ABT-773 is Unlikely to Have a Clinically Important Effect on the Pharmacokinetics of Theophylline

Linda E. Gustavson, Xin Ye, Joseph E. Beason, Titus O. Chira, Martha A. Ewen, Maria M. Paris, Laura A. Williams; Abbott Laboratories, Abbott Park, IL, USA

ABSTRACT
Background: ABT-773 is a potent ketolide antimicrobial under development for the treatment of respiratory tract infections. It may be coadministered with theophylline (Theo) in patients.

Methods: A double-blind, 2-period, randomized crossover study in 18 healthy subjects examined the pharmacokinetics (PK) and safety of ABT-773 300 mg or placebo q12h x 5 days when coadministered with Theo (300 mg BID) relative to Theo/placebo. The 90% confidence intervals (CI) fell within the 0.80 to 1.25 range, suggesting no clinically important PK interaction between Theo and ABT-773.

RESULTS

Table 1. Study Site and Investigator

Study Site and Investigator

<table>
<thead>
<tr>
<th>Site</th>
<th>Study Period</th>
<th>Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waukegan, IL</td>
<td>Period 1</td>
<td>Laura A. Williams, M.D., M.P.H.</td>
</tr>
<tr>
<td>Waukegan, IL</td>
<td>Period 2</td>
<td>Laura A. Williams, M.D., M.P.H.</td>
</tr>
</tbody>
</table>

Table 2. Summary of Study Day 5 Theophylline Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Theo</th>
<th>ABT-773</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>271 ± 62*</td>
<td>239 ± 55</td>
</tr>
<tr>
<td>Cmin (µg/mL)</td>
<td>9.5 ± 2.4*</td>
<td>8.4 ± 2.0</td>
</tr>
<tr>
<td>AUC0-24 (µg•h/mL)</td>
<td>271 ± 62*</td>
<td>239 ± 55</td>
</tr>
</tbody>
</table>

Table 3. Results of Two-One-Sided Tests Procedure Based on Log of Study Day 5 Theophylline Concentration Profiles

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test Reference Estimate</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>1.132 (1.083-1.183)</td>
<td></td>
</tr>
<tr>
<td>Cmin</td>
<td>1.118 (1.074-1.163)</td>
<td></td>
</tr>
<tr>
<td>AUC0-24</td>
<td>1.124 (1.062-1.191)</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSIONS

• Coadministration of theophylline and ABT-773 led to small increases (14-15%) in the point estimates for theophylline Cmax, Cmin, and AUC0-24 compared to administration of theophylline with placebo.

• The 90% confidence intervals for theophylline Cmax, Cmin, and AUC0-24 were contained entirely within the 0.80 to 1.25 range so that the regimens are likely to be bioequivalent.

• All of the adverse events were mild to severe.

• Coadministration of theophylline plus ABT-773 was safe and well tolerated.

REFERENCES


ABSTRACT

INTRODUCTION

METHODS

RESULTS

CONCLUSIONS

SUMMARY

REFERENCES

Table 1. Excretion of Radioactivity in Humans After Oral Administration of [14C]ABT-773

Table 2. Pharmacokinetic Parameters of [14C]ABT-773 Following a Single 150 mg Oral Dose
ABSTRACT (Revised)

Background: Treatment failures caused by multidrug-resistant (MDR) Streptococcus pneumoniae pose a serious therapeutic challenge. We evaluated the effectiveness of ABT-773, a new ketolide antibiotic, for treatment of immunocompetent mice with multidrug-resistant S. pneumoniae bacteremic pneumonia.

Objectives: To establish an immunocompetent murine pneumonia model to evaluate the effectiveness of ABT-773 for treatment of MDR S. pneumoniae.

Methods: 8-week-old Balb/c mice were inoculated intranasally with 50 µl of frozen stock for each experiment. 5-10 CFU from an overnight culture were used as inoculum. ABT-773 powder was formulated in 2% ethanol and D5W adjusted to pH 6.0-6.5; ceftriaxone was formulated in D5W. Mice were treated for 3 days with subcutaneous injections of ABT-773 (50 mg/kg q24h or 25 mg/kg q12h) or placebo (D5W s.c.).

Results: All mice evaluated before therapy had documented bacteremic pneumonia with low colonies and local culture positivity. ABT-773 (50 mg/kg q24h) was significantly more effective than placebo (D5W s.c.; p<0.05) for reducing lung colony counts by 2.5 log10 over 24h and bacteremia persisted through Day 6. ABT-773-treated mice (50 mg/kg q24h) showed a trend towards a dose-response effect against S. pneumoniae resistant to penicillin (MIC: 4 µg/ml) and ceftriaxone (MIC: 2 µg/ml). Inoculum ranged from 5.1 to 6.3 log10 CFU/ml, corresponding to LD33. Mice were treated for 3 days with subcutaneous injections of ABT-773 (50 mg/kg q24h) or placebo. The current model can be used to study disease pathogenesis, host responses, and other new antimicrobial agents.

Conclusions: ABT-773 showed significant antimicrobial efficacy for treatment of MDR S. pneumoniae bacteremic pneumonia in immunocompetent mice. Our findings should extend to humans. This model can also be used to study disease pathogenesis, host responses, and other new antimicrobial agents.

OUTCOME MEASURES

1. Quantitative cultures of blood, lung homogenate, and bronchoalveolar lavage fluid (BAL). Lower limits of detection were 10, 5 and 2 CFU/ml, respectively.

2. Lung histopathology scores were assigned by the pathologist in a blinded manner according to predefined criteria (Figure 5a).

3. Pulmonary function defined by whole body plethysmography:

   • 2.5 times per time point were screened and included (10); after inoculation and protein binding in mice serum.

RESULTS

• ABT-773 50 mg/kg q24h and 25 mg/kg q12h regimens were highly effective for treatment of MDR S. pneumoniae bacteremic pneumonia or immunocompromised mice.

• Clinical studies in humans are warranted.

• The current model can be used to study disease pathogenesis, host responses, and other new antimicrobial agents.

CONCLUSIONS

• ABT-773 50 mg/kg q24h and 25 mg/kg q12h regimens were highly effective for treatment of MDR S. pneumoniae bacteremic pneumonia or immunocompromised mice.
ABT-773 Demonstrates Bactericidal Effects Against Susceptible and Resistant Streptococcus pneumoniae and Haemophilus influenzae in Rat Pulmonary Infection


INTRODUCTION

ABT-773 is a ketolide antibiotic with potent activity against respiratory pathogens and is currently in clinical development.

RESULTS

Pharmacokinetic: ABT-773 Plasma Concentrations in Rat (Bolusiway Method)

Pharmacokinetics: ABT-773 plasma levels were determined using high-performance liquid chromatography methods. ABT-773 was administered as a single intravenous bolus dose of 7 mg/kg to Sprague-Dawley rats (approximately 250 g). Plasma samples were collected at various time points following bolus dosing and analyzed by reverse-phase high-performance liquid chromatography.

METHODS

In vitro susceptibility (MIC) values were determined using NCCLS-recommended microdilution methods. The minimal inhibitory concentration (MIC) values for ABT-773 against various bacterial strains were determined using Mueller-Hinton broth microdilution plates. The MIC was defined as the lowest concentration of ABT-773 that resulted in no visible growth after incubation for 18 to 24 hours.

REFERENCES


The In Vivo Activities of ABT-773 Against Streptococcus pneumoniae and Haemophilus influenzae on Respiratory Tract Infections Models of Mice

T. Fujikawa*, S. Miyazaki, Y. Ishii, N. Furuya, A. Ohno, T. Matsumoto, K. Tateda, K. Yamaguchi; Dept. of Microbiology, Toho Univ. School of Med., Tokyo, Japan

ABSTRACT

Background: ABT-773 is a novel ketolide antimicrobial agent. Previous reports showed that ABT-773 had potent in vitro activities against respiratory pathogens. At 40th ICAAC, we also reported that ABT-773 had potent activities against recent clinical isolates causing respiratory tract infection in Japan.

In this study, we examined the therapeutic effects of ABT-773 in murine respiratory tract infection due to S. pneumoniae or H. influenzae.

Methods: (A) S. pneumoniae infection model: Four-week-old male CBA/J mice (15 mice/group) were intranasally infected with S. pneumoniae. Drug administration was started 2 days after infection and continued twice a day for 3 days. About 15 h after the last administration of the test drugs, the number of bacteria in the infected tissue was measured. (B) H. influenzae infection model: Four-week-old male BALB/c mice (15 mice/group) were intranasally infected with H. influenzae. Drug administration was started 2 days after infection and continued thrice a day for 3 days, with the drugs being given twice a day. Mice were sacrificed 15 h after final administration, and the infected issues were removed aseptically and homogenized.

