Animal models and PK/PD

Examples with selected antibiotics
Examples of animal models

- Amoxicillin
- Amoxicillin-clavulanate
- Macrolides
- Quinolones
Amoxicillin in mouse thigh infection model

Serum levels following:
- 7 mg/kg subcutaneous dose in renally impaired mice
- 500-mg oral dose in normal human volunteers

40% of dosing interval (3.2 h)

Andes D, Craig WA. AAC 1998, 42:2375
Amoxicillin in mouse thigh infection model

Serum levels following:
- 7 mg/kg subcutaneous dose in renally impaired mice
- 500-mg oral dose in normal human volunteers

Andes D, Craig WA. AAC 1998, 42:2375
Amoxicillin is effective at this dose against strains with MICs of up to 2 mg/L.
Amoxicillin in mouse thigh infection model

Serum levels following
- 7 mg/kg subcutaneous dose in renally impaired mice
- 500-mg oral dose in normal human volunteers

30% of dosing interval (2.4 h)

Amoxicillin is effective at this dose against strains with MICs of up to 2 mg/L:
500 mg human dose tid therefore expected to be as effective or more effective

Amox dosed at 7 mg/kg/8 h

Andes D, Craig WA. AAC 1998, 42:2375
Maximal bactericidal activity of amoxicillin and cefpodoxime with strains of *S. pneumoniae* in mouse thigh model

Craig, W. 2001
AMX/CA efficacy against *S. pneumoniae*

Rat *S. pneumoniae* pneumonia model

<table>
<thead>
<tr>
<th>AMX/CA MIC (µg/ml)</th>
<th>T&gt;MIC (%) of dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>90 mg/kg/d</td>
</tr>
<tr>
<td>4</td>
<td>875/125 mg tid</td>
</tr>
<tr>
<td>8</td>
<td>500/125 mg tid</td>
</tr>
<tr>
<td>2</td>
<td>2000/125 mg bid</td>
</tr>
<tr>
<td>2</td>
<td>1000/125 mg tid</td>
</tr>
</tbody>
</table>

AMX/CA efficacy against *S. pneumoniae*

Rat *S. pneumoniae* pneumonia model

AMX/CA efficacy against *S. pneumoniae*

Rat *S. pneumoniae* pneumonia model

AMX/CA MIC 2 μg/ml
AMX/CA MIC 4 μg/ml
AMX/CA MIC 8 μg/ml

90 mg/kg/d
35-40 mg/kg/d
500/125 mg tid
875/125 mg tid
875/125 mg bid
1000/125 mg tid
2000/125 mg bid

T>MIC (% of dosing interval)

AMX/CA efficacy against *S. pneumoniae*

**Rat *S. pneumoniae* pneumonia model**

- AMX/CA MIC 2 µg/ml
- AMX/CA MIC 4 µg/ml
- AMX/CA MIC 8 µg/ml

Fluoroquinolone unbound AUC:MIC and bacterial killing

Rat *S. pneumoniae* pneumonia model

S. pneumoniae and H. influenzae pneumonia in rats: ED$_{50}$ based on $\geq 3 \log_{10}$ reduction in cfu/lung

AZI, CLARI approved human dosing provides PK similar to approx. 25 mg/kg/d in this model

Adapted from Mitten et al. Antimicrob Agents Chemother 2001; 45: 2585–2593
**S. pneumoniae** and **H. influenzae** pneumonia in rats: 
**ED$_{50}$** based on $\geq 3 \log_{10}$ reduction in cfu/lung

![Graph depicting ED$_{50}$ for S. pneumoniae and H. influenzae](image)

- **ED$_{50}$** (mg/kg/d)
- **MIC** (µg/ml)

- **AZI SP**
- **CLARI SP**
- **AZI HI**
- **CLARI HI**

**H. influenzae**

- Macrolide resistant **S. pneumoniae** (efflux)

**ED$_{50}$** of macrolide resistant **S. pneumoniae**: $>100$ mg/kg/d

Adapted from Mitten et al. *Antimicrob Agents Chemother* 2001; 45: 2585–2593
S. pneumoniae and H. influenzae pneumonia in rats: ED_{50} based on $\geq 3 \log_{10}$ reduction in cfu/lung

AZI, CLARI at approved human dosing are effective against macrolide susceptible pneumococci, but are not effective against H. influenzae or macrolide resistant pneumococci

Adapted from Mitten et al. Antimicrob Agents Chemother 2001; 45: 2585–2593
Conclusions

- In vitro testing provides useful information that can be correlated with results of animal infection models and human infections.
- Animal models can detect small differences in MICs based on correlations with appropriate PK/PD parameters (T>MIC or AUC:MIC ratio).