Mouse Models for Antibacterial PK/PD

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Disclosures

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• Member ABIM
Outline

- What PK/PD questions can the models address?
- What study variables impact PK/PD answers?
- Can the model PK/PD results predict clinical efficacy?
Why do we conduct PK-PD infection models?
Improving the Probability of Positive Outcome

Bug → Drug → Host → Bug
What do we do?
Tie Drug Potency to Antimicrobial Exposure = Pharmacodynamics

MIC = minimum inhibitory concentration; AUC = area under the curve; T = time

- **MIC**
- **Peak:MIC**
- **AUC:MIC Ratio**
- **Time Above MIC**

**Legend:**
- **MIC** = minimum inhibitory concentration; **AUC** = area under the curve; **T** = time
In vivo PK/PD Work Horse(s)

• Murine thigh and lung models
  – Mimics soft tissue/sepsis and pneumonia, respectively
  – Neutropenic
  – Organism burden primary endpoint
  – Supports growth of most bacteria
  – Multiple drug administration routes
  – Large group of comparator antibacterial agents
  – Outcomes correlated with treatment success in patients
  – Useful for trial dosing regimen selection and susceptibility breakpoint development
Study Design

-2 hr

Antibiotic Therapy

24 hr

Infect

Dose (mg/kg/24 h)

Change in Log_{10} CFU/Thigh over 24 Hours

Pharmacodynamic Analysis

Bacterial Burden Assessment
How do we determine how much and how often to administer an antibiotic?
PK/PD Driver – Dose or Interval

Dose Level

Dosing Frequency
Dose Fractionation Design

Change in $\log_{10}$ CFU/Thigh

Dose (mg/kg/24 h)

-3
-2
-1
0
1
2
3
4
5

q3
q6
q12
q24

Dose Fractionation Analysis

## PK/PD Patterns Activity

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Antibacterial</th>
<th>Dosing Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concentration-dependent killing and prolonged persistent effects</strong></td>
<td>Quinolones, Aminoglycosides, Ketolides, and Daptomycin</td>
<td>Maximize concentrations; Cmax/MIC or AUC/MIC</td>
</tr>
<tr>
<td><strong>Time-dependent killing and minimal or no persistent effects</strong></td>
<td>Beta-lactams</td>
<td>Optimize duration of exposure; %T&gt;MIC</td>
</tr>
<tr>
<td><strong>Time-dependent killing and moderate to prolonged persistent effects</strong></td>
<td>Macrolides, Azithromycin, Clindamycin, Tetracyclines, Glycylcyclines, Glycopeptides, Glycopeptides, Oxazolidinones</td>
<td>Optimize amount of drug; AUC/MIC</td>
</tr>
</tbody>
</table>
Dose fractionation in the mouse models reliably defines the PK/PD driver.
How do we define the PK/PD target?

Dose Level
Nonlinear regression and Hill equation to estimate Emax (difference from untreated control), P50 (dose giving 50% of Emax) and slope (N) of the dose-response relationship.

\[ \Delta \text{CFU} = \frac{(E_{\text{max}}) \text{Dose}^N}{\text{Dose}^N + P_{50}^N} \]

Introduce additional isolates, preferably with MIC variation.
PK/PD Target Variables

- Protein Binding
- Pharmacokinetics
- Infection Site
- Strain Variability
- MIC Variability
- Resistance Mechanism

Right Dose
PK/PD Target
Impact of Strain to Strain Variation on the PK/PD Target

Strain Variability

Change in Log10 CFU/Thigh

Time Above MIC (%)
Impact of Strain to Strain Variation on the PK/PD Target

E_{\text{max}} 7.7
E_{\text{D50}} 37.1
N 1.51
R^2 0.80

<table>
<thead>
<tr>
<th>Organism</th>
<th>Stasis %T &gt; MIC</th>
<th>1 log kill %T&gt;MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>47</td>
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<tr>
<td>6</td>
<td>37</td>
<td>43</td>
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<tr>
<td>7</td>
<td>35</td>
<td></td>
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<tr>
<td>8</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>29</td>
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<tr>
<td>10</td>
<td>28</td>
<td>43</td>
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<tr>
<td>11</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>37</td>
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<tr>
<td>13</td>
<td>32</td>
<td>39</td>
</tr>
<tr>
<td>14</td>
<td>27</td>
<td>37</td>
</tr>
<tr>
<td>Mean</td>
<td>31</td>
<td>39</td>
</tr>
<tr>
<td>Median</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>SD</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>%CV</td>
<td>0.19</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Strain Variability
Impact of MIC Variation on the PK/PD Target

MIC (mg/L):

- 0.008
- 0.03
- 0.12
- 0.5
- 2
- 8

T>MIC (%):

