Integration of Target Site Pharmacokinetics and \textit{in-vitro} Pharmacodynamics in the Assessment of Existing and New Anti-Infictive Agents

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Resistance Development

Source: Centers for Disease Control and Prevention

This chart shows the increase in rates of resistance for three bacteria that are of concern to public health officials: methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant Pseudomonas aeruginosa (FQRP). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC.
Approved Antibacterial Agents
1983-2004

Source: Spellberg et al., Clinical Infectious Diseases, May 1, 2004 (modified)
Figure 3: Investment Escalation per Successful Compound

Investment required for one successful drug launch (discovery through launch)


The figure shows one estimate of the total investment required to "launch" (i.e., market) a successful drug in two time periods. Most of the recent cost increases are within the "critical path" development phase, between discovery and launch.
Pharmacokinetics
conc. vs time

Pharmacodynamics
conc. vs effect

PK/PD
effect vs time
**Time above MIC**

- Concentration (µg/mL)
  - 0
  - 8
  - 12
  - 16
- MIC
- Time (hours)
- t > MIC

**AUC<sub>24</sub>/MIC**

- Concentration (µg/mL)
  - 0
  - 4
  - 8
  - 12
  - 16
- MIC
- Time (hours)

**C<sub>max</sub> / MIC**

- Concentration (µg/mL)
  - 0
  - 4
  - 8
  - 12
  - 16
- MIC
- Time (hours)
- C<sub>max</sub>

**PK**

- Serum

**PD**

- MIC
Pharmacokinetics

Problems:

• Protein Binding

• Tissue Distribution
# Protein Binding of Cephalosporines

<table>
<thead>
<tr>
<th>Cephalosporine</th>
<th>Protein Binding</th>
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<tbody>
<tr>
<td>Cefonicid</td>
<td>98</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>90-95</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>89-93</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>89</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>85</td>
</tr>
<tr>
<td>Ceforanide</td>
<td>80-82</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>74</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>73</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>71</td>
</tr>
<tr>
<td>Cefmetazole</td>
<td>70</td>
</tr>
<tr>
<td>Cefixime</td>
<td>65</td>
</tr>
<tr>
<td>Cephapirin</td>
<td>62</td>
</tr>
<tr>
<td>Moxalactam</td>
<td>53-67</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>40</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>36</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>25</td>
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Effect of Protein Binding on Antimicrobial Activity

MICs of Staphylococcus aureus (Data from Kunin et al. (1973))

- MIC Broth
- MIC Serum
- $C_f$ for MIC Serum

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>$f_b$</th>
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<tbody>
<tr>
<td>AMPI</td>
<td>0.22</td>
</tr>
<tr>
<td>METHI</td>
<td>0.37</td>
</tr>
<tr>
<td>BENZ</td>
<td>0.65</td>
</tr>
<tr>
<td>NAF</td>
<td>0.90</td>
</tr>
<tr>
<td>OXA</td>
<td>0.93</td>
</tr>
<tr>
<td>CLOXO</td>
<td>0.95</td>
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vascular space

- plasma protein binding
- blood cell binding, diffusion into blood cells, binding to intracellular biological material

extravascular space

- binding to extracellular biological material
- tissue cell binding, diffusion into tissue cells, binding to intracellular biological material
Tissue Concentrations

Tissue can be looked at as an aqueous dispersed system of biological material. It is the concentration in the water of the tissue that is responsible for pharmacological activity.

Total tissue concentrations need to be interpreted with great care since they reflect hybrid values of total amount of drug (free + bound) in a given tissue.

‘Tissue-partition-coefficients’ are not appropriate since they imply homogenous tissue distribution.
We continue ... to extend our long-standing interest in the application of dose-response principles by viewing drugs and their actions directly at the level of the drug target, rather than indirectly via plasma concentrations
Lazy
The **free (unbound) concentration** of the drug **at the receptor site** should be used in PK/PD correlations to make prediction for pharmacological activity.
Blister Fluid

- Blister fluid is a ‘homogenous tissue fluid’
- Protein binding in blister fluid needs to be considered
Ampicillin

Cloxacillin

- Serum
- Free blister fluid
Microdialysis

- Microdialysis allows to monitor the free tissue concentrations.
No net flux method

If $C_{in} > C_T$, then $C_{out} < C_{in}$
If $C_{in} < C_T$, then $C_{out} > C_{in}$
Cefpodoxime (Protein binding 17-30%)

Cefixime (Protein binding 65%)
iv dose of 10 mg/kg cefpodoxime (n=6)
Summary

Animal Studies

• Free concentrations in muscle and lung are almost identical and much lower than the total plasma concentrations.

