Macrolides & Ketolides

Elizabeth D. Hermsen, Pharm.D.
Infectious Diseases Research Fellow
University of Minnesota
College of Pharmacy

Objectives

• Participant should be able to explain macrolide/ketolide mechanism of action.
• Participant should be able to identify one important pharmacodynamic parameter each for macrolides and ketolides.
• Participant should be able to list three reasons why ketolides may be beneficial over macrolides.

Protein Synthesis
Mechanism of Action

Structure: Macrolides vs. Ketolides

- Carbamate Extension
- Increased potency via domain II

Keto Group
- Acid stability
- Lack of induction of MLSβ resistance

Structure: Acid Stability

Incubation at pH 1 at 37°C
Spectrum of Activity

<table>
<thead>
<tr>
<th></th>
<th>Ery</th>
<th>Clari</th>
<th>Azi</th>
<th>Teli</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>S. viridans</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>S. agalactiae</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>L. pneumophila</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C. pneumoniae</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>B. pertussis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>N. meningitidis</td>
<td>±</td>
<td>--</td>
<td>±</td>
<td>+</td>
</tr>
</tbody>
</table>

Spectrum of Activity (cont.)

• While clarithromycin, azithromycin, and telithromycin have some activity versus certain anaerobes, these agents should not be used as monotherapy for anaerobic infections
• More studies necessary for ketolides

Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Ery</th>
<th>Clari</th>
<th>Azi</th>
<th>Teli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (hrs.)</td>
<td>1.5</td>
<td>4</td>
<td>68</td>
<td>10</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>25</td>
<td>50</td>
<td>35</td>
<td>60</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>1.5</td>
<td>3</td>
<td>18</td>
<td>?</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>70</td>
<td>70</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>Metabolism</td>
<td>yes</td>
<td>yes*</td>
<td>yes</td>
<td>yes (3A4)</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>15</td>
<td>20</td>
<td>10**</td>
<td>15†</td>
</tr>
</tbody>
</table>

*active metabolite formed
** ~50% excreted unchanged in biliary tract
†~70% excreted in feces
Pharmacodynamics

\[ \text{AUC} / \text{MIC} = 100 / 0.5 = 200 \]
\[ \text{Cpmax} / \text{MIC} = 10 / 0.5 = 20 \]
\[ T > \text{MIC} \sim 22 \text{hrs} \]

\[ \text{AUC} = 100 \text{ mg h} / \text{L} \]

\[ \text{MIC} = 0.5 \]

Pharmacodynamics (cont.)

- **Macrolides**
  - T>MIC -- 50%
  - azithromycin?

- **Ketolides**
  - concentration-dependent
  - AUC/MIC


Adverse Reactions

- Diarrhea and GI upset – all
  - Erythromycin>clarithromycin>azithromycin
  - telithromycin
- Abnormal taste/smell – clarithromycin, telithromycin
- Blurred vision – telithromycin
- Hepatotoxicity – azithromycin, telithromycin (↑ LFTs): erythromycin (cholestatic hepatitis)
- Hypersensitivity – all
Drug Interactions

- CYP3A4 inhibition – erythromycin > clarithromycin
  - Carbamazepine, cyclosporine, tacrolimus, digoxin, theophylline, warfarin, simvastatin, protease inhibitors (saquinavir, indinavir, ritonavir, etc.)
- Rifampin induces P450 – increased clearance of erythromycin and clarithromycin
- Ritonavir and indinavir inhibit CYP3A4 – increased AUC’s for erythromycin and clarithromycin
- pH – macrolides are more active at basic pH

U.S. Trends in Gram-Positive Resistance

1980 to 2002

Mechanisms of Resistance: Macrolides

- Ribosomal (erm - erythromycin ribosomal methylase)
  - ~30%
  - ermA, ermB, ermC, ermF
  - Inducible or constitutive
  - resistance to all macrolides, lincosamides, and group B streptogramins (MLS)
- Efflux pump
  - ~70%
  - mef – streptococci; mar - staphylococci
  - resistance varies

Mechanisms of Resistance: Macrolides

- 23S rRNA or ribosomal protein mutations
  - L4 and L22 mutations – *S. pneumoniae*
  - Rare
- Drug modification
  - mpt, Inu
  - staphylococci, *E. faecium*
  - Rare

Mechanism of Resistance: Macrolides and Ketolides (*erm*)

Resistance: Breaking it Down
Resistance: Breaking it Down

**Ketolides** bind more strongly than **macrolides** to domain II.

Macrolides have weaker affinity for domain II.
Resistance: Breaking it Down

- **Efflux**
  - Increased MIC's
  - Less effective versus ketolides
    - Tight ribosomal binding, increased intrinsic activity, poor substrates?
- **23S rRNA or ribosomal mutations**
  - Different L4 mutation
  - Rare

