The case against MIC
- Better decisions with pharmacometrics and systems approaches

Elisabet Nielsen
Pharmacometrics Research Group
Department of Pharmaceutical Biosciences
Uppsala University - Sweden
Approaches for PKPD assessment

“A PKPD model describes the \textbf{time course} of the effect in response to administration of a drug dose”

Pharmacometrics and systems approaches

- Characterize
  - the time course of Pharmacokinetics
  - the time course of Pharmacodynamics
- Use the models to perform predictions and to support decisions
  - bacterial killing and selection of resistance to support dosing decisions
- Make use of all available data and accumulate knowledge
Minimum Inhibitory Concentration (MIC)

- Start inocula (5x10^5 CFU/ml)
- Static antibiotic concentrations
- Incubate 37°C, 16-20 hrs
- MIC defined as the lowest static drug concentration that inhibits visible growth

Translation to dosing decisions unclear!
Pharmacometric approach vs MIC

Time-kill experiments

- Moxifloxacin
- Vancomycin
- Benzylpenicillin
- Cefuroxime
- Erythromycin

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Moxifloxacin</th>
<th>Vancomycin</th>
<th>Benzylpenicillin</th>
<th>Cefuroxime</th>
<th>Erythromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0625 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.125 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64 x MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pharmacometric approach vs MIC

Pharmacometric approach

Bacterial specific params
\( k_{\text{growth}}, k_{\text{death}}, B_{\text{max}} \)

Drug specific params
\( E_{\text{max}}, EC_{50}, \gamma \)

Observed and model predicted bacterial count (CFU/ml)

Time (h)
Pharmacometric approach vs MIC


Static drug concentration

Dynamic drug concentration

Observed and model predicted bacterial count (log CFU/ml)

Time (h)
Pharmacometric approach vs PK/PD index

Pharmacometric approach:
- Patient PK and PKPD model
- Simulate dose fractionation study
- Predicted bacterial count at 24h

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC</th>
<th>0 x MIC</th>
<th>0.0625 x MIC</th>
<th>0.125 x MIC</th>
<th>0.25 x MIC</th>
<th>0.5 x MIC</th>
<th>1 x MIC</th>
<th>1.5 x MIC</th>
<th>2 x MIC</th>
<th>4 x MIC</th>
<th>8 x MIC</th>
<th>16 x MIC</th>
<th>32 x MIC</th>
<th>64 x MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moxifloxacin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benzylpenicillin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cefuroxime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Erythromycin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Observed and model predicted bacterial count (CFU/ml) vs Time (h)
Pharmacometric approach vs PK/PD index

Simulated dose fractionation study

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Class</th>
<th>PK/PD index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td>β-lactam</td>
<td>( T_{&gt;MIC} )</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>β-lactam</td>
<td>( T_{&gt;MIC} )</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Macrolide</td>
<td>( \frac{AUC}{MIC} (T_{&gt;MIC}) )</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Fluoroquinolone</td>
<td>( \frac{AUC}{MIC} )</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Glycopeptide</td>
<td>( \frac{AUC}{MIC} )</td>
</tr>
</tbody>
</table>

PKPD models – predictive of PK/PD indices

Is the PK/PD index sensitive to the PK profile?

Pharmacometric approach vs PK/PD index

Simulated dose fractionation study

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Class</th>
<th>PK/PD index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td>β-lactam</td>
<td>$T_{&gt;\text{MIC}}$</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>β-lactam</td>
<td>$T_{&gt;\text{MIC}}$</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Macrolide</td>
<td>AUC/MIC ($T_{&gt;\text{MIC}}$)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Fluoroquinolone</td>
<td>AUC/MIC</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Glycopeptide</td>
<td>AUC/MIC (or $T_{&gt;\text{MIC}}$)</td>
</tr>
</tbody>
</table>

**Benzylpenicillin**

PK Adults – $T_{>\text{MIC}}$

PK Newborn – AUC/MIC

The selection & target PK/PD index might change due to PK differences

Pharmacometric approach vs PK/PD index

In vivo
Dose fractionation study
Meropenem
P. aeruginosa 12467

In silico replication
P. aeruginosa ATCC27853
Kristoffersson et al.

**Pharmacometric approach vs PK/PD index**

**Meropenem**

**Typical:**
Adult, CrCL=100 ml/min
2-comp PK, $t_{1/2,\beta} \sim 1.4$ h
(Li et al, J Clin Pharmacol 2006)

**Augmented CL:**
Adult, CrCL=250 ml/min
2-comp PK, $t_{1/2,\beta} \sim 0.9$ h
(Li et al, J Clin Pharmacol 2006)

**Renal dysfunction:**
Adult, CrCL=15 ml/min
2-comp PK, $t_{1/2,\beta} \sim 3.5$ h
(Li et al, J Clin Pharmacol 2006)

**Preterm neonate:**
GA 31w
2-comp PK, $t_{1/2,\beta} \sim 2.0$ h
(van den Anker et al, AAC 2009)

---

Pharmacometric approach vs PK/PD index

- Pharmacometric models are predictive of PK/PD indices
  - when replicating the same PK profile

- The selection & target PK/PD index might not be consistent across PK profiles
  - indicates that the indices might not translate well between populations

- Advantage of a pharmacometric approach
  - PK model is kept as an independent part in the overall model
  - No need to select (one or more) PK/PD indices
Benefits of pharmacometrics and systems approaches

- Characterize the full time-course of the Pharmacodynamics
  - Efficacy assessments at different time points (not only 24h)
  - Efficacy for susceptible bacteria
  - Efficacy for less-susceptible bacteria (heteroresistance)
  - Changes in susceptibility (adaptive resistance)
  - Effect of drug combinations (additive, synergy or antagonism)

- Make use of all available data and accumulate knowledge
  - Of special importance for efficacy assessments for antimicrobials, where clinical data is generally poor in information content (cure/no cure)
Benefits of pharmacometrics and systems approaches

- Clinical gentamicin PK study
  - 894 samples, 61 neonates
  - Population PK model
- *In vitro* PD data
  - Static time-kill exp.
  - Dynamic time-kill exp.
  - Single and repeated dosing

Benefits of pharmacometrics and systems approaches

Acknowledgements

Pharmacometrics group, Uppsala University, Sweden
Roche Pharma Research and Early Development, Innovation Center Basel
Stiftelsen för Strategisk Forskning (SFF)

Thanks to:
• Lena Friberg
• Mats Karlsson
• Otto Cars
• Dan Andersson
• Diarmaid Hughes
• Ami Mohamed
• Anders Kristoffersson
• David Khan
• Waqas Sadiq