Introduction

Dirithromycin is a macrolide antibiotic which is metabolized to an active compound, erythromycinyclamine.\(^1\) Dirithromycin, in an oral formulation, was recently approved by the United States Food and Drug Administration for use in community-acquired pneumonia caused by pneumococci, \textit{Mycoplasma pneumoniae} and \textit{Legionella pneumophila}.\(^2\) Chlamydia pneumoniae is also a frequent cause of community-acquired respiratory tract infection including pneumonia and bronchitis in adults and children.\(^3,4\) Therefore, we evaluated the in-vitro activity of dirithromycin, erythromycinyclamine and erythromycin against 12 isolates of \textit{C. pneumoniae}.

Materials and methods

Antimicrobial agents

Dirithromycin, erythromycinyclamine and erythromycin were provided as powders by Lilly Pharmaceuticals (Indianapolis, IN, USA). The drugs were solubilized by suspending them in 10 mL of distilled water with 0.5 mL 95% ethanol and 30 \(\mu\)L of 1 M NaOH. The drugs were prepared as stock dilutions in concentrations of 1280 mg/L according to their stated potencies. Stock solutions were frozen at \(-70^\circ\)C and were serially diluted in Dulbecco’s minimal essential medium to the appropriate concentrations on the day of use.

Chlamydia strains

The 12 \textit{C. pneumoniae} isolates tested included TW 183 (Washington Research Foundation, Seattle, WA, USA); nine clinical isolates from Brooklyn: T2023 (ATCC VR-1356), T2043 (ATCC VR-1355), T2337, BAL 14, BAL 15, BAL 16, BAL 37, BAL 48, and BAL 62; one isolate from Wisconsin: W6805; and one isolate from Atlanta: CDC/CWL-029 (ATCC VR-1310).

Sensitivity testing

Susceptibility testing of \textit{C. pneumoniae} was performed in tissue culture using HEp-2 cells grown in 96-well microtitre plates.\(^5\) Each well was inoculated with 0.1 mL of the test strain diluted to yield \(10^2\)–\(10^4\) inclusion-forming units (IFU) per mL, centrifuged at 1700g for 1 h and then overlaid with 0.1 mL of each drug dilution. After 72 h, cultures were fixed and stained for inclusions with fluorescein-conjugated antibody to the LPS genus antigen (Pathfinder, Kallestad Diagnostics, Chaska, MN, USA). The MIC was taken as the lowest antibiotic concentration at which no inclusions were seen. The minimal chlamydiodical concentration (MCC) was determined by aspirating the antibiotic-containing medium, washing wells twice with phosphate-buffered saline and overlaying them with antibiotic-free medium, freezing the cultures at \(-70^\circ\)C and then thawing them, passing the disrupted cell monolayers on to new cells, incubating them for 72 h,
then fixing and staining as described above. The MCC was taken as the lowest antibiotic concentration which resulted in no inclusions after passage. All tests were run in triplicate.

Synergy was determined by a chequerboard method and was defined as a fractional inhibitory index of \(0.5\). Antagonism was defined as a fractional inhibitory concentration index of \(2.0\).

Results

As shown in the Table, erythromycin was the most active agent tested, with an MIC\(_{90}\) of 0.062 mg/L. Both dirithromycin and erythromycyclamine had MIC\(_{90}\) values of 2 mg/L and MCC\(_{90}\) values of 1 mg/L. The apparent one dilution lower MCC is within the standard error of this test. The fractional inhibitory concentration index for dirithromycin plus erythromycyclamine was 1 for all 12 C. pneumoniae strains tested.

Discussion

C. pneumoniae may be isolated from 10–20% of children and adults with community-acquired pneumonia and bronchitis and from 11% of children presenting with acute exacerbations of asthma.\(^3,4,6\) Few published data exist for describing the clinical response to C. pneumoniae infection, or the efficacy of any treatment for eliminating the organism from the respiratory tract. The results of the only published treatment study where cultures were performed found that erythromycin and clarithromycin were equivalent in eradicating C. pneumoniae from the respiratory tract of children with community-acquired pneumonia.\(^4\)

Dirithromycin has a spectrum and degree of in-vitro antimicrobial activity against most bacteria and M. pneumoniae similar to that of erythromycin.\(^1,7\) The activity against C. pneumoniae was similar to that reported by Segreti & Kapell for Chlamydia trachomatis,\(^8\) which also had an MIC\(_{90}\) of 2.0 mg/L. These authors found that the combination of dirithromycin and erythromycyclamine was additive against C. trachomatis.

Compared with erythromycin, dirithromycin has a long elimination half-life enabling once-daily administration.\(^3\) It is also highly concentrated in some tissues including nasal mucosa, tonsil tissue and bronchial secretions.\(^1\) These properties would suggest that dirithromycin may have a role in the treatment of respiratory infections caused by C. pneumoniae even though its activity in vitro was 32-fold less than that of erythromycin. None of the published controlled trials comparing dirithromycin with erythromycin and other macrolides have involved cultures of C. pneumoniae, thus microbiological efficacy could not be assessed.\(^9,11\) Clinically, these studies detected no significant differences between dirithromycin and the other drugs. The in-vitro activity may not always predict microbiological efficacy in vivo. Even though clarithromycin is 10- to 100-fold more active than erythromycin against C. pneumoniae in vitro,\(^5\) it may not be more effective in terms of eradicating the organism from the respiratory tract. Block et al.\(^4\) reported that erythromycin and clarithromycin eliminated C. pneumoniae from the nasopharynx of 86% and 79% of children with radiologically documented pneumonia, respectively. Determination of the role of dirithromycin for the treatment of C. pneumoniae infection will depend on the results of prospective, controlled studies utilizing culture.

Acknowledgement

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References


<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC (mg/L)</th>
<th>MCC (mg/L)</th>
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<tbody>
<tr>
<td></td>
<td>range 50%</td>
<td>90% range 90%</td>
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<tr>
<td>Erythromycin</td>
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<td>0.062</td>
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<tr>
<td>Dirithromycin</td>
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<td>1</td>
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<tr>
<td>Erythromycyclamine</td>
<td>0.5–4</td>
<td>1</td>
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</tbody>
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Table. Susceptibilities of 12 isolates of C. pneumoniae to erythromycin, dirithromycin and erythromycyclamine
Activity of dirithromycin against *C. pneumoniae*


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