---

Spectrum of Activity Revisited

<table>
<thead>
<tr>
<th></th>
<th>Ery</th>
<th>Clari</th>
<th>Azi</th>
<th>Teli</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S. pneumoniae</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erm (MLS&lt;sub&gt;B&lt;/sub&gt;)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td>mef</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td><strong>S. pyogenes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erm (MLS&lt;sub&gt;B&lt;/sub&gt;)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>±</td>
</tr>
<tr>
<td>mef</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>+</td>
</tr>
</tbody>
</table>
Indications & Therapeutic Uses

<table>
<thead>
<tr>
<th></th>
<th>Ery</th>
<th>Clari</th>
<th>Azi</th>
</tr>
</thead>
<tbody>
<tr>
<td>AECB</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CAP</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>---</td>
<td>x</td>
<td>---</td>
</tr>
<tr>
<td>Otitis media</td>
<td>x</td>
<td>x*</td>
<td>x*</td>
</tr>
<tr>
<td>SSTI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

*FDA approved for pediatrics only

---

Indications & Therapeutic Uses: Telithromycin

• Specifically developed for use in respiratory tract infections (RTIs)
  – ~10% worldwide morbidity/mortality related to RTIs
  – ~75% antibiotic consumption due to RTIs
  – upper RTIs -- common cause of absence from work or school
  – lower RTIs -- can be fatal in high-risk groups


Therapeutic Uses:

• *H. influenzae* is the leading cause of AECB, followed by *S. pneumoniae* and *M. catarrhalis*

Therapeutic Uses:

- *M. catarrhalis* causes AECB, CAP, and sinusitis
- >90% produce β-lactamase


Therapeutic Uses:

- *S. pyogenes* is the most common cause of acute pharyngitis


Therapeutic Uses:

- **S. pneumoniae** is the most common bacterial pathogen in RTIs
- cause of ~500,000 cases of pneumonia/year in the U.S.
- 2-3 million cases of CAP/year in the U.S.
  - ~10 million visits to physicians’ offices
  - ~500,000 hospitalizations
  - ~45,000 deaths


---

**Graph:**

- **MIC** values for different antibiotics and strains of **S. pneumoniae**


---

**Graph:**

- **MIC** values for different antibiotics and strains of **S. pneumoniae**

### Dosing Regimens

<table>
<thead>
<tr>
<th></th>
<th>Ery (po/iv)</th>
<th>Clar (po)</th>
<th>Azi (po/iv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AECB</td>
<td>250mg qid</td>
<td>500mg q12</td>
<td>Z pack**</td>
</tr>
<tr>
<td>CAP</td>
<td>250mg qid</td>
<td>250mg q12</td>
<td>Z pack</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>250mg qid</td>
<td>250mg q12</td>
<td>Z pack</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>---</td>
<td>500mg q12</td>
<td>---</td>
</tr>
<tr>
<td>Otitis media</td>
<td>400/1200mg</td>
<td>7.5mg/kg</td>
<td>30mg/kg</td>
</tr>
<tr>
<td>SSTI</td>
<td>250mg qid</td>
<td>250mg q12</td>
<td>Z pack</td>
</tr>
</tbody>
</table>

*for H. influenzae, 250mg for S. pneumonia and M. pneumoniae
**500mg on day 1, 250mg days 2-5

### Cost

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ery-Tab</td>
<td>500mg bid x10d</td>
<td>$9.32</td>
<td></td>
</tr>
<tr>
<td>ERYC</td>
<td>250mg qid x10d</td>
<td>$32.99</td>
<td></td>
</tr>
<tr>
<td>E-Mycin</td>
<td>250mg qid x10d</td>
<td>$19.99</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biaxin</td>
<td>500mg bid x10d</td>
<td>$86.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>250mg bid x10d</td>
<td>$88.99</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zithromax</td>
<td>Z-Pak</td>
<td></td>
<td>$42.99</td>
</tr>
</tbody>
</table>

www.walgreens.com

### What does this all mean?

- Pharmacodynamics of ketolides support once-daily dosing
- Comparable adverse effects for ketolides versus macrolides
- Ketolides show good activity versus common respiratory tract pathogens
- Ketolides represent good empirical choice for RTIs due to coverage and efficacy versus resistant microorganisms
- Ketolides may serve as alternative to fluoroquinolones
HOWEVER…

• New class -- concerns about unknown toxicities and drug interactions, general lack of experience
• Not in guidelines for CAP as a ketolide
• Questions about use as a first-line agent?
• Two tablets -- possible non-adherence
• Only available in oral formulation
• concerns about activity versus *H. influenzae* and *ermB S. pyogenes*
• Cost?

Objectives

• Participant should be able to explain macrolide/ketolide mechanism of action.
• Participant should be able to identify one important pharmacodynamic parameter each for macrolides and ketolides.
• Participant should be able to list three reasons why ketolides may be beneficial over macrolides.