Results: As a part of results, the efficacy of ABT-773 and reference drugs on pulmonary infection due to S. pneumoniae (PRSP) in vivo was as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Dosage Log10CFU/Tissue</th>
<th>MIC Dosage Log10CFU/Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-773</td>
<td>0.12</td>
<td>100x2</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&gt;32</td>
<td>100x2</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>1</td>
<td>100x2</td>
</tr>
<tr>
<td>Cefdinir</td>
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<td>100x2</td>
</tr>
<tr>
<td>Penicillin G</td>
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</tr>
<tr>
<td>Ampicillin</td>
<td>8</td>
<td>100x2</td>
</tr>
</tbody>
</table>

Conclusion: The therapeutic effect of ABT-773 against S. pneumoniae was the most potent of all test drugs. Previous and these data suggest that ABT-773 is an available agent for the treatment of infections caused by most respiratory pathogens.

INTRODUCTION

- ABT-773 is a new ketolide antimicrobial agent with potent in vitro activity against major respiratory pathogens.
- Recently, isolation frequency of erythromycin- and/or penicillin-resistant S. pneumoniae was 40% or more in Japan. In addition, that of lactose-negative ampicillin-resistant (BLANR) S. pneumoniae in Japan is 30-40%, which was much higher than other countries.

In this study, we examined the efficacy of ABT-773 against erythromycin and/or penicillin-resistant S. pneumoniae and BLANR H. influenzae in murine respiratory tract infection models.

- The in vivo activity of ABT-773 compared with those of imipenem, teicoplanin, and a fluoroquinolone.

METHODS

- Strains:
  - S. pneumoniae TUM471 (PRSP, erm+)
  - S. pneumoniae TUM117 (PRSP, erm-)
  - H. influenzae TUH267 (BLANR)

- All strains were isolated clinically or in hospital.

- Antimicrobial agents were as follows: ABT-773, clarithromycin, cefdinir, telithromycin, ceftriaxone, penicillin G, ampicillin and teicoplanin.

- In vitro susceptibility test:
  - MICs were determined by a broth microdilution method according to NCCLS guidelines (M7-A5 and M2-A9).
  - Calf-reared Mueller-Hinton broth with 2% bovine blood and Haemophilus Test Medium broth were used for Streptococcus pneumoniae and Haemophilus influenzae, respectively.

- Mouse models:
  - The noncompromised mouse model of pneumococcal pneumonia:
    - Five-week-old CBA/J mice were intranasally infected with S. pneumoniae under ketamine-xylazine anesthesia. Drug administration was commenced 2 days after infection and continued thrice a day for 3 days, with the drugs being given twice a day. Mice were sacrificed 15 h after final administration, and the infected tissues were removed aseptically and homogenized (Fig. 1).
  - The number of bacteria was determined by agar plating.
  - The mouse model of bronchopneumonia caused by H. influenzae:
    - For airway injury, 1% formalin was injected intranasally into 3.5-week-old ICR mice under anesthesia. Oral administration was commenced 2 days after infection and continued thrice a day for 3 days, with the drugs being given twice a day. Mice were sacrificed 15 h after final administration, and the infected tissues were removed aseptically and homogenized (Fig. 1). The number of bacteria was determined by agar plating.

- The therapeutic effect of ABT-773 against erythromycin and/or penicillin-resistant S. pneumoniae strains (Table 1, Fig. 2, 3 and 4).

Finally, previous reports showed that ABT-773 had potent activities against recent clinical isolates causing respiratory tract infection in Japan. At 40th ICAAC, we also reported that ABT-773 had potent activities against recent clinical isolates causing respiratory tract infection in Japan. ABT-773 is a novel ketolide antimicrobial agent.

CONCLUSIONS

- The reduction of the viable counts in lungs of mice treated with ABT-773 was more than other reference drugs against both S. pneumoniae strains (Table 1, Fig. 2, 3 and 4)

REFERENCES


Figure 1. Therapeutic Schedules in Murine Respiratory Tract Infection Models

Figure 2. The Number of Bacteria in Lungs of Mice Treated with ABT-773 and Reference Drugs on Pulmonary Infection Caused by S. pneumoniae TUH267

Figure 3. The Efficacy of ABT-773 and Telithromycin Against Murine Pulmonary Infection Caused by S. pneumoniae TUH267

Figure 4. The Number of Bacteria in Lungs of Mice Treated with ABT-773 and Reference Drugs on Pulmonary Infection Caused by H. influenzae TUH267

Figure 5. The Number of Bacteria in the Infected Tissues of Mice Treated with ABT-773 and Reference Drugs on Bronchopneumonia Caused by H. influenzae TUH267

Table 1. The Efficacy of ABT-773 and Reference Drugs in Murine Respiratory Tract Infections
**Table 1. Activity of ABT-773 and Two Macrolides Against S. aureus Strains**

<table>
<thead>
<tr>
<th>Strain Type</th>
<th>Phenotype</th>
<th>Strain Source</th>
<th>MICs (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>ABT-773</td>
</tr>
<tr>
<td></td>
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<td>MIC50</td>
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<tr>
<td>Methicillin-susceptible</td>
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<td>Methicillin-resistant</td>
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**Table 2. Activity of ABT-773 and Two Macrolides Against S. epidermidis Strains**

<table>
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<th>Strain Source</th>
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<td></td>
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<td>ABT-773</td>
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<td>Methicillin-susceptible</td>
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<tr>
<td>Methicillin-resistant</td>
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**Table 3. Activity of ABT-773 and Two Macrolides Against S. haemolyticus Strains**

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</tr>
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<td>ABT-773</td>
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<tr>
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**Table 4. Activity of ABT-773 and Two Macrolides against other CoNS**

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<th>Strain Type</th>
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</tr>
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<tbody>
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<td></td>
<td></td>
<td></td>
<td>ABT-773</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>MIC50</td>
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<tr>
<td>Methicillin-susceptible</td>
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</tr>
<tr>
<td>Methicillin-resistant</td>
<td></td>
<td></td>
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</table>
**Activity of a New Ketolide ABT-773 In Vitro Against S. pneumoniae Non-susceptible to Penicillin or Macrolides**

E.O. Mason, Jr, L.B. Lambeth, S.L. Kaplan, and the U.S. Multicenter Pneumococcal Surveillance Study Group; Baylor Coll. of Med. and Texas Children's Hosp., Houston, TX, USA

**ABSTRACT**

Increasing pneumococcal resistance to penicillins continues to present therapeutic problems for physicians treating children with respiratory tract infections. New antibiotics with additional therapeutic options if resistance can be demonstrated may be important in the treatment of pneumococcal infections. ABT-773, a novel ketolide, is currently being evaluated in multiple clinical trials. This study investigated the in vitro activity of ABT-773 and other antibiotics against S. pneumoniae isolates. The study enrolled all isolates of S. pneumoniae from otitis media patients (children 0-18 years) in the 1997-1998 year and continuing until 2000.

**METHODS**

Susceptibility of all isolates tested based on published NCCLS breakpoints were:

**RESULTS**

The MIC50, MIC90, and MIC ranges of penicillin intermediate and penicillin-resistant isolates were in all antibiotics tested.

**DISCUSSION**

With the increase in erythromycin resistance, new agents must be available to treat community-acquired respiratory infections. ABT-773 demonstrated activity against penicillin and macrolide-resistant pneumococci. These new ketolides may become important alternatives in the treatment of children with acute otitis media. The wide spectrum of activity of the ketolides against pneumococci and their increased potential to treat penicillin-resistant pneumococci offer promise in therapeutic options for physicians. The MICs of ABT-773 and other antibiotics against S. pneumoniae isolates were:

**Figure 1. Increase in Macrolide (Erythromycin) Non-susceptible S. pneumoniae over Six Years**

- 1% ≤ 20% ≤ 30% ≤ 40% ≤ 50% ≤ 60% ≤ 70% ≤ 80% ≤ 90% ≤ 100%

**Figure 2. All Isolates**

- 10% 20% 30% 40% 50% 60% 70% 80% 90%

**Figure 3. Penicillin Intermediate Isolates**

- 0% 10% 20% 30% 40% 50% 60% 70% 80% 90%

**Figure 4. Penicillin Resistant Isolates**

- 0% 10% 20% 30% 40% 50% 60% 70% 80% 90%

**Figure 5. Erythromycin Susceptible Isolates**

- 0% 10% 20% 30% 40% 50% 60% 70% 80% 90%

**Figure 6. Erythromycin Susceptible Isolates**

- 0% 10% 20% 30% 40% 50% 60% 70% 80% 90%
Mutation Prevention Concentration of ABT-773 versus Four Other Agents Against Streptococcus pneumoniae and Haemophilus influenzae

Melinda M. Neuhauer*, Jennifer L. Prairie, Susan L. Pendland*
*The University of Houston, Houston, TX, USA; **The University of Illinois at Chicago, Chicago, IL, USA

ABSTRACT

Mutation Prevention Concentration (MPC) is the antibiotic concentration hypothesized to prevent the emergence of resistant bacteria. The purpose of this study was to compare the MPC of ABT-773 with azithromycin, cefuroxime, ciprofloxacin, and amoxicillin/clavulanate against clinical strains of Streptococcus pneumoniae and Haemophilus influenzae.

