In vitro activity of telithromycin, a new ketolide, against Chlamydia pneumoniae

Naoyuki Miyashita*, Hiroshi Fukano, Yoshihito Niki and Toshiharu Matsushima

Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki City, Okayama 701-0192, Japan

The in vitro activity of telithromycin, a new ketolide, was compared with those of roxithromycin, azithromycin, clarithromycin and erythromycin A against 20 strains of Chlamydia pneumoniae. The MICs and minimal chlamydiacidal concentrations of telithromycin for the 20 C. pneumoniae strains both ranged between 0.031 and 0.25 mg/L. Telithromycin was twice as active as roxithromycin, azithromycin and erythromycin A, but less active than clarithromycin. These results appear to indicate that telithromycin is an effective antibiotic that should play some role in the treatment of respiratory tract infections caused by C. pneumoniae.

Materials and methods

Antimicrobial agents

The antimicrobial agents tested were telithromycin and roxithromycin (Hoechst-Marion-Roussel Ltd, Tokyo, Japan), erythromycin A (Shionogi Co., Osaka, Japan), clarithromycin (Taisho Pharmaceutical Co., Osaka, Japan) and azithromycin (Pfizer Pharmaceutical Co., Tokyo, Japan). Solutions of the agents were prepared following the manufacturer’s instructions.

Chlamydial strains

Twenty C. pneumoniae strains were used in this study. TW-183, AR-39 and AR-388 were obtained from the Washington Research Foundation, Seattle, WA, USA. IOL-207 and Kajaani-6 were acquired from P. Saikku, National Public Health Institute, Oulu, Finland. Fifteen wild-type strains (designated KKpn-1–15), which were isolated from nasopharyngeal swab specimens collected from patients with acute respiratory tract infections at Kawasaki Medical School Hospital, Japan, were also tested. The clinical isolates were positively stained with C. pneumoniae-specific monoclonal antibody. These clinical isolates were morphologically different from TWAR (TW-183, AR-39 and AR-388) strains from the USA.

Measurement of MICs and minimal chlamydiacidal concentrations (MCCs)

One millilitre of culture medium [Eagle’s minimal essential medium (Nissui Pharmaceuticals Co., Tokyo, Japan) and 10% heat-inactivated fetal calf serum (Gibco-BRL Life Technologies Inc., Grand Island, NY, USA)] containing...
10⁵ HEp-2 cells/mL were dispensed into each well of plastic 24-well culture plates, which were then incubated in 5% CO₂ at 35°C for 48 h. After confirming growth of a confluent monolayer, the culture fluid was removed from the wells by aspiration. Next, 10⁴ inclusion-forming units/mL of each chlamydial strain were inoculated into each well. Then plates were centrifuged at 900 g for 60 min, and 1 mL of each preparation of the culture medium containing 1 mg/L of cycloheximide (Nakarai Tesque Inc., Tokyo, Japan) and one concentration (final concentrations range from 0.008 to 2 mg/L) of the test antibiotic was dispensed into each well. After incubation in 5% CO₂ at 35°C for 72 h, the cultures were fixed and stained for inclusions with the fluorescein isothiocyanate-conjugated monoclonal antibody to the chlamydial genus-specific antigen (Chlamydia FA Seiken; Denka Seiken, Tokyo, Japan). The MIC was defined as the lowest concentration at which no inclusions were found. The MCCs were determined by aspirating the antibiotic-containing medium, washing the wells twice with phosphate-buffered saline, and adding antibiotic-free medium. The infected cells were frozen at –70°C, thawed, passed onto new cells, incubated for 72 h, and then fixed and stained as described above. The MCC was the lowest antibiotic concentration which resulted in no inclusions after passage. All tests were run in triplicate.

Results

The MIC and MCC ranges of telithromycin and the other four macrolides for *C. pneumoniae* used in this study are shown in the Table. The MICs and MCCs of telithromycin for the 20 *C. pneumoniae* strains both ranged between 0.031 and 0.25 mg/L. Telithromycin was twice as active as roxithromycin, azithromycin and erythromycin A, but less active than clarithromycin (range from 0.016 to 0.063 mg/L).

Discussion

*C. pneumoniae* is well recognized as a respiratory pathogen, causing upper and lower respiratory tract infections and pneumonia. Macrolides have been demonstrated to be active *in vitro* against *C. pneumoniae*. Clinical studies on erythromycin A and clarithromycin, in which cultures were performed, demonstrated that these macrolides are effective drugs for the treatment of respiratory infection associated with *C. pneumoniae*. We have previously reported on the experimental and clinical effectiveness of macrolides against acute chlamydial respiratory tract infections. The therapeutic effect of a 7 day course of clarithromycin at doses of 5 and 10 mg/kg of body weight administered orally bd and of azithromycin at a dose of 10 mg/kg of body weight administered orally od to mice with experimental *Chlamydia psittaci* pneumonia was excellent, with a 100% survival rate at 14 or 21 days after infection. This finding was the same as that for treatment with minocycline administered at 10 mg/kg bd. These results with excellent *in vivo* activities were also observed following treatment with roxithromycin (N. Miyashita & Y. Niki, unpublished data). We also studied the clinical efficacy of roxithromycin in 14 patients with chlamydial respiratory infection. Roxithromycin was administered orally to these 14 patients (seven with *C. pneumoniae* infection) at a dosage of 300 mg daily for 3–21 days. The clinical efficacy was excellent (92.9% efficacy rate).

In our study, telithromycin showed good *in vitro* anti-*C. pneumoniae* activity higher than that of roxithromycin, azithromycin and erythromycin A. Roblin & Hammarschlag found the MIC₅₀ and MIC₉₀ of telithromycin against 19 isolates of *C. pneumoniae*, including a reference strain, TW-183, to be 0.0625 and 0.25 mg/L, respectively. Subsequently, the same group reported the same results in a different study. Our results were almost consistent with former reports although the type of *C. pneumoniae* isolates differed. Our MCC results were consistent with those of Roblin et al., but not with those of Gustafsson et al., who found MCC values to be almost 100 times higher than the MIC values. This may be because of a difference in the technique used for passage (not freezing) and a pre-incubation time of 2 h in their study. This technique may reflect a situation more similar to what occurs *in vivo*. Based on the above and previous reports of the potent and broad antibacterial activity of telithromycin, we can conclude that

<table>
<thead>
<tr>
<th>Agent</th>
<th>MIC (mg/L)</th>
<th>MCC (mg/L)</th>
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</thead>
<tbody>
<tr>
<td>Telithromycin</td>
<td>0.031–0.25</td>
<td>0.063</td>
</tr>
<tr>
<td>Erythromycin A</td>
<td>0.063–0.25</td>
<td>0.125</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>0.063–0.25</td>
<td>0.125</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.125–0.5</td>
<td>0.125</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.016–0.063</td>
<td>0.31</td>
</tr>
</tbody>
</table>

In the Table, *in vitro* activities of telithromycin and other macrolides against 20 strains of *C. pneumoniae* are shown.
telithromycin could be a useful oral agent for the acute treatment of respiratory tract infections. Prospective studies of telithromycin for the treatment of community-acquired pneumonia should be able to determine the role of this drug in the treatment of such infections.

References


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