Clinical Use of Antimicrobial Pharmacodynamic Programs

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Introduction
Prescribers seem to operate with two preconceived premises:
- If a little antibiotic is good, a whole lot of antibiotic is better
  • Concentration dependent vs independent
- If one antibiotic is good, two or three antibiotics have to be better
  • Synergy vs. antagonism vs. indifference

“We know everything about antibiotics except how much to give”

Attributed to Maxwell Findland, M.D.

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)

In-vitro ↔ Animal ↔ Human

Potential Applications of Pharmacodynamics

- Tool in the antibiotic development process
  ■ Already part of the FDA Points to Consider Document
  ■ Part of Marketing Strategy in the Detailing and Counter Detailing of Antibiotics
  ■ Parameter for antibiotic formulary selection
    – Hospitals or Health Plans
  ■ Patient specific management tool
    – Dose, route, interval and/or method of administration
  ■ Clinical gauge for the development of bacterial resistance
    – Direct vs Collateral Damage

E-Max Model

Concentration Range with Commercial Dosage Forms

Bacterial Killing

Antibiotic Concentration

Effect
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**Concentration Dependent or Independent Bacterial Killing**

**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

**Dosing Strategies for Concentration Dependent Killer**

- Optimize AUC / MIC or Cp-max / MIC ratio
- Use concentration dependent killer first to quickly reduce bacterial burden
- Antibiotic combinations
  - Use products of different chemical class
  - Use antibiotics with different mechanisms of action
  - Probably not wise to use two concentration dependent products together

**Dosing Strategies for Concentration Independent Antimicrobial Agents**

- Select agent with long half-life, low protein binding, and large Vd
- More frequent dosage administration
- Continuous infusion of antibiotic
- Repository antibiotic dosage forms
- Block excretion (probenecid)
- Select product with active metabolite
- Select class product with lowest MIC

**Pharmacodynamic Outcome Parameters**

- AUC / MIC = 100 / 0.5 = 200
- Cp-max / MIC = 10 / 0.5 = 20
- T > MIC ~ 24hrs
- AUC = 100 mg h / L

Rate & Extent of bacterial killing a function of antibiotic concentration

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

Proposed Pharmacodynamic Parameters

Parameter*  Antimicrobial
T>MIC β-lactams, macrolides, aztreonam, carbapenems & clindamycin
AUC/MIC Aminoglycosides, fluoroquinolones, azithromycin, tetracyclines, vancomycin & quinupristin/dalfopristin
Cp-max/MIC Aminoglycosides & fluoroquinolones

* Covariance of parameters with antibiotic dose

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
  - PCN-R S. pneumoniae
  - Anthrax
  - 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 Model Variables

- Validation of new models
- pH
- Aerobic / Anaerobic
- Protein Binding
- Exponential vs Stationary Growth Phase
- Variability in Bacterial Growth that is Media Dependent
- Antibiotic Stability
- Antibiotic Carryover
- Inoculum Size (Different size used for MIC determination & Experiments)
- Number and Duration of Experiments
- Duplicate vs Triplicate Experiments
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In-Vitro Modeling Variables
- Intensity of Sampling
- How many pathogens required representing a species
- Defining Terms
- Lower Counting Limit
- Handling Data that Falls Below Counting Limit
- Appropriate Endpoints
  - 99% vs 99.9% vs 99.99%
  - Slope analysis
  - AUKC
- Evaluation or Accounting for Bacterial Regrowth

Pharmacodynamic Outcome Parameters
- Optimal Range of Data for Identifying Outcome Parameter
- Fitting Data to Mathematical Models
- Handling Data after >3 Log Kill
- Appropriate Use of Descriptive and Inferential Statistics for Small Data Sets

Animal Model Variables
- Model Validation
- How well does “Infection Model” emulate Human Infection (Acute vs. Chronic)?
- Species Variability Animal, Age, Genetics
- Immune Status
- Inoculum size
- Bacterial Isolate Used (MIC / Virulence)
- Drug Dose and Frequency (Simulation of Human PK)

Adequate Range of Dose or PK Parameters
- Manipulation of Drug Clearance
- Time Interval Between Creating Infection & Treatment
- Method of Processing Samples
- Route of Administration
- Dosage Form or Formulation
- Duration of Treatment
- Duration of Follow-up
- Endpoint

Which Pharmacodynamic Parameter is Most Important?
- Cp-max / MIC ratio vs AUC / MIC ratio?
- Can differences & distinctions in pharmacodynamic parameters really be addressed in human studies?
  - All patients are similarly dosed
  - Variety of infections being treated
  - Diversity of pathogens exist

AUC vs Cpmax

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

Curves different or the same?
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**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