METHODS

Bacterial Strains

8 Clinical Isolates

- S. pneumoniae (n=4)
  - penicillin/erythromycin susceptible (S)
  - penicillin/erythromycin resistant (R)
- H. influenzae (n=2)
  - beta-lactamase negative (BL) (n=2)
  - beta-lactamase positive (P) (n=2)

3 Control Strains: for MICs

- S. pneumoniae ATCC 49619
- H. influenzae ATCC 43524
- Staphylococcus aureus ATCC 29213

Antimicrobial Agents

- ABT-773 (Abbott Laboratories)
- Azithromycin (United States Pharmacopeia)
- Cefuroxime (United States Pharmacopeia)
- Ciprofloxacin (United States Pharmacopeia)
- Amoxicillin/clavulanate (2:1 ratio) (United States Pharmacopeia)

Concentrations Tested

Multiples of the MIC: 0.5x, 1x, 2x, 4x, 8x, 16x, 32x, 64x

Media (Hemi, Lenetz, K5)

- Agar Media
  - 5% sheep blood agar (S. pneumoniae)
  - Chocolate agar (H. influenzae)

Inoculum

MICs: 5 x 10^4 CFU/mL
MPCs: 10^5 CFU/mL, for S. pneumoniae

The inoculum for the MPC assays was prepared by first making a direct suspension of the organism and adjusting with sterile saline until the turbidity matched a 2.0 McFarland standard using a spectrophotometer at 620nm. Each suspension was then diluted in broth medium 10-fold and incubated in an Innsova Shaker Incubator (New Brunswick Scientific, Edison, NJ) for six hours. The organism was centrifuged and repippeted in a minimal amount of broth. The exact inoculum size for the MPC assays was determined via colony counts.

Procedures

MICs: Agar Dilution MICs were performed in duplicate per NCCLS guidelines.
MPCs: A 200 µL aliquot of the concentrated inoculum was plated on the antibiotic containing media and incubated at 35°C in humidified air. The plates were examined at 24 and 48 hours for growth. All procedures were performed in duplicate. The MPC was defined as the lowest concentration at which there was no visible growth at 48 hours. The ratio of the MPC:MIC was expressed as the mutation selection window (MSW).

RESULTS

Table 1. MIC and MPC of ABT-773, Azithromycin, Cefuroxime, Ciprofloxacin, and Amoxicillin/Clavulanate Against Clinical Isolates of S. pneumoniae and H. influenzae

<table>
<thead>
<tr>
<th>Isolate</th>
<th>ABT-773</th>
<th>Azithromycin</th>
<th>Cefuroxime</th>
<th>Ciprofloxacin</th>
<th>Amoxicillin/Clavulanate</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae (S)</td>
<td>0.015/0.03</td>
<td>0.03/0.06</td>
<td>0.03/0.06</td>
<td>0.06/0.12</td>
<td>0.03/0.06</td>
</tr>
<tr>
<td>S. pneumoniae (R)</td>
<td>0.015/0.03</td>
<td>0.03/0.06</td>
<td>0.03/0.06</td>
<td>0.06/0.12</td>
<td>0.03/0.06</td>
</tr>
<tr>
<td>H. influenzae (BL)</td>
<td>4/8</td>
<td>8/16</td>
<td>8/16</td>
<td>16/32</td>
<td>8/16</td>
</tr>
<tr>
<td>H. influenzae (P)</td>
<td>4/8</td>
<td>8/16</td>
<td>8/16</td>
<td>16/32</td>
<td>8/16</td>
</tr>
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</table>

DISCUSSION

- To date, most MPC studies have focused on the fusospirinolides. This study was the first to compare the MPC and MSW of 5 different classes of antimicrobial agents against common community-acquired bacterial pathogens. ABT-773 consistently demonstrated a low MPC and MSW against S. pneumoniae.
- Against penicillin/erythromycin susceptible strains of S. pneumoniae, ABT-773, azithromycin, and amoxicillin/clavulanate demonstrated a low MPC and MSW. Cefuroxime also demonstrated a low MPC but a wider MSW.
- Against penicillin/erythromycin resistant strains of S. pneumoniae, ABT-773 was the only agent that demonstrated a low MPC.
- Against H. influenzae, ciprofloxacin demonstrated the lowest MPC. ABT-773 and azithromycin demonstrated higher MPCs, but maintained a low MSW.

Table 2. HRF of ABT-773, Azithromycin, Cefuroxime, Ciprofloxacin, and Amoxicillin/Clavulanate Against Clinical Isolates of S. pneumoniae and H. influenzae

<table>
<thead>
<tr>
<th>Isolate</th>
<th>ABT-773</th>
<th>Azithromycin</th>
<th>Cefuroxime</th>
<th>Ciprofloxacin</th>
<th>Amoxicillin/Clavulanate</th>
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<tbody>
<tr>
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<td>0.015/0.03</td>
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<td>0.06/0.12</td>
<td>0.03/0.06</td>
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<tr>
<td>S. pneumoniae (R)</td>
<td>0.015/0.03</td>
<td>0.03/0.06</td>
<td>0.03/0.06</td>
<td>0.06/0.12</td>
<td>0.03/0.06</td>
</tr>
<tr>
<td>H. influenzae (BL)</td>
<td>4/8</td>
<td>8/16</td>
<td>8/16</td>
<td>16/32</td>
<td>8/16</td>
</tr>
<tr>
<td>H. influenzae (P)</td>
<td>4/8</td>
<td>8/16</td>
<td>8/16</td>
<td>16/32</td>
<td>8/16</td>
</tr>
</tbody>
</table>

MPCs were determined via 24 hour incubation at 35°C on BHI plates.

- The University of Houston, Houston, TX, USA; **The University of Illinois at Chicago, Chicago, IL, USA

CONCLUSION

ABT-773 demonstrated a low MPC and MSW against S. pneumoniae and H. influenzae. It was the only agent that demonstrated a low MPC. Cefuroxime also demonstrated a low MPC, but with a wider MSW. Only ABT maintained a low MPC and MSW.
**In Vitro Activity of ABT-773, a Novel Ketolide, Against Clinical Isolates of Gram-Positive and Gram-Negative Cocci**

M. Inoue*, Y. Sato, R. Oyauchi, R. Okamoto
Kitasato Univ. Sch. of Med., Sagamihara, Japan

**BACKGROUND**

ABT-773 is a novel 14-membered macrolide belonging to the ketolides. ABT-773 has potent activity against gram-positive including EM resistant strains and gram-negative cocci.

**METHODS**

Bacteria: All clinical isolates were collected from Kitasato hospital during 2000.

Susceptibility Tests: MICs were determined by agar dilution method according to standard method of Japanese Society of Chemotherapy (JSCC) and NCCLS guidelines (M7-A5). Antimicrobial agents and abbreviations were ABT-773, telithromycin (HMR), azithromycin (AZM), clarithromycin (CAM), erythromycin (EM), rokitamycin (RKM), cefdinir (CFDN), penicillin G (PCG), ampicillin (ABPC), vancomycin (VCM), levofloxacin (LVFX).

Detection of the Resistance Genes: EM-resistant strains were investigated to detect the genes, ermRS and mef.

The ermR primer:

<table>
<thead>
<tr>
<th>Primer Target</th>
<th>5'–AA TCCTTCTTCAACAA TCAG–3'</th>
<th>5'–AAA CCATTGCTGAAACATG–3'</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>1600 bp</td>
<td>800 bp</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>600 bp</td>
<td>300 bp</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>1200 bp</td>
<td>600 bp</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

• ABT-773 has potent activity against EM resistant cocci. Especially ABT-773 was more active against EM resistant Streptococcus and M. catarrhalis than other macrolides. The MIC50/MIC80/IC80 (µg/mL) of ABT-773 were 0.06/0.12/0.12 against S. pneumoniae and S. agalactiae, 0.12/0.25/0.25 against S. pyogenes, respectively (Table 1).

• ABT-773 also had potent activity against EM susceptible and EM inducible resistant streptococci. The MIC50/IC80 of ABT-773 were 0.25/0.50 µg/mL against S. aureus and 0.12/0.25 µg/mL against M. catarrhalis (Table 2).

• ABT-773 also showed good activity against gram-negative bacteria, M. catarrhalis and H. influenzae. The MIC50/IC80 of ABT-773 were 0.12/0.25 µg/mL against M. catarrhalis and 0.06/0.12 µg/mL against H. influenzae (Table 3).

• The ermR-positive S. pneumoniae (KU4975, KU5008) showed inducible resistant phenotype (Fig. 1).

