflammatory tissues and fluids that are maintained throughout the dosing period. Together with its excellent microbiological profile against common and atypical/intracellular pathogens—including resistant strains—and low potential to induce resistance, this makes telithromycin a promising new antibacterial for the treatment of community-acquired RTIs of the upper and lower respiratory tract.

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References


Tissue kinetics of telithromycin

47. Amsden, G. W. & Gray, C. L. (2001). Serum and WBC pharmacokinetics of 1500 mg of azithromycin when given either as a single dose or over a 3 day period in healthy volunteers. *Journal of Antimicrobial Chemotherapy* 47, 61–6.


