Pharmacodynamic Modeling of Antibiotic Behavior

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Objectives
- Participant will be able to define the difference between concentration dependent and concentration independent killing of bacteria by antibiotics.
- Participant will be able to state three advantages of in-vitro pharmacodynamic modeling over the use of animal models or human clinical trials.
- Participant will be able to identify three antibiotic pharmacodynamic outcome parameters.
- Participant will be able to identify three clinical areas where antibiotic pharmacodynamic concepts are likely to be applied.

Overview Pharmacodynamic Modeling Practices
- Define PD terms & concepts
- In-vitro models
- Animal models
- Human trials
- Applying pharmacodynamics to fluoroquinolones
- Clinical use of pharmacodynamics
**Pharmacokinetics vs Pharmacodynamics**

Pharmacokinetics - mathematically describes the relationship of antibiotic concentration vs time (half-life, distribution volume, AUC, etc.)

Pharmacodynamics - describes the relationship of antibiotic concentration vs pharmacologic effect or bacterial death (PD Outcome Parameters)

- Pre-clinical & through Phase I - Phase IV
- In-vitro ↔ Animal ↔ Human

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**Concentration Independent or Time Dependent Bacterial Killing**

![Graph showing bacterial killing](image)

- Rate & extent of bacterial kill essentially unchanged regardless of antibiotic concentration

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**Concentration Dependent or Time Independent Bacterial Killing**

![Graph showing bacterial killing](image)

- Rate & extent of bacterial killing a function of antibiotic concentration

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Concentration Dependent vs Concentration Independent

- Can we use one term to describe antibiotic performance against all bacteria?
  - Gram positive vs Gram negative vs Anaerobes vs Atypicals:
    - Different or no cell wall
    - Altered influx and/or efflux
    - Potentially same antibiotic target but likely different binding efficiency
  - Can same pharmacodynamic parameter and range of values be used for all pathogens and all infections?

Pharmacodynamic Outcome Parameters

- **AUC/MIC**
  - Free Drug
  - **Cp-max/MIC**
  - **T>MIC**

Proposed Pharmacodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&gt;MIC</td>
<td>β-lactams, macrolides, aztreonam, carbapenems &amp; clindamycin</td>
</tr>
<tr>
<td>AUC/MIC</td>
<td>Aminoglycosides, fluoroquinolones, azithromycin, tetracyclines, vancomycin &amp; telithromycin quinupristin/ dalfopristin</td>
</tr>
<tr>
<td>Cp-max/MIC</td>
<td>Aminoglycosides &amp; fluoroquinolones</td>
</tr>
</tbody>
</table>

*Covariance of parameters with antibiotic dose
Fluoroquinolone Pharmacodynamic Outcome Parameters

- Gram Negatives
  - AUC/MIC ratio ≥ 125
- S. pneumoniae
  - AUC/MIC ratio ≥ 25-50
- Anaerobes
  - AUC/MIC ratio ≥ 50

Wright D. JAC 46:669-683, 2000

ICAAC Pharmacodynamics Consensus Forum September 2002

- FQ AUC/MIC breakpoint for gram negatives
  - 204/312 (65.4%) said AUC/MIC of 100-125
- FQ AUC/MIC breakpoint for S. pneumoniae
  - 125/296 (42.2%) said AUC/MIC of 35
  - 27.7% said AUC/MIC of 50
  - Only 63/296 (21.3%) said AUC/MIC of 100-125
- T>MIC Beta-lactam breakpoint
  - 209/312 (67%) said T>MIC = 50% dosing interval

In-vitro Modeling


- Provides a reproducible environment to quickly & inexpensively answer therapeutic questions
- Can manipulate both Cp-max and drug clearance simultaneously
- Can address situations where clinical data is likely to be extremely limited or impractical
  - PCN-R S. pneumoniae
  - Anthrax, HIV, etc
- Generic antibiotics
  - Can test a wide range of parameter values without concern for therapeutic failure or ADR
- Means to address parameter covariance
- Can pursue academic questions that cannot be pursued in humans
In vitro Pharmacodynamic Model

In vitro Pharmacodynamic Model

In-Vitro Modeling Variables
- Evaluation of bacterial regrowth
- Pharmacodynamic outcome parameters
- Optimal range of data for identifying outcome parameter/s
- Fitting data to mathematical models
- Handling data after 3 Log Kill
- Appropriate use of descriptive and inferential statistics for small data sets
Which Pharmacodynamic Parameter is Most Important?
- **Cp-max / MIC ratio vs AUC / MIC ratio?**
- Can such differences & distinctions in pharmacodynamic parameters really be addressed in human studies?
  - Inclusion criteria limit patient variability
  - All patients are similarly dosed
  - Variety of infections being treated
  - Variable conditions & environment
  - Diversity of pathogens

Which is better AUC/MIC or Cpmax/MIC?