• ABT-773 and HMR3647 did not show inducer activity against both ermR-positive S. pneumoniae (KU4975, KU5008). EM and AZM showed inducer activity against both ermR-positive S. pneumoniae at only concentration of 0.25 µg/mL (Fig. 2).

**REFERENCES**

A Multi-center Study Comparing the Activity of a Novel Ketolide ABT-773 to Beta-lactams, Macrolides, and Fluoroquinolones Against Respiratory Tract Pathogens Isolated in 2000-2001 in the Province of Québec, Canada

K. Weiss*, C. Restieri, H. Guay, P. Dolce, L.A. Galarneau, P. Harvey, C. Lafiere, I. Lecorche, J.F. Paradis, H. Senay, D.E. Low and the GRAM Network (Groupe contre la Résistance aux Anti-Microbiens); Hôpital Maisonneuve-Rosemont, University of Montréal, Montréal, Québec, Canada

ABSTRACT

Increasing resistance among respiratory pathogens is a growing challenge for clinicians. We have tested 1163 non-duplicate microorganisms isolated in the province of Québec, Canada between October 2000 and March 2001: 474 Streptococcus pneumoniae, Sp; 589 Moraxella catarrhalis, Mc; 100 Moraxella, Sp; 589 Moraxella catarrhalis, Mc; Susceptibility testing and interpretation was done following NCCLS guidelines and recommendations.

Results

The following antibiotics were tested at the following concentrations for S. pneumoniae penicillin (0.05-4 mg/L), ceftaroline (0.03-8 mg/L), cephalothin (0.05-8 mg/L), cefuroxime (0.05-8 mg/L), cefprozil (0.06-8 mg/L), clarithromycin (0.06-8 mg/L), erythromycin (0.05-8 mg/L), tetracycline (0.05-8 mg/L), gentamicin (0.05-8 mg/L), and ABT-773 (0.015-4 mg/L). For H. influenzae/parainfluenzae, a direct beta-lactamase test was used, and concentrations up to 32 mg/L were tested for clarihrromycin, cefuroxime, and cefprozil.

Insurer strains were defined as strains isolated from a sterile site such as blood, CSF or articular fluid. Strains isolated from other sites were categorized as non-invasive (respiratory tract, eye, ear).

RESULTS

Table 1. Number of Streptococcus pneumoniae Strains

<table>
<thead>
<tr>
<th>Strain Isolate</th>
<th>12th Month</th>
<th>1st Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>384</td>
<td>390</td>
</tr>
<tr>
<td>Sp, Rest of Québec</td>
<td>234</td>
<td>214</td>
</tr>
<tr>
<td>Mc, Rest of Québec</td>
<td>214</td>
<td>194</td>
</tr>
<tr>
<td>Mc, Montréal</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mc, Québec City</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

DISCUSSION/CONCLUSION

Penicillin, macrolides and ciprofloxacin resistance is increasing for S. pneumoniae.

New fluoroquinolones such as gatifloxacin and moxifloxacin still have a low resistance rate; however, resistant strains harbouring double-step mutations (parC and gyrA) are already present in our environment and causing clinically relevant conditions.

The MIC₉₀ for levofloxacin increased from 1 mg/L in 1998 to 2 mg/L in 2000-2001, suggesting a slow shift toward resistant strains.

There was a noticeable difference in terms of resistance for penicillin, clarithromycin and ciprofloxacin. This raises the potential issue of the decreasing virulence of resistant strains.

Penicillin, macrolides and ciprofloxacin resistance is increasing for H. influenzae/parainfluenzae and Moraxella catarrhalis, Mc.

For H. influenzae/parainfluenzae, a direct beta-lactamase test was used, and concentrations up to 32 mg/L were tested for clarithromycin, cefuroxime, and cefprozil.

Insurer strains were defined as strains isolated from a sterile site such as blood, CSF or articular fluid. Strains isolated from other sites were categorized as non-invasive (respiratory tract, eye, ear).

Table 2. MIC₉₀ and % of Resistance of Streptococcus pneumoniae Strains

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC₉₀ (mg/L)</th>
<th>% R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin (I + R)</td>
<td>2.0</td>
<td>100</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1.0</td>
<td>100</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>100</td>
</tr>
</tbody>
</table>

DISCUSSION/CONCLUSION

Penicillin, macrolides and ciprofloxacin resistance is increasing for S. pneumoniae.

New fluoroquinolones such as gatifloxacin and moxifloxacin still have a low resistance rate; however, resistant strains harbouring double-step mutations (parC and gyrA) are already present in our environment and causing clinically relevant conditions.

The MIC₉₀ for levofloxacin increased from 1 mg/L in 1998 to 2 mg/L in 2000-2001, suggesting a slow shift toward resistant strains.

There was a noticeable difference in terms of resistance for penicillin, clarithromycin and ciprofloxacin. This raises the potential issue of the decreasing virulence of resistant strains.

The % of beta-lactamase strains among penicillin resistant strains for penicillin, clarithromycin and ciprofloxacin. This raises the potential issue of the decreasing virulence of resistant strains.
ABSTRACT
Background: ABT-773 is a new ketolide which has potent antibacterial activity against penicillin- and macrolide-resistant gram-positive bacteria. Its activity against important respiratory pathogens has been evaluated as part of the BSAC Respiratory Resistance Surveillance programme in the British Isles.

METHODS
Seventeen laboratories in Great Britain isolated S. pneumoniae, H. influenzae and M. catarrhalis from lower respiratory tract specimens (mainly sputum) taken from patients with community-acquired lower respiratory tract infections during the 1999-2000 winter season. They were centrally tested by NCCLS MIC methodology.

RESULTS:
About 40% of macrolide-resistant S. pneumoniae remained susceptible to clindamycin indicating that either an efflux mechanism or inducible methylation (MLS_B) mechanism was responsible for resistance in these isolates.

CONCLUSION
Pathogens isolated from patients in Great Britain with community-acquired respiratory infections are highly susceptible to ABT-773, including those which are macrolide- or penicillin-resistant.

INTRODUCTION
The British Society for Antimicrobial Chemotherapy (BSAC) has established a long-term surveillance programme (minimum five years) in collaboration with the pharmaceutical industry to monitor antimicrobial resistance in common respiratory pathogens in the United Kingdom and Republic of Ireland. The pathogens monitored are Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.

ABT-773 (Abbott Laboratories, North Chicago, Illinois) is a novel ketolide which has potent antibacterial activity against penicillin- and macrolide-resistant gram-positive bacteria. Its activity against these important respiratory pathogens has been evaluated as part of the BSAC’s programme in the British Isles.

RESULTS
The minimum inhibitory concentrations (MIC50 and MIC90) are shown in Table 2.

Table 1. Antimicrobials Studied by BSAC

<table>
<thead>
<tr>
<th>S. pneumoniae (n = 556)</th>
<th>H. influenzae (n = 825)</th>
<th>M. catarrhalis (n = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-773</td>
<td>Penicillin</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>0.08</td>
<td>0.015</td>
<td>0.06</td>
</tr>
<tr>
<td>0.015</td>
<td>–</td>
<td>≥ 0.12</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Amoxicillin/Clavulanate</td>
<td>–</td>
</tr>
<tr>
<td>–</td>
<td>0.25</td>
<td>≥ 0.12</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Cefuroxime</td>
<td>–</td>
</tr>
<tr>
<td>≥ 16</td>
<td>≥ 16</td>
<td>≥ 16</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Ciprofloxacin</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>0.015</td>
<td>0.03</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythromycin</td>
<td>0.03</td>
</tr>
<tr>
<td>0.06</td>
<td>0.25</td>
<td>≥ 0.12</td>
</tr>
</tbody>
</table>

About 40% of macrolide-resistant S. pneumoniae remained susceptible to clindamycin indicating that either an efflux mechanism or inducible methylation (MLS_B) mechanism was responsible for resistance in these isolates.

CONCLUSION
Pathogens isolated from patients in Great Britain with community-acquired respiratory infections are highly susceptible to ABT-773, including those which are macrolide- or penicillin-resistant.
**INTRODUCTION**

S. pyogenes, S. pneumoniae, S. aureus, and H. influenzae are important pathogens causing community-acquired lower respiratory tract infections (LRTI) and infections of the ear, nose and throat. S. pyogenes and S. pneumoniae are known to cause serious complications, such as streptococcal toxic shock syndrome and pneumococcal pneumonia, respectively.

**MATERIALS & METHODS**

**Study Design and Sources of Organisms**

Right lungs from different geographical areas participated in this comparative study (Fig. 1). Isolation of S. pyogenes, S. pneumoniae, and H. influenzae was performed by culture on Columbia agar plates containing 5% sheep blood, and McConkey agar plates, respectively. Amoxicillin- and clavulanic acid-resistant strains were identified using the Hydroxy-beta-D-glucuronidase test. A total of 574 isolates were included: 190 S. pneumoniae, 181 S. pyogenes, 149 S. aureus, and 54 H. influenzae.