**Fluoroquinolone Serum AUC / MIC Ratios**

<table>
<thead>
<tr>
<th>AUC-24 (mg•hr/L)</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>20</td>
<td>10</td>
<td>20</td>
<td>40</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>48</td>
<td>24</td>
<td>48</td>
<td>96</td>
<td>192</td>
<td>384</td>
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<tr>
<td>Moxifloxacin</td>
<td>48</td>
<td>24</td>
<td>48</td>
<td>96</td>
<td>192</td>
<td>384</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>51</td>
<td>25</td>
<td>51</td>
<td>102</td>
<td>204</td>
<td>408</td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>8</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>+ Gemifloxacin AUC / MIC ratio for S. pneumoniae = 8 / 0.015 = 533</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- AUC likely higher in real patients vs human volunteers
- Correct values for extent of protein binding

**Commercial Pharmacodynamic Software**

- AUIC program developed by Drs Aldelman & Schentag - Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, NY
- Attempts to optimize antibiotic therapy using population pharmacokinetics and generates a AUIC for specific situation
- Not rigorously tested

**Limitations of PK/PD Programs**

- PK models derived from a variety of patient populations or healthy volunteers
- Question of how well your patient is represented by the pharmacokinetic data pool?
- MIC data not available in some institutions
- (S)ensitive, (I)ntermediate, or (R)esistant
- Summation of AUC/MIC parameters treats the impact of concentration & time dependent antibiotics the same
- Toxicity of agent not factored into program
- Software program could recommend a potentially toxic dose
- Claims of reduced bacterial resistance not validated

**Inability of a Commercially Available Antibiotic Utilization Information and Consultation Program to Predict Outcome or Time to Event in GNNP**

- No correlation between measured & estimated AUC for aminoglycosides
- Estimated sum of beta-lactam & aminoglycoside AUIC not predictive of outcome or time to event in 64 cases of GNNP
- Use of pharmacodynamic parameters such as AUC/MIC for aminoglycosides & T>MIC for beta-lactams not predictive of outcome or time to event

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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

\[ P. \text{ aeruginosa} \]

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>( P. \text{ aerug} \ #1 )</th>
<th>( P. \text{ 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>
</tr>
<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>
<tr>
<td>Colistin</td>
<td>0.125</td>
<td>0.125</td>
</tr>
</tbody>
</table>

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

Role of Pharmacodynamics in Developing Antibiotic Dosing Strategies

- Can we reinvent Colistin?
  - Identify Right Dose & Interval
  - Maximize antibiotic efficacy
  - Minimize antibiotic induced toxicity

Polymyxins

- Class of novel basic polypeptide antibiotics (A, B, C, D, & E)
  - Identified in 1947 by both British & American Scientists
    - UK: B. aerosporus– aerosporin (polymyxin A)
    - USA: B. polymyxa – polymyxin (polymyxin D)
  - Work by damaging the cell membrane
    - Disrupts cell permeability
    - Exclusively a Gram negative antibiotic
    - Exceptions: Proteus spp. & Neisseria spp.
  - Pharmacokinetics poorly studied
    - Data currently available uses older technology

Polymyxin E Adverse Events

- Pain at injection site
- Nephrotoxicity (20-25%)
  - Contributing factor to polymyxin demise
  - With controlled therapy can safely be given
- Neurologic ADR’s (7-29%)
  - Paresthesia
  - Dizziness
- NMJ Blocking
  - Pareses associated with levels > 100 mg/L
- Causes release of histamine & SHT
  - Hypersensitivity (polymyxin B > E)

Garrod, L. & O’Grady, F.: Antibiotic & Chemotherapy 1971
Colistin Parenteral Dosing

- Usually maximum of 5 mg/Kg/day
  - Daily dose divided & given BID or TID
  - Doses of 6-8 mg/Kg/day for more serious infections
- Usually maximum of 2.5 mg/Kg/dose
  - Do not use colistin sulfate parenterally
  - Observation that ADR’s dose related
  - Given IV over 20-30 minutes
- Virtually no pharmacokinetic/pharmacodynamic data or dosing

In vitro Pharmacodynamic Model

Simulated Colistin Parameters

<table>
<thead>
<tr>
<th>Cmax (mg/L)</th>
<th>T ½ (Hrs)</th>
<th>AUC</th>
<th>AUC/ MIC</th>
<th>Cmax/ MIC</th>
<th>T&gt;MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mg/L IM use</td>
<td>3 hours</td>
<td>26 mg hr/L</td>
<td>208</td>
<td>48</td>
<td>70%</td>
</tr>
<tr>
<td>18 mg/L IV use</td>
<td>3 hours</td>
<td>78 mg hr/L</td>
<td>624</td>
<td>144</td>
<td>90%</td>
</tr>
</tbody>
</table>

High vs Low Dose X 24Hrs

High & Low Dose BID vs High Dose QD
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Colistin Conclusions
- Evidence colistin is a concentration dependent killer of P. aeruginosa
- QD dosing strategy seems to offer comparable performance to BID
- Concomitant use of ceftazidime appeared synergistic while ciprofloxacin appeared indifferent
- QD strategy could reduce colistin ADR's
- Because colistin is a generic drug clinical trials to validate findings unlikely

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 no 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
- Over time, we will see if objective antibiotic dosing using will prevent, limit, or delay the emergence of resistant pathogens
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