- Use different Cpmax & t1/2 to produce same AUC but Peak/MIC different

**AUC/MIC \sim 250**

**Ciprofloxacin vs P. aeruginosa**

Animal Model Limitations

- How well does “infection model” emulate human infection
  - Acute vs. Chronic
  - Thigh vs other body sites
- Species variability (animal, age, genetics, etc)
- Immune status
  - Agent used to suppress immune system
  - Timing and level of pre-suppression
- Inoculum size
- Bacterial isolate(s) used (MIC, level of virulence, etc)
- Drug dose and frequency (how well does it emulate the human host)
  - Pharmacokinetic variability
- Adequate range of dose or pharmacokinetic parameters
- Manipulation of drug clearance

Animal Model Limitations

- Time interval between creating infection and treatment
- Route of administration
- Antibiotic dosage form or formulation
- Duration of treatment
- Duration of follow-up
- Endpoint
- Method of processing samples

Human Clinical Trial Limitations

- Inclusion and exclusion criteria tend to “standardize patient”
- Empiric dosing regimens produce limited variability in serum-concentration-time curves and pharmacokinetic parameters
- Limited range or unequal weighting of values for pharmacodynamic parameters
- Each patient is somewhat unique in the severity and scope of infection
- Treat different infections with a variety of pathogens in same clinical trial
- Tend to mix patients with different infections and pathogens into the pharmacodynamic evaluation
- Difficult to control for other clinical interventions
Applications of Pharmacodynamics

Potential Applications of Pharmacodynamics
- Tool in the antibiotic development process
- Part of marketing strategy in the detailing of antibiotics
- Parameter for antibiotic formulary selection
- Patient specific management tool
- Clinical gauge for the development of bacterial resistance

E-Max Model
- Concentration Range with Commercial Dosage Forms
- Bacterial Killing
- Toxic Effects
- Antibiotic Concentration
Pharmacodynamics & Antibiotic Development

- Apriori identify effect of all variables (pH, %PB, etc) on antibiotic performance
- Can help in decision to move forward or abandon antibiotic development
- Identify nature of antibiotic performance against specific pathogens of interest

Fluoroquinolone Serum AUC/MIC Ratios

<table>
<thead>
<tr>
<th></th>
<th>AUC-24</th>
<th>MIC (mg/L)</th>
<th>2.0</th>
<th>1.0</th>
<th>0.5</th>
<th>0.25</th>
<th>0.125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>32/22</td>
<td>11</td>
<td>22</td>
<td>44</td>
<td>88</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>75/50</td>
<td>25</td>
<td>50</td>
<td>100</td>
<td>200</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>48/24</td>
<td>12</td>
<td>24</td>
<td>48</td>
<td>96</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>51/41</td>
<td>21</td>
<td>41</td>
<td>82</td>
<td>124</td>
<td>328</td>
<td></td>
</tr>
</tbody>
</table>

- AUC function of dose & interval, higher in patients vs volunteers
- AUC values corrected for extent of protein binding,
- * T=total AUC-24 hrs & F=free AUC-24 hrs

Pharmacodynamics & Marketing

- Easy to “manufacture” data
- Mixture of some science and a lot of marketing
- Creditability can be compromised if you are wrong
- Prescribers might actually put into practice what you tell them

The AUC/MIC or AUIC Concept

- Retrospective evaluation of 74 patients with LRTI treated with intravenous Ciprofloxacin
- 82% of pathogens Gram negative
- 15% S. aureus (50% received concomitant rifampin)
- AUC/MIC ratio > 125 minimal breakpoint for clinical and microbiological cure
  - AUC/MIC ratio of 250 – 500 better in terms of clinical and microbiologic response

- Prospective evaluation of 313 adult patients with UTIs, respiratory infections, and skin & soft tissue infections (134 with identified org)
- 58% of isolates accounted for by 5 species
- 16% S. pneumoniae & 11% S. aureus
- Levofoxacin (500 mg PO & IV)
- Cp-max/MIC ratio > 10:1 associated with successful clinical & microbiological outcome
  - Cp-max/MIC & AUC/MIC highly correlated (r=0.942)

Pharmacodynamics of *S. pneumoniae*

CID 33:2091-2095, 2001

UIC or AUC / MIC vs. Cp-max / MIC Ratio

UC / MIC > 100-125 for all pathogens?