**RESULTS**

A total of 159 isolates were selected for testing. All strains were susceptible to penicillin except one (MIC: 0.25 mg/L). The rate of macrolide resistance was 4.7%, but all strains were susceptible to ABT-773. Penicillin resistance was detected in isolates from four geographic areas. The frequency of resistance was 0% to 100% (Table 1).

**Antibacterial Minimal Inhibitory Concentration [mg/L]**

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC50</th>
<th>MIC90</th>
<th>S (%)</th>
<th>I (%)</th>
<th>R (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>0.06</td>
<td>0.25</td>
<td>12.0</td>
<td>88.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.06</td>
<td>0.25</td>
<td>45.0</td>
<td>55.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.03</td>
<td>0.06</td>
<td>99.3</td>
<td>0.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.03</td>
<td>0.06</td>
<td>100.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Resistance to penicillin among pneumococci has remained very low in Germany. Only one isolate showed reduced susceptibility to ABT-773 (MIC: 1 mg/L). The 95% confidence interval for ABT-773 was 0.06/2 mg/L and 7/4 mg/L for amoxicillin and amoxicillin-clavulanic acid, respectively. Resistance to ABT-773 was observed in 0% to 100% of the isolates. Penicillin resistance was detected in isolates from four geographic areas. The frequency of resistance was 0% to 100% (Table 1).

**REFERENCES**


2. S. aureus, S. pyogenes, E. coli, H. influenzae.

3. ABT-773 is a promising new agent for the treatment of community-acquired respiratory tract infections.

4. ABT-773 showed excellent activity against macrolide-susceptible strains.
**ABSTRACT**

Antibiotic resistance in respiratory pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* is a global problem. Antibiotic resistance in these pathogens is an important issue for infection control and antimicrobial therapy. Our study was designed to assess the activity of ABT-773 against antibiotic susceptible and resistant *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.

**RESULTS**

- ABT-773 demonstrated excellent activity against *M. catarrhalis* and *H. influenzae*.
- ABT-773 was very active against respiratory pathogens and the most active agent tested against macrolide-susceptible and -resistant *S. pneumoniae*.
- ABT-773 was the most powerful agent tested against respiratory isolates of *S. pneumoniae*.
- ABT-773 was active against both mef* and erm* producing *Streptococcus pneumoniae*.
- ABT-773 was approximately as active as azithromycin against *H. influenzae*
- ABT-773 demonstrated excellent activity against *M. catarrhalis*.

**REFERENCES**


2. ABT-773 was active against both mef* and erm* producing *Streptococcus pneumoniae*.

**CONCLUSION**

- ABT-773 was the most powerful agent tested against respiratory isolates of *Streptococcus pneumoniae*.
- ABT-773 was active against penicillin-resistant, macrolide-resistant, doxycycline-resistant and ciprofloxacin-resistant *Streptococcus pneumoniae*.
- ABT-773 was active against both mef* and erm* producing *Streptococcus pneumoniae*.
- ABT-773 was approximately as active as azithromycin against *H. influenzae*
- ABT-773 demonstrated excellent activity against *M. catarrhalis*.

**ACKNOWLEDGMENTS**

This study was supported in part from Abbott Laboratories (Canada and USA).
**Abstract**

ABT-773 is a semi-synthetic ketolide, a new class of quinolone-based macroline antimicrobial. Its mechanism of action is different from erythromycin and other ketolides, and it is active against both extracellular and intracellular strains of Legionella pneumophila. In this study, we evaluated the in vitro activity of ABT-773 against L. pneumophila, its pharmacokinetics in guinea pigs, and its efficacy compared to saline and erythromycin in a murine model of Legionnaires' disease.

**Methods**

**In Vitro Activity**

- **Growth Inhibition in Alveolar Macrophages**: ABT-773 was more active against L. pneumophila than erythromycin in alveolar macrophages. ABT-773 appeared to have about the same activity against intracellular bacteria as does another ketolide, azithromycin.

- **Antimicrobial Inhibition of Intracellular Growth**: ABT-773 was as effective as erythromycin against L. pneumophila in infected macrophages, and in a guinea pig model of Legionnaires' disease. These data support studies of ABT-773 in patients with L. pneumophila pneumonia.

**Pharmacokinetics**

- **Pharmacokinetic Study**: ABT-773 was given in a single intraperitoneal dose to guinea pigs. The drug was rapidly absorbed and eliminated with a mean terminal half-life of 18.0 h. The area under the curve (AUC) for ABT-773 was significantly greater than for erythromycin.

- **Concentrations in Tissues**: ABT-773 concentrations were significantly lower in the ABT-773 treatment group animals that died before Day 13 than in saline treatment group animals. ABT-773 in the lung at Day 9, but not other days, was significantly higher than erythromycin.

**Results**

- **Bacterial Growth Inhibition**: ABT-773 resulted in a decreased mortality rate when compared to saline treatment, and also substantial clearing of the bacterium in the lungs. S. aureus and Mycobacterium avium were also cleared from the lungs.

**Discussion**

The results of this study demonstrate the potential usefulness of ABT-773 in the treatment of L. pneumophila pneumonia. ABT-773 has a very broad spectrum of activity, and it is active against both extracellular and intracellular strains of L. pneumophila. These data support further investigation of ABT-773 in patients with L. pneumophila pneumonia.

**Conclusion**

ABT-773 is a promising new antibiotic for the treatment of L. pneumophila pneumonia. Further studies are needed to determine the optimal dosing regimen and to evaluate its efficacy in clinical trials.

**Acknowledgments**

Funding for this study was provided by Pfizer Inc. The authors declare no conflicts of interest.
**ABSTRACT**

Background: ABT-773 (ABT) is a novel semisynthetic antibiotic that differs from the natural macrolide-erythromycin (Ery) with an 11,12-position cyclic carbamate group in addition to the 3-keto group. ABT has broad-spectrum activity against Gram-positive bacteria, some Gram-negative bacteria, and against streptococcal bacteria that are resistant to 3-keto macrolides. ABT showed a better in vitro activity against E. faecalis and E. faecium than experimental antimicrobials against similar bacteria. Definitions: The in vivo efficacy of ABT and Ery was studied in a mouse peritonitis model. Both the antibiotics were administered by subcutaneous injection immediately following intraperitoneal inoculation of enterococci in sterile rat fecal extract.

**RESULTS**

In Vivo Susceptibility Testing

Table 1. Bacterial Strains Used in the Study

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Drug</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. faecalis</td>
<td>Ery</td>
<td>≥8</td>
</tr>
<tr>
<td>E. faecium</td>
<td>Ery</td>
<td>≥128</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The MICs of the antibiotics are shown in Table 1. ABT displayed better in vitro activity against enterococci than Ery and intermediate enterococci. The MICs for ABT were 4 to 8 fold lower than those for Ery, suggesting that the greater mortality at 100 µg/kg was in part due to drug toxicity. In an Ery-resistant E. faecium strain, ABT displayed 3.5 times lower PD50 value than Ery (PD50 value of 36.4 µg/kg body weight). It is of note that the PD50 value of ABT for OG1RF was first determined via the PO route and was 9 times higher than with the 0.062 mg/kg regimen, suggesting that the greater mortality at 100 µg/kg was in part due to drug toxicity.

**CONCLUSIONS**

ABT-773 showed in vivo efficacy against Ery susceptible and intermediate enterococci tested. As well as in vivo results, ABT-773 in a more potent than Ery in the mouse peritonitis model.

**REFERENCES**


2. MIC between 1 and 4 µg/mL; Erys, cured of Ery resistance by novobiocin.
INTRODUCTION

ABT-773, a novel ketolide, has demonstrated in vitro activity against a variety of anaerobic bacteria. While several studies have investigated the susceptibility profile of ABT-773, additional data on the activity of this new ketolide would be useful.

OBJECTIVE

The purpose of this study was to determine the in vitro bactericidal activity and postantibiotic effect of ABT-773 and amoxicillin/clavulanate against common anaerobic isolates.

METHODS

Isolates

2 clinical isolates of Peptostreptococcus anaerobius (PA)
PA 3871
PA 3827

2 clinical isolates of Peptostreptococcus anaerobius (PA)
PA 3871
PA 3827

Inoculum

5 x 10^6 CFU/mL – MICs and time-kill experiments
1 x 10^9 CFU/mL – PAE experiments

Media

Wilkins-Chalgren broth, prereduced

Antimicrobial Agents

ABT-773 (Abbott Laboratories)
Amoxicillin/clavulanate (2:1 ratio) (United States Pharmacopoeia)

Concentrations Tested

2x MIC
8x MIC

Procedures

MICs were performed in duplicate per NCCLS guidelines using the microbroth dilution procedure.

