In vitro activity of a novel ketolide ABT-773 against invasive strains of Streptococcus pneumoniae


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New ketolides such as ABT-773 are a promising group of antibiotics in an era of increasing antibiotic resistance. We tested 704 invasive strains of Streptococcus pneumoniae collected from 1990 to 1998. Overall resistance was 8.3, 4.6, 4.5 and 3.6% for penicillin, cefuroxime, erythromycin and clarithromycin, respectively. By using a recommended breakpoint for susceptibility of <0.5 mg/L, no strains showed reduced susceptibility to ABT-773. ABT-773 was very active against all penicillin-resistant strains (MIC > 2 mg/L, with a mean geometric mean <0.06 mg/L), and against all 33 erythromycin-resistant strains, irrespective of the mode of resistance [mef- or erm(B)-mediated]. ABT-773 is a very active and promising agent against invasive strains of S. pneumoniae, including multiresistant strains.

Introduction

Increasing resistance of Streptococcus pneumoniae to penicillins, cephalosporins, quinolones and macrolides constitutes a growing challenge. Bacteraemia caused by S. pneumoniae remain a major cause of morbidity and mortality, particularly in the elderly. The worldwide prevalence of macrolide resistance varies considerably, being high in Japan, Italy (42%) and France (47.3%), intermediate in the USA (23.3%) and UK (18.4%), and lower in Canada (12%). New ketolides are a promising group of antibiotics against penicillin- and macrolide-resistant strains of S. pneumoniae. Macrolide resistance in S. pneumoniae occurs either by target modification through erm genes, which encode 23S rRNA methylases, and which is associated with a high-level resistance, or through an efflux pump encoded by the mef(E) gene. Recently, insertions in the L4 ribosomal protein of a Canadian S. pneumoniae isolate were found to be associated with reduced susceptibility to the ketolide telithromycin. The objective of this study was to evaluate the in vitro activity of the new ketolide ABT-773 against invasive strains of S. pneumoniae.

Materials and methods

Strains

From 1990 to 1998, all strains of S. pneumoniae isolated from sterile sites (blood, CSF, pleural or articular fluids) were stored and frozen at −70°C. Three large teaching tertiary care hospitals (two adult: Hôpital Maisonneuve-Rosemont, Montreal, and Hôpital de l’Enfant-Jesus, Quebec City; and one paediatric: The Montreal Children’s Hospital, Montreal) participated in the study. A total of 704 single clinical isolates of S. pneumoniae were included in this survey (634 blood, 51 CSF, 19 other). Patients comprised 390 males (55.3%) and 314 females (44.7%) with an age range of 0.1–102 years and a median age of 33.2 years.

Strains were identified using standard procedures: Gram’s stain, optochin susceptibility test and bile solubility test.

Antibiotics and susceptibility testing

Penicillin, cefuroxime and erythromycin were purchased from Nucrotechnics (Scarborough, Ontario, Canada). Clarithromycin and ABT-773 were provided by Abbott

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Canada (Montreal, Quebec, Canada). The isolates were tested against the following antibiotics at the following concentrations (mg/L): penicillin, 0.03–4; cefuroxime, 0.06–8; erythromycin, 0.06–8; clarithromycin, 0.06–8; and ABT-773, 0.06–8.

MICs were determined using a broth microdilution method according to NCCLS recommendations. A 0.5 McFarland equivalent suspension was prepared from an overnight sheep blood agar culture of *S. pneumoniae*. This solution was then diluted 1:10 to yield $10^7$ cfu/mL. Five microlitres of this suspension was added to a cation-adjusted Mueller–Hinton supplemented with 5% lysed horse blood in order to reach a final concentration of $5 \times 10^4$ cfu/well. Trays were incubated at 35°C for 24 h in ambient air. The lowest concentration of antibiotic showing no growth was recorded as the MIC. Quality control was assessed by testing *S. pneumoniae* ATCC 49619.