*S. pneumoniae*

- 20 cases (3 with bacteremia)
- 3 patients AUC/MIC < 50 (Ratio = 25, 1 patient)
- 8 patients AUC/MIC < 100

All patients successfully treated

Sensitivity for AUC/MIC of 100 & 125 were 45% & 40%, respectively

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**Levofloxacin vs. S. pneumoniae**

**AUC/MIC Ratios 40-500**

![Graph showing log CFU/mL over time](image)

- GC
- 40
- 80
- 120
- 150
- 180
- 200
- 250
- 300
- 350
- 500

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**Target Attainment of Satisfactory AUC/MIC Ratio > 30**

- Step 750mg HD AUC/MIC
- Step 500mg LD AUC/MIC

Using Levofloxacin 750mg vs 500mg PK & Trust MIC Data

10,000 Monte Carlo Simulations

Grant, D. & Quintiliani, R., 2003

Higher dose shifts percent of *S. pneumoniae* likely to respond to therapy

AUC/MIC 500mg 750mg

30  92.7%  98.0%
Sample Case Report

- 53 year old male involved in MVA with multiple head & abdominal injuries. Admitted to SICU placed on respirator 8 days ago.
- Patient spikes temperature to 103.5 F
- WBC’s increase to 21,000/mm3 & CXR demonstrates new infiltrate
- Following culture results are returned from BAL specimen obtained ~48 hours ago

Antibiotic Resistant

*P. aeruginosa*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>P. aerug #1</th>
<th>P. aerug #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;4</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;32</td>
<td>32</td>
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<tr>
<td>Imipenem</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Zosyn</td>
<td>&gt;128/4</td>
<td>&gt;128/4</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;16</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;16</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>

Obtained: University of Kentucky, R. Rapp, Pharm. D.
Clinical Case

- 12 yr 50Kg male suffered 68% BSA burn (house fire)
- Hospitalized for 5 months multiple courses of antibiotic including aminoglycosides
  - Scr = 0.9 mg/dl but no lean body mass
  - Previous nephrotoxic episodes with tobramycin
  - Mismatch between age & Scr with tobramycin T1/2
  + BC & SC for P. aeruginosa
- Amikacin 16mg/L, gentamicin 8mg/L, tobramycin 8mg/L, imipenem >16mg/L, P/T >125mg/L, Ceftazidime >32mg/L
- Meropenem R, Ceftazidime >128mg/L (Estrip), & colistin 2mg/L

Started on colistin 5mg/Kg LD then 2.5 mg/Kg QD & ceftazidime LD then 250 mg/hr continuous infusion
- IC with parents
- Colistin pre < 5mg/L, 25 min post 23 mg/L, and 8 hour post < 5 mg/L
- Ceftazidime Cpo = 32 mg/L
- Patient completed ~2wk course of therapy, although the patient had a positive culture for VRE, his BC’s were negative for P. aeruginosa

Pharmacodynamics:

- Most of the pharmacodynamic data available is:
  - In-vitro or animal data
  - Encompass a limited number of pathogens
  - Primarily available for fluoroquinolones
  - Use blood concentration as a surrogate marker
- There are limited Journal standards for publishing pharmacodynamic data
  - No accepted method for validating new models
  - No standard for validating in-vitro or animal findings in humans

Summary

- Pharmacodynamics will continue to advance as a science and will become more sophisticated:
  - PD parameters will be validated for different antibiotics, pathogens & infections in patients
  - Bedside application
  - Part of formulary selection
  - Presently a “disconnect” between the FDA & the pharmaceutical industry regarding PD data
- Over time, we will see if objective antibiotic dosing using will prevent, limit, or delay the emergence of resistant pathogens