Time-kill assays were performed in duplicate according to NCCLS guidelines. The inoculum was confirmed at time zero; subsequent viable counts were performed at 2, 6, and 24 hours. The rate and extent of killing were determined by plotting viable counts (log_{10} CFU/mL) against time (hours). The lower limit of detection was 1.3 log_{10} CFU/mL. Bactericidal activity was defined as a ≥ 3 log_{10} decrease in CFU/mL, while bacteriostatic activity was defined as a < 3 log_{10} decrease in CFU/mL.

The PAEs of the antimicrobial agents were determined using a method of repeated washing. A tube containing no antimicrobial agent was included as a growth control. All tubes were incubated for 1 hour on a shaking platform in a 35°C anaerobic incubator (Bactron; Sheldon Manufacturing, Cornelius, Oregon). At the end of a 1-hour exposure period, the antibiotics were removed by repeated washing (three times). Viable counts were performed at this time and every hour thereafter until the broth became cloudy. The PAE was defined as TC_{10}, where T was the time required for the count in the test culture to increase 1 log_{10} above the count observed immediately after drug removal, and C was the time required for the count in the untreated control to increase 1 log_{10} above the count observed immediately after drug removal.

RESULTS

Table 1. MICs and PAEs of ABT-773 and Amoxicillin/clavulanate Against Anaerobes

<table>
<thead>
<tr>
<th>MICs (µg/mL)</th>
<th>ABT-773</th>
<th>Amoxicillin/clavulanate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF 2800</td>
<td>BF 3181</td>
<td>BF 2800</td>
</tr>
<tr>
<td>PA 3871</td>
<td>PA 3827</td>
<td>PA 3871</td>
</tr>
</tbody>
</table>

Table 2. Time-Kill Results of ABT-773 and Amoxicillin/clavulanate (AC) Versus Amoxicillin/clavulanate (AC) Against B. fragilis (n=2) and P. anaerobius (n=2) Expressed as Number of Strains with 1, 2, and ≥3 log_{10} Decrease in Counts Compared to Time 0

<table>
<thead>
<tr>
<th>MIC</th>
<th>AC BF</th>
<th>BF BF</th>
<th>BF AC</th>
<th>BF AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

• ABT-773 exhibited potent activity against the 2 Peptostreptococcus isolates (MICs 0.004–0.008 µg/mL).
• ABT-773 demonstrated less activity against the 2 B. fragilis isolates (MICs 1 µg/mL).

The purpose of this study was to compare the time-kill kinetics and postantibiotic effect of ABT-773 and amoxicillin/clavulanate against common anaerobic isolates. The activity of ABT and AC was similar for BF and PA isolates. The killing rate was slower with ABT 8x MIC for BF, with only bacteriostatic activity at 2x MIC. In contrast, the killing rate of ABT 8x MIC was faster against both strains of PA. Re-growth was observed in the PA strains with 2x MIC at 24 hours. Bacteriostatic activity with AC was observed in PA due to a high MIC. ABT demonstrated a longer PAE than AC against all organisms and at all concentrations. At high concentrations (8x MIC), ABT demonstrated bactericidal activity and a moderate PAE against all strains. Further studies are needed to determine the role of ABT in anaerobic infections.
Pharmacokinetics of ABT-773, a New Semi-synthetic Ketolide in Neutropenic Lung-Infected Mice: A Population-Approach

Dawei Xuan, Ph.D.*, Min Ye, M.S., Myo Kim, Pharm.D., Charles H. Nightingale, Ph.D.** and David P. Nicolau, Pharm.D.*

1Department of Pharmacy Research, 2Division of Infectious Diseases, 3Office of Research Administration, Hartford Hospital, Hartford, Connecticut, USA

ABSTRACT

BACKGROUND: ABT-773 is an investigational ketolide antimicrobial agent with an in vitro anti-staphylococcal activity against meticillin- susceptible and resistant S. pneumoniae (SP). The objective of this study was to determine the pharmacokinetic profile of ABT-773 in neutropenic mice with SP lung infection. Desir’derv in this study are intended to be used in a subsequent investigation which will evaluated the pharmacodynamics of this compound in the context of pneumococcal pneumonia.

METHODS: Neutropenic IC mice were infected with 2x10^6 CFU/mL starting inoculum via intratracheal inoculation. Mice were treated with a single oral administration of ABT-773 (25, 50, 100 or 200 mg/kg) as a solution in 10% DMSO–ethanol and 90% 0.1% pluronic 65 polyethylene glycol buffer solution 12 hours prior to infection. Serum samples were collected and ABT-773 concentrations were measured using a validated high-performance liquid chromatographic (HPLC) assay with fluorescence detection (retention at 234nm and emission at 244nm). Population PK analysis was performed using the NONMEM computer program.

RESULTS: ABT-773 showed a non-linear PK, noted by the increases in half-life (3 to 27.2h) and AUC/CL/F ratio, with doses from 25 to 200 mg/kg. A non-linear one-compartment model with parallel capacity-limited and linear first-order elimination described the interindividual variability in pharmacokinetic parameters and an additive error model best describes the residual error in the model. ABT-773 exhibits non-linear PK, which can be described by a non-linear one-compartment model with parallel capacity-limited and linear first-order elimination.

CONCLUSION: ABT-773 exhibits non-linear PK, which can be described by a non-linear one-compartment model with parallel capacity-limited and linear first-order elimination.

OBJECTIVE

This study was conducted to determine the pharmacokinetic profile of ABT-773 after oral administration in neutropenic mice. Data derived in the present study are intended to be used in a subsequent investigation that will evaluate the pharmacodynamic profile of this compound in the context of pneumococcal pneumonia.

MATERIALS & METHODS

Antimicrobial Agents: ABT-773 (Lot No. 31-558-A2) and ABT-426 (Lot No. A26-375, used as internal standard) were provided by Abbott Laboratories (Abbott Park, IL).

Animal: Specific pathogen-free female IC mice weighing 25 g (Harlan Sprague Dawley Inc., Indianapolis, IN) at age of approximately 8 weeks were used. Mice were kept under standard laboratory conditions for at least 7 days before the study.

RESULTS

- ABT-773 serum levels were measured by a validated reverse-phase high-performance liquid chromatographic (HPLC) method with fluorescence detection.
- ABT-773 serum levels were measured by a validated reverse-phase high-performance liquid chromatographic (HPLC) method with fluorescence detection.

CONCLUSION

- ABT-773 exhibits non-linear PK, which can be described by a non-linear one-compartment model with parallel capacity-limited and linear first-order elimination.

ACKNOWLEDGMENTS

- The final pharmacokinetic parameter estimates are shown in Table 3. The potential PK parameters were determined by the plot of the observed versus the population predicted concentration of ABT-773 in the infected animals (Figure 3, A).
- ABT-773 exhibits non-linear PK, which can be described by a non-linear one-compartment model with parallel capacity-limited and linear first-order elimination.
ABSTRACT

ABT-773 is a novel ketolide currently in Phase III clinical trials. The drug shows good activity against Haemophilus influenzae. In this study, we investigated the mechanism of action of ABT-773 against H. influenzae and compared the effect on bacterial protein synthesis synthesized by the use of ribosomes. In vitro transcription/translation assays with whole cell extracts from ABT-773 and erythromycin showed the tightest binding affinity to ribosomes of H. influenzae by inhibiting protein synthesis synthesis and up-regulating ribosomal protein expression. However, ABT-773 has a more prolonged molecular PAE (post-antibiotic effect) than erythromycin, which is consistent with previously reported microbiological data (Huang et al., 2001). Ribosome binding assays using ribosomes isolated from H. influenzae NP200 revealed that ribosome binding affinity of ABT-773 is more than 20-fold tighter than that of erythromycin. Further studies of binding kinetics showed ABT-773 has 4 to 6-fold better drug accumulation rate and 20 to 25 slower dissociation rate as compared to erythromycin. The results of in vivo experiments support the findings of the in vitro studies. ABT-773 contributes to the faster drug accumulation, slow dissociation and prolonged molecular PAE of ABT-773 in H. influenzae.

INTRODUCTION

Macrolides inhibit bacterial cell growth by binding to bacterial ribosomes and consequently disrupting normal protein synthesis. Macrolides are a safe antibiotic class with good activity against Gram-positive bacteria. However, the new drug accumulation into cells results in higher MICs for H. influenzae.

ABT-773 is a novel ketolide currently derived from macrolide erythromycin. Because it possesses significant ribosomelysis and the well-established macrolide antibacterial activity, erythromycin, clindamycin, and azithromycin, it may be a therapeutically useful host of antibacterial agent and has entered Phase III clinical trials for the treatment of diarrheal upper and lower respiratory tract infections. Tight ribosome binding may trap a larger amount of drug in the cell and improve the effectiveness of protein synthesis inhibition. In addition, tight binding may contribute to a slower drug dissociation rate and prolonged post-antibiotic effect.