For ABT-773, a recommended breakpoint for susceptibility of $\leq 0.5$ mg/L was used.5

**Determination of macrolide-resistance mechanisms**

The macrolide-resistance mechanism was determined for 28 erythromycin-resistant *S. pneumonia* strains by PCR using specific primers as described previously.6

**Results and discussion**

High levels of *in vitro* resistance to $\beta$-lactams and macrolides in *S. pneumoniae* have been reported throughout the world. However, in many instances the differences in resistance patterns between invasive strains, considered to be always clinically significant, and non-invasive strains have not been clearly established. Some published data indicate that resistance is higher among non-invasive strains, notably those isolated from the respiratory tract or eye specimens.2 In our study, 8.3% of the strains were resistant to penicillin, 4.7% to cefuroxime, 4.5% to erythromycin, 3.6% to clarithromycin and none to ABT-773 (Table 1). There were no significant differences between paediatric and adult isolates. Although still low, there was an important increase in the level of resistance to all antibiotics except ABT-773 when comparing the 1990–1994 and 1995–1998 periods. ABT-773 was found to be highly active against all macrolide-resistant strains irrespective of the mode of resistance [erm(B) or mef]. Among the erythromycin-resistant stains, 18 were characterized as erm(B) positive and 10 as mef positive. ABT-773 was also very active against all penicillin non-susceptible (PNSP) strains, with a geometric mean MIC $< 0.06$ mg/L (Table 2). For ABT-773, the highest recorded MIC was 0.125 mg/L (Table 2). The two strains with an MIC of 0.125 mg/L were both harbouring the mef determinant. Only 22% (13/59) of PNSP were also resistant to erythromycin. All the penicillin-resistant strains were also resistant to cefuroxime; however, none showed reduced susceptibility to erythromycin. ABT-773 has been shown to be very active against other respiratory pathogens such as *Haemophilus influenzae* and *Moraxella catarrhalis*.7 It also has excellent activity against intracellular *Legionella* spp., and against *Chlamydia pneumoniae*.8 Experimental data have demonstrated that it binds to ribosomes isolated from either susceptible or resistant *S. pneumoniae* 10- to 100-fold more strongly than erythromycin.9 In this study, ABT-773 showed excellent *in vitro* activity against a large number of clinically significant *S. pneumoniae* strains, irrespective of their resistance patterns. Preliminary data have shown ABT-773 to be bactericidal for *S. pneumoniae in vitro*, making it a promising new agent against *S. pneumoniae* infections.10 In addition, a plasma $C_{\text{max}}$ of 0.6 mg/L has been reported after a single 400 mg oral dose, which is four times the highest MIC recorded in this study. This compound may become an option for invasive *S. pneumoniae* infections in adults and children, and may represent an interesting alternative to the newer quinolones which are targeted towards treatment of Gram-positive infections.

**Table 1.** Prevalence of antimicrobial resistance in invasive *S. pneumoniae* from 1990 to 1998

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Penicillin (I and R)$^a$</td>
<td>6.8</td>
<td>9.7</td>
<td>8.3</td>
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<tr>
<td>Erythromycin</td>
<td>1.2</td>
<td>7.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.9</td>
<td>6.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>3</td>
<td>6.1</td>
<td>4.7</td>
</tr>
<tr>
<td>ABT-773$^b$</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$I, intermediate (MIC 0.1–1 mg/L); R, high-level resistance (MIC $> 2$ mg/L).

$^b$Using tentative breakpoints.3
Activity of ABT-773 against S. pneumoniae

Table 2. MIC<sub>50</sub> and MIC<sub>90</sub> (mg/L) of different antibiotics against 704 invasive strains of S. pneumoniae

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Penicillin sensitive (645)</th>
<th>Penicillin intermediate (31)</th>
<th>Penicillin resistant (28)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>&lt;0.06</td>
<td>&lt;0.06</td>
<td>0.5</td>
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<tr>
<td>Erythromycin</td>
<td>&lt;0.06</td>
<td>&lt;0.06</td>
<td>&lt;0.06</td>
<td>8</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&lt;0.06</td>
<td>&lt;0.06</td>
<td>&lt;0.06</td>
<td>4</td>
</tr>
<tr>
<td>ABT-773</td>
<td>&lt;0.06</td>
<td>&lt;0.06</td>
<td>&lt;0.06</td>
<td>&lt;0.06</td>
</tr>
</tbody>
</table>

Acknowledgement

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References


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