• It suggests that free concentrations measured in human muscle maybe reasonable predictors for free concentrations in human lung.
Clinical study
Cefpodoxime and Cefixime

• To compare the soft tissue distribution of these two antibiotics after 400mg oral dose in healthy male volunteers by microdialysis

• Two way cross-over, single oral dose study
Microdialysis
Clinical Microdialysis

Cefpodoxime
400 mg po

Cefixime
400 mg po

# Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cefpodoxime</th>
<th>Cefixime</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_P$ [mg*h/L]</td>
<td>22.4 (8.7)</td>
<td>25.7 (8.4)</td>
</tr>
<tr>
<td>$\text{AUC}_T$ [mg*h/L]</td>
<td>15.4 (5.2)</td>
<td>7.4 (2.1)</td>
</tr>
<tr>
<td>$C_{\text{max},P}$ [mg/L]</td>
<td>3.9 (1.2)</td>
<td>3.4 (1.1)</td>
</tr>
<tr>
<td>$C_{\text{max},T}$ [mg/L]</td>
<td>2.1 (1.0)</td>
<td>0.9 (0.3)</td>
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</table>
Azithromycin
Tissue Concentrations

500 mg p.o. from Foulds et al. (1990)
Intracellular Ion-Trapping by Lysosomes

Extralysosomal Space

BH⁺  

Lysosome

BH⁺  

B

pH 7.4  

pH 5.0

BH⁺  

B
Tissue concentration (IF) of azithromycin (50 mg/kg sc) in infected (S. aureus) and uninfected rat thigh (same animal)

AUC = 3,528 vs 4,398
P<0.01

Scaglione et al., ICAAC 2006
Phagocyte Delivery of Azithromycin

- Phagocytes absorb azithromycin in circulation and tissue.
- WBCs migrate to sites of infection in tissues.
- Phagocytes release azithromycin in response to bacteria.

A = azithromycin

from Schentag et al. (1991)
Conclusion

Microdialysis has opened the door to get better information about the drug concentrations at the site of action.

This, in combination with appropriate PK/PD-models, will allow for better dosing decisions than traditional approaches based on blood concentrations and MIC.
Ceftazidime
K. pneumoniae in neutropenic mice

Craig 2002
Temafloxacin
S. pneumoniae in neutropenic mice

Craig 2002
Pharmacodynamics

Problems:

• MIC is imprecise
• MIC is monodimensional
• MIC is used as a threshold
• When MIC does not explain the data, patches are used (post-antibiotic effect, sub-MIC effect)
MIC
The Current Paradigm

MIC is poison for the mind.

H. Mattie (1994), after a long after-dinner discussion
Kill Curves
Kill Curves of Ceftriaxone

**S. pneumoniae ATCC6303**
MIC: 20 ng/mL

**H. influenzae ATCC10211**
MIC: 5 ng/mL
Kill Curves of Ceftriaxone

**S. pneumoniae ATCC6303**
MIC: 20 ng/mL

**H. influenzae ATCC10211**
MIC: 5 ng/mL
PK-PD Model

\[
\frac{dN}{dt} = \left( k - \frac{k_{\text{max}} \cdot C_f}{E C_{50} + C_f} \right) \cdot N
\]

Maximum Growth Rate Constant \( k \)
Maximum Killing Rate Constant \( k-k_{\text{max}} \)

Initially, bacteria are in log growth phase
Single Dose
Piperacillin vs. E. coli

![Graph showing CFU/mL vs. Time (h) for different doses of Piperacillin vs. E. coli control.]
Dosing Interval
Piperacillin (2g and 4g) vs. E. coli

q24h

q8h

q4h
Sigmoidal $E_{\text{max}}$-Models

The graph shows the relationship between log CFU/mL and time (h). The axes are labeled as follows:

- **Log CFU/mL** on the vertical axis (y-axis)
- **Time (h)** on the horizontal axis (x-axis)

Key parameters and terms include:

- **MIC**
- **SC**
- **EC$_{50}$**
- **$k_s$**
- **$k_{\text{max}}$**

The graph depicts how different concentrations (represented by $k_s$ and $EC_{50}$) affect the log CFU/mL over time.
Saturation in Growth

\[
\frac{dN}{dt} = k_s \cdot \left( 1 - \frac{N}{N_{\text{max}}} \right) \cdot N
\]
Delay in the Onset of Growth

\[
\frac{dN}{dt} = k_s \cdot (1 - e^{-d_{g,t}}) \cdot N
\]
Delay in the Onset of Kill

\[
\frac{dN}{dt} = \left( k_s - \frac{k_{\text{max}} \cdot C^h}{EC_{50}^h + C^h} \cdot \left(1 - e^{-dk \cdot t}\right) \right) \cdot N
\]
Modified Sigmoidal $E_{\text{max}}$-Model

\[
\frac{dN}{dt} = \left( k_s \cdot \left( 1 - \frac{N}{N_{\text{max}}} \right) \cdot \left( 1 - e^{-d_g \cdot t} \right) - \frac{k_{\text{max}} \cdot C^h}{EC_{50}^h + C^h} \cdot (1 - e^{-d_k \cdot t}) \right) \cdot N
\]

Example 1

- Same PK
- Same MIC
- Same $t > \text{MIC}$
- Same $\text{AUC}/\text{MIC}$
- Same $\text{C}_{\text{max}}/\text{MIC}$
- Same $k$ (Growth Rate)

- Different $\text{EC}_{50}$ (Sensitivity)
- Different $k_{\text{max}}$ (Maximum Kill Rate)
PK-PD modeling based on Kill Curves

Condition 1

Condition 2

Control (CFU/mL)
Treated (CFU/mL)
Antibiotic concentration
Modified $E_{\text{max}}$ Model:

\[
d\frac{N}{dt} = k - \left( k_1 \cdot \frac{1 - \frac{C_r}{lC_{50} + C_r}}{EC_{50} + C} + k_2 \right) \cdot C \cdot N \cdot \left(1 - e^{-z\cdot t}\right)
\]

\[
C_r = C_0 \cdot \left( e^{-k_e \cdot (t - t_{\text{lag}})} - e^{-\alpha \cdot (t - t_{\text{lag}})} \right)
\]

Comparing to $E_{\text{max}}$ model:

\[
K_{\text{max}} = k_1 \left( 1 - \frac{C_r}{lC_{50} + C_r} \right) + k_2
\]
Two sub-population model

OBS: same growth rate for sensitive (S) and resistant (R)

Growth \( (k_0) \)

Bacteria pool

Bacteria (S)

Bacteria (R)

Drug (C)

Killing

\( f_s(C) \)

\( f_r(C) \)
**Model Comparison – *P. aeruginosa***

**P. aeruginosa**

Modified $E_{\text{max}}$ model (simultaneous fit)

**P. aeruginosa (MIC = 0.15 mg/L)**

Two sub-population model (simultaneous fit)
After oral administration, faropenem daloxate is rapidly absorbed and immediately converted in plasma to its active moiety faropenem.

Advantages of using the pro-drug instead of faropenem sodium:
- higher oral bioavailability (70-80%)
- less gastrointestinal side effects
450 mg q24

150 mg q8

CFU Change

C (mg/L)

0 2 04 0 6 0 8 0

t (h)

0 1 10 100 1000 10000

C (mg/L)

0 2 04 0 6 0 8 0

t (h)

0 1 10 100 1000 10000

CFU Change

C (mg/L)

0 2 04 0 6 0 8 0

t (h)

0 1 10 100 1000 10000

CFU Change

C (mg/L)

0 2 04 0 6 0 8 0

t (h)

0 1 10 100 1000 10000
Faropenem daloxate
300 mg q12h

Fed

Fasted
Faropenem daloxate
300 mg q12h
Fed

S. pneumo. #49619

Fasted
MIC$_{90}$ values for Bacteroides fragilis (——), Streptococcus spp. (······), methicillin-susceptible Staphylococcus aureus (----), and ESBL-producing Enterobacteriaceae (······).

Burkhardt & Derendorf, JAC (2006)
Summary

- A **simple comparison** of serum concentration and MIC is usually **not sufficient** to evaluate the PK/PD-relationships of anti-infective agents.

- **Protein binding** and **tissue distribution** are important pharmacokinetic parameters that need to be considered. **Microdialysis** can provide information on local exposure.

- PK-PD analysis based on MIC alone can be misleading.

- Microbiological **kill curves** provide more detailed information about the PK/PD-relationships than simple MIC values.
Proposal

Wild Card Patent Extension

A company that receives approval for a new antibiotic, or a new indication for an existing antibiotic, that treats a targeted pathogen would be permitted to extend the market exclusivity period for another of the company’s FDA-approved drugs.
## Acknowledgements

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