To understand the mechanism of action of ABT-773 against H. influenzae, we designed experiments to look at accumulation and dissociation of ABT-773, the binding affinity, inhibition of protein synthesis and molecular PAE. The results were compared with that of erythromycin, a traditional macrolide.

MATERIALS AND METHODS

Materials: A H. influenzae NP006 is from Abbott culture collection. It was grown in Mueller-Hinton broth with 5% (v/v) lactose, glucose, and yeast extract at 37 °C. Erythromycin, clindamycin and aminocyclic antibiotic co-coupled to a sulfadiazine reporter gene construct were added at Abbott Laboratories (IL, USA) when ABT-773 was made at Abbott.

Competition Ribosome Binding Assay: Ribosomes were purified from H. influenzae NP006. Competitor ribosome binding assays were used to determine the concentration at which 50% of competitor ribosomes are present. The concentration at which 50% of competitor ribosomes are present was used to construct a competitive binding curve for the comparison of drug to ribosomes. The tubes were then centrifuged at 100,000 x g for 2 hrs.

Protein Synthesis Assays: E. coli S-30 extracts were prepared for in vitro protein synthesis using an E. coli cell-free transcription-translation system. The reaction mixture contained 0.5 µg of ribosomal protein, 0.1 mM complete amino acid mix, various concentrations of ABT-773 or erythromycin (10^(-10) to 10^(-5)M) and 5 µl of Premix (Promega, Inc) in 15 µl reaction containing 10 mM MgCl2, 150 mM KCl, 50 mM Tris-Cl, pH 7.2, 0.1 mM EDTA, 20% glycerol, and 1 mM ATP. After 40 min incubation, the reaction was stopped by adding 10 µl of 1 N NaOH. The radioactivity of the S-30 extract was measured using a liquid scintillation counter. Data were expressed as percent inhibition of protein synthesis as compared to control.

Macrolide/Ketolide Transport Studies: In vitro incubations for 40 min at 37 °C were performed using ribosomes isolated from H. influenzae NP200. Approximately one A260 unit of ribosome was incubated at room temperature for 2 hrs with [14C]-ABT-773 (27.2 mCi/mmol), ribosome binding buffer (10 mM Tris-HCl, pH 7.2; 10 mM glucose; 0.13 µM [14C]-ABT-773, ribosome binding buffer (10 mM Tris-HCl, pH 7.2; 0.1 mM EDTA, 150 mM KCl, 50 mM Tris-Cl, pH 7.2; 20% glycerol, and 1 mM ATP). The tubes were then centrifuged at 100,000 x g for 2 hrs. NP200 revealed that ribosome binding affinity of ABT-773 is more than 20-fold tighter than that of erythromycin. Further studies of binding kinetics showed ABT-773 has 4 to 6-fold better drug accumulation rate and 20 to 25 slower dissociation rate as compared to erythromycin.

SUMMARY

ABT-773 more effectively inhibits protein synthesis in H. influenzae than the classic macrolide-erythromycin due to its greater affinity for H. influenzae ribosomes. ABT-773 inhibits protein synthesis in H. influenzae NP006 by 50% at an IC50 of 0.5 µg/mL, whereas erythromycin has an IC50 of 1 µg/mL. ABT-773 treatment up-regulates ribosomal protein gene expression in E. coli.

ABT-773 binds to 30S ribosomes tightly to H. influenzae Ribosomes. Inhibition of Protein Synthesis by H. influenzae NP006 treated with ABT-773, 50 µg/mL, and ABT-773-treated H. influenzae NP006 cells were grown in Mueller-Hinton broth with 5% (v/v) lactose, glucose, and yeast extract at 37 °C. Erythromycin and clindamycin were added to the culture at a final concentration of 0.5 µg/ml. Cells were incubated for 90 min. RNA was isolated immediately after incubation.

In Vivo Ribosome Transport Assays: In vitro incubations for 40 min at 37 °C were performed using ribosomes isolated from H. influenzae NP200. Approximately one A260 unit of ribosome was incubated at room temperature for 2 hrs with [14C]-ABT-773 (27.2 mCi/mmol), ribosome binding buffer (10 mM Tris-HCl, pH 7.2; 10 mM glucose; 0.13 µM [14C]-ABT-773, ribosome binding buffer (10 mM Tris-HCl, pH 7.2; 0.1 mM EDTA, 150 mM KCl, 50 mM Tris-Cl, pH 7.2; 20% glycerol, and 1 mM ATP). The tubes were then centrifuged at 100,000 x g for 2 hrs. NP200 revealed that ribosome binding affinity of ABT-773 is more than 20-fold tighter than that of erythromycin. Further studies of binding kinetics showed ABT-773 has 4 to 6-fold better drug accumulation rate and 20 to 25 slower dissociation rate as compared to erythromycin. The results were compared with that of erythromycin, a traditional macrolide.

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To understand the mechanism of action of ABT-773 against H. influenzae, we designed experiments to look at accumulation and dissociation of ABT-773, the binding affinity, inhibition of protein synthesis and molecular PAE. The results were compared with that of erythromycin, a traditional macrolide.
Development of a Rapid Method to Identify Point Mutations for Quinolone Resistance in *Streptococcus pneumoniae*

**M. Bui**, G. Stone, A. Nilius, R. Flamm; Abbott Laboratories, Abbott Park, IL, USA

**ABSTRACT (Revised)**

**Background:** The quinolone-resistant enterococci (QRE) is a major health threat with significant mortality and morbidity. The susceptibility of QRE is dependent on the presence of specific mutations in the DNA gyrase (GyrA) subunit and topoisomerase IV (ParC) subunit. Thus, the development of a rapid and accurate method to identify point mutations in the GyrA and ParC genes is crucial for identifying QRE and determining appropriate antibiotic treatment.

**Materials & Methods:**

1. A total of 37 bacterial strains were selected from the American Type Culture Collection.

2. Ribotypes were typed using the NCCLSB ribotyping method.

3. Sensitivity to 10 different quinolones was determined.

4. The PCR products were amplified using the QIAGENQP system and sequenced.

5. The quinolone resistance associated with mutations in the GyrA (ser84 or glu88) and ParC (ser79 or asp83) subunits was determined using a PCR-OLA method.

**Results:**

- The OLA was a rapid and accurate method for identifying point mutations in the GyrA and ParC genes.

- The OLA detected point mutations in the GyrA (ser84 or glu88) and ParC (ser79 or asp83) subunits.

- The OLA was also able to identify mutations in the other subunits, such as ParE and ParB.

**Conclusion:**

- The PCR-OLA method is a rapid and accurate method for identifying point mutations in the GyrA and ParC genes.

- This method can be used for routine clinical diagnostics to determine appropriate antibiotic treatment for QRE.

**REFERENCES**


- The newer quinolones such as levofloxacin, moxifloxacin and gatifloxacin are being used to treat respiratory infections, but they are also associated with resistance to quinolones in *S. pneumoniae*.

**INTRODUCTION**

- QRE are a major health threat with significant mortality and morbidity.

- The susceptibility of QRE is dependent on the presence of specific mutations in the DNA gyrase (GyrA) subunit and topoisomerase IV (ParC) subunit.

- The OLA is a rapid and accurate method for identifying point mutations in the GyrA and ParC genes.

**RESULTS**

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- The OLA was also able to identify mutations in the other subunits, such as ParE and ParB.

**Table 1. Primers Used for Primary Target Amplification (5' to 3')**

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>GyrAser84</td>
<td>ATGTCGCAAGAGCCTTCTG</td>
<td>GyrA</td>
</tr>
<tr>
<td>ParCasp83</td>
<td>GTGCGTGCATTACTTACG</td>
<td>ParC</td>
</tr>
</tbody>
</table>

**Table 2. Ligation Probes for OLA (5' to 3')**

<table>
<thead>
<tr>
<th>Probe</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLAser79</td>
<td>TCT Biotin-TTCCACCCACACGGGGATTC pTTCTATCTATGATGCCATGGTTC-Dig</td>
</tr>
<tr>
<td>OLAasp83</td>
<td>TAT Biotin-TTCCACCCACACGGGGATTA pTTCTATCTATGATGCCATGGTTC-Dig</td>
</tr>
</tbody>
</table>

**Table 3. Ciprofloxacin MICs and OLA Results for 53 Strains of *S. pneumoniae***

<table>
<thead>
<tr>
<th>Strain</th>
<th>MIC (µg/mL)</th>
<th>OLAser79</th>
<th>OLAasp83</th>
<th>OLAser84</th>
<th>OLAasp83</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.125</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
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<td>+</td>
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</tr>
<tr>
<td>3</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**CONCLUSION**

- The PCR-OLA method is a rapid and accurate method for identifying point mutations in the GyrA and ParC genes.

- This method can be used for routine clinical diagnostics to determine appropriate antibiotic treatment for QRE.