- 0
- 10
- 20
- 30
- 40
- 50

- Cephalosporins
- Penicillins
- Carbapenems

N=65, >1000 X MIC range

MIC Variability
Impact of Resistance and ESBL Production

Change in $\log_{10}$ CFU/Thigh over 24 Hours

Time Above MIC (percent)

N=20 organisms, 4 cephalosporins

Impact of Resistance and ESBL Production

Impact of Protein Binding

24-Hr AUC/MIC

- Gati: Total 23%, Free 23%
- Sita: Total 30%, Free 30%
- Moxi: Total 50%, Free 50%
- Gemi: Total 67%, Free 25%
- Garen: Total 78%, Free 25%
- Levo: Total 25%, Free 25%
- Cipro: Total 25%, Free 25%

Protein Binding

Andes & Craig  40th and 41st ICAAC, 2000 and 2001
Impact of Infection Site

Tedezolid fAUC/MIC

- Lung
- Thigh

Oxazolidinone and MRSA

Infection Site

Mouse ELF: Blood Penetration > 10

Lepak AAC 2012;56:5916
Louie AAC 2011;55:3453
Impact of Infection Site

Pharmacokinetics

- Plasma Total Drug
- Plasma Free Drug
- ELF Total Drug
Impact of Infection Site

Impact of Infection Site on AUC/MIC and Change in Log10 CFU/Organ.

- Lung ELF AUC/MIC
- Thigh plasma fAUC/MIC

Pharmacokinetics & Infection Site

Graph showing the relationship between AUC/MIC and log10 CFU/Organ change.
## ELF/Plasma Penetration: Mouse and Man

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mouse ELF:Plasma Ratio</th>
<th>Man ELF:Plasma Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftibiprole</td>
<td>0.69</td>
<td>0.26</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.60</td>
<td>0.80</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.77</td>
<td>1.16</td>
</tr>
<tr>
<td>Tedezolid</td>
<td>10</td>
<td>2-4</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>10-20</td>
<td>1.12</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1.0</td>
<td>0.30-0.85</td>
</tr>
</tbody>
</table>
### In vivo PK/PD Target Identification

 (>100 individual drugs)

<table>
<thead>
<tr>
<th>Penicillins</th>
<th>Aminoglycosides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Aztreonem</td>
<td>Ketolides</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Polyenes</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>Plectasins</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Macrolides</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>Oxazolidinones</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Triazoles</td>
</tr>
<tr>
<td>Glycylcyclines</td>
<td>Beta peptides</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Pleuromutalins</td>
</tr>
</tbody>
</table>
Mouse models can define the PK/PD target, but there are important variables to consider.
Let’s put this pre-clinical PK-PD in context with clinical efficacy
Why Does This Work?

Despite:

- Different doses (mg/kg)
- Faster half-life in small animals

BUT:

- Drug target is in the organism and NOT the host
- Exposure relative to MIC is the determinant
PK-PD INFECTION MODELS
Do They Forecast Success?

Preclinical data: Craig/Andes
PK-PD INFECTION MODELS
Do They Forecast Success?

Preclinical data: Craig/Andes
PK-PD INFECTION MODELS
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Preclinical data: Craig/Andes

Surveillance data: EUCAST (2016). MIC distributions and ECOFFs.


PK-PD INFECTION MODELS  
Do They Forecast Success?


Surveillance data: EUCAST (2016). MIC distributions and ECOFFs.


PK-PD INFECTION MODELS

Do They Forecast Success?

• Relationship between the regulatory approval and the probability of pre-clinical PK-PD target attainment
  o The study period was December 1996 through 2011
• Indications included community- and hospital-acquired pneumonia
  o For CAP, S. pneumoniae was the index pathogen
  o For HAP, the index pathogen was antibiotic spectrum dependent
  o 14 antibiotics that gained regulatory approval and 6 that failed to gain approval

- Cefditoren
- Ceftaroline
- Ceftobiprole
- Daptomycin
- Doripenem
- Ertapenem
- Faropenem
- Garenoxacin
- Gatifloxacin
- Gemifloxacin
- Levofloxacin
- Linezolid
- Moxifloxacin
- Televancin
- Teilithromycin
- Tigecycline
- Trovafloxacin

From ICPD
PK-PD INFECTION MODELS

Do They Forecast Success?

The Answer: Yes! The probability of regulatory approval increases with the probability of PK-PD target attainment.

Note: PK-PD target was net-bacterial stasis in neutropenic mice for CAP agents and 1-2 log_{10} unit reduction in bacterial burden for HAP agents.
But, A Mouse is Not a Human

- **Host susceptibility**
  - Difference in lung anatomy
  - Different pattern recognition receptors
  - Lower pulmonary WBC and no defensins

**RESULT**
- Variable susceptibility to human lung pathogens

- **Pharmacokinetics**
  - Penetration into AM and ELF sometimes, but not often same as humans
Murine infection models can be used to forecast effective regimens in patients
“It all started with a mouse.”
- Walt Disney