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- This method can be used for routine clinical diagnostics to determine appropriate antibiotic treatment for QRE.
The Contributions of Prodrug Modification to the Pharmacokinetic Profile of A-315675, a Potent Neuraminidase Inhibitor

A. Kempf-Grote*, K. McDaniel, C. Maring, K. Marsh; Abbott Laboratories, Abbott Park, IL, USA

ABSTRACT

A-315675, 5-[1R,2S]-1-(acetylamino)-2-methoxy-2-methylpentyl]-4-
O-(2-morpholinoethyl)-picolinic acid, is a highly potent inhibitor of 
respiratory influenza virus replication, with uniform subnanomolar IC 
values, against influenza neuraminidase from the three most 
important medically important subtypes (H1N1, A2 and B). A collection of 
water and oral prodrugs was explored as an avenue to achieve 
improved oral bioavailability. Screening studies in plasma and liver S-9 compared rates of 
conversion to A-315675. Comparisons were made between the in vitro stability of selected 
prodrugs and the corresponding pharmacokinetic profile after IV or oral dosing in rat or dog. From 
this series of prodrugs, the ethyl ester (A-315677) was selected as a promising compound for 
clinical development.

The pharmacokinetic profile of A-315675 was evaluated in cynomolgus monkey, beagle dog 
and Sprague-Dawley rat following IV and oral administration of both the parent compound and the 
ethyl ester prodrug. Plasma concentrations of A-315675 increased rapidly after oral 
administration and peaked at 1-2 hours post dosing. Increases in A-315675 peak concentrations ranged from 3-fold in dog to ~50-fold in rat after oral dosing of the prodrug. The increase in peak plasma concentrations was accompanied by a greater than two-fold increase in bioavailability in dog and a 15-fold increase in bioavailability 
in the rat. The oral bioavailability of A-315675 derived from the prodrug was ~30% in beagle dog,

MATERIALS & METHODS

In Vitro Stability Methods

- Pooled human, dog and rat plasma
- Pooled liver, kidney and lung S-9 fractions from dog; pooled human liver S-9 fractions
- Sequential incubations at 37°C
- HPLC/MS/MS for loss of prodrug and appearance of parent compound

Pharmacokinetic Protocol

- Male Sprague-Dawley derived rats (200-300 g, p=4 per group)
- Male/female beagle dogs (7-11 kg, n=6)
- Female cynomolgus monkey (3-5 kg, n=6)
- Fasted overnight prior to dosing
- Dosed once p.o.
- Blood samples collected at 1.5, 6, 12 and 24 hours after dosing
- Plasma frozen within one hour of collection

Table 1. Inhibition of Neuraminidases*

<table>
<thead>
<tr>
<th>Compound</th>
<th>A2</th>
<th>H1N1</th>
<th>A2</th>
<th>H1N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-315675</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>A-315677</td>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

RESULTS

CONCLUSIONS

- Selective and sensitive analytical methods have been developed for the simultaneous 
  quantitation of A-315675 and selected prodrugs using HPLC/MS/MS.
- In vivo stability in all selected prodrugs in dog plasma was not predictive of the in vitro 
  conversion.
- In vitro stability studies in liver S-9 were more useful as a screening tool for the prediction of 
  in vivo behavior.
- Aside prodrugs were slowly and incompletely converted to A-315675, providing high plasma 
  concentrations of prodrug after IV and oral dosing in dog.
- Ester prodrugs were rapidly converted to A-315675, providing high plasma concentrations of 
  the parent compound after IV and oral dosing in dog and monkey.
- Ester prodrug provided comparable pharmacokinetic profiles of A-315675 in rat, dog and 
  monkey.

Figure 3. In Vitro Conversion of A-315675 Prodrugs in Plasma vs. Liver S-9 Fractions

Figure 4. In Vitro Stability of A-315677 in Dog Liver, Kidney S-9 Fractions

Table 2. Pharmacokinetics of A-315675 Following a Single Dose

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose</th>
<th>t1/2</th>
<th>Vß</th>
<th>AUC</th>
<th>CLp</th>
<th>F</th>
</tr>
</thead>
</table>

Table 1. Pharmacokinetics of A-315675 at Selected Doses

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose</th>
<th>t1/2</th>
<th>Vß</th>
<th>AUC</th>
<th>CLp</th>
<th>F</th>
</tr>
</thead>
</table>

Figure 5. Effect of Prodrug on the Plasma Concentrations of A-315675

Figure 6. Plasma Concentrations of A-315675 After a 2.5 mg/kg IV or Oral Dose of Either A-315675 or A-315677 in Dog and Monkey

Table 2. Inhibition of Neuraminidases*
ABSTRACT

In line with our objective to develop new molecules that effectively address the growing problem of antibiotic-based resistance, we have been pursuing a design strategy which allows for the introduction of an extended side-chain unit that can be attached to the ketolide core. In this communication, we describe the synthesis of an extended side-chain unit that allows for the introduction of a variety of functional groups or amino acids. This approach has led to the development of several agents with excellent activity against both macrolide-susceptible and -resistant microbes.

INTRODUCTION

For half a century, macrolide antibiotics have been a preferred drug class for the safe and effective treatment of respiratory tract infections. Today, the growing prevalence of antibiotic resistance among respiratory pathogens has spurred efforts to identify new molecules that would collectively form the antifungal/health drug. The introduction of extended side-chain units that can be attached to the ketolide core has led to the discovery of new classes of antibiotics with potent activity against antibiotic-resistant pathogens. One interesting area has been the exploration of the potential of ketolides to inhibit the growth of Streptococcus pneumoniae, a pathogenic organism that causes respiratory infections. In this area, we have identified several agents with excellent activity against both macrolide-susceptible and -resistant strains. In vitro, these agents are reported as the minimum inhibitory concentration (MIC) as determined by the agar dilution method. The killing activity of these agents is reported as the minimum bactericidal concentration (MBC) as determined by the broth dilution method. The results of these investigations will be published in the near future.

SYNTHESIS

Table 1. Synthetic Modification of a-6-O-Arylated 11,12-Ketolide Intermediates

Table 2. In Vitro Antibacterial Activity of a-6-O-Arylated 11,12-Ketolide Intermediates

RESULTS

Table 3. In Vitro Antibacterial Activity of A-217213 and Reference Agents

DISCUSSION

The results of our investigations demonstrate that the introduction of extended side-chain units can lead to the discovery of new classes of antibiotics with potent activity against antibiotic-resistant pathogens. In particular, the introduction of heteroatoms into the ketolide core has resulted in the discovery of new agents with excellent activity against both macrolide-susceptible and -resistant strains. These agents are reported as the minimum inhibitory concentration (MIC) as determined by the agar dilution method. The killing activity of these agents is reported as the minimum bactericidal concentration (MBC) as determined by the broth dilution method. The results of these investigations will be published in the near future.

CONCLUSION

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REFERENCES

5. Antibacterial Activity of 6-O-Substituted Ketolides. MIC (µg/mL) In Vitro.

Figure 1. Minimized Conformation of A-217213 (Green) Superimposed with Single Crystal X-Ray Structure of A-189773 (Gray).
In Vitro and In Vivo Activities of A-217213, a New Ketolide Antibiotic, Against Respiratory Tract Pathogens

A. M. Nilius*, M. Mitten, M. H. Bui, D. Hensey-Rudloff, R. Clark, Z. Ma, J. Meulbroek, and R. K. Flamm; Abbott Laboratories, Abbott Park, IL, USA

ABSTRACT

Background: The in vitro and in vivo efficacy of A-217213 was determined against pathogens isolated in community-acquired respiratory tract infections and compared with telithromycin (TEL) and azithromycin (AZM).

Methods: MICs were determined using the NCCLS broth microdilution or agar dilution method. Effective and lethal doses were calculated to protect 50% of mice from lethal systemic infection (LSI) after ip inoculation with 180 x LD50 of M. catarrhalis in which susceptibility to antifungal and macrolide efflux and the activity of A-217213 was determined in LSI in mice.

Results:

Conclusions: A-217213 was more active than azithromycin and telithromycin against S. pneumoniae and S. aureus. A-217213 was as active as azithromycin and telithromycin against MLS-S. M. catarrhalis and required the lowest dose to treat rat pulmonary infection with LSI.

INTRODUCTION

Antimicrobial resistance in bacterial species commonly involved in community-acquired respiratory tract infections is a growing clinical problem. Macrolide resistance in S. pneumoniae, comprised of various patterns of penicillin, macrolide, tetracycline-sulfonamide, cefuroxime, clindamycin, and chloramphenicol-resistant, is increasing rapidly. P. aeruginosa and S. aureus, polymicrobial pathogens in hospital-acquired infections, are also multidrug-resistant. (Deen 1984, Deen 1996, Deen 1999).

Materials and Meth...