The pharmacological and microbiological basis of PK/PD: why did we need to invent PK/PD in the first place?

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The situation in the early 90's …

- anti-infective drug dosing was largely irrational or not based on sound pharmacodynamics/toxicodynamics
  - search for low doses for fear of toxicity
  - “errors” in drug dosages at registration
  - misunderstanding of what is an optimal schedule and what it implies

- pharmacokinetics was mainly used to establish “drug presence” rather than to make true correlations with efficacy
PK/PD of antiinfectives: what has been done?

Over the last 10 years, three major concepts have emerged and proven useful:

• dose-effect relationships are not the same for all anti-infectives
  • beta-lactams vs. fluoroquinolones or aminoglycosides

• integration of PK/PD within pre-clinical and early clinical development allows prediction of success or failure of new antimicrobials

• PK/PD may help in preventing the emergence of resistance
PK/PD in action in the Regulatory in the USA

PK/PD - Potential Benefits

- Facilitate Early Selection of Lead Drug Candidate (e.g., Pre-Clinical Screening)
- Select Appropriate Dosage Regimen (e.g., Phase 1/2)
- Better Understand Clinical / Microbiological Outcome (e.g., Phase 3)
- More Efficient Drug Development Program

FDA
July 1998

http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm
PK/PD in action in the Regulatory in the USA

FDA

November 2002

IDSA/PhRma/FDA Working Group Meeting
November 19-20, 2002

- Agenda
- Minutes Day 1 and Day 2

IDSA/PhRma/FDA Working Group Mtg. Presentations:

2. Drug Development for Resistant Pathogens by Francis P. Tally, M.D.
3. Developing Drugs for the Treatment of Infections due to Resistant Pathogens by Edward Cox, M.D., M.P.H.
4. Use of PK/PD to Facilitate Development of Drugs for Treatment of Resistant Pathogens by William A. Craig, M.D.
5. Use of PK/PD to Facilitate Development of Drugs for Treatment of Resistant Pathogens by James A. Poupad, Ph.D.
6. Exposure-Response: Application to Antimicrobial Drug Development by Philip Colangelo,

http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm
"Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance.

A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

The possibility of approving a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP* working parties…"

* Committee for Proprietary Medicinal Products
The basis of PK/PD

Dosage regimen → Concentration versus time in serum → Concentration versus time in tissues and other body fluids → Pharmacologic or toxicologic effect

absorption, distribution, elimination → Concentration versus time at site of infection → Antimicrobial effect versus time

PHARMACOKINETICS

PHARMACODYNAMICS

Craig (1998) CID 26:1-10
Moving from PK to PD …

Pharmacokinetics
conc vs time

Pharmacodynamics
conc vs effect

PK/PD
effect vs time
Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation

The combination of in vitro modelling, proper design of animal model experiments, and the willingness to obtain sparse pharmacokinetic information on patients in clinical trials allows an in depth understanding of which aspects of drug exposure are most closely linked to therapeutic outcome as well as to toxicity.

By providing such information to clinicians, drug therapy can achieve the goal of maximal therapeutic effect while engendering the lowest probability of encountering a drug exposure-related adverse event.
Main PK/PD properties of antibiotics

Available antibiotic can be divided in 3 groups

• time - dependent (T > MIC)
• AUC / MIC - dependent
• both AUC / MIC AND peak / MIC -dependent

Caveat: this applies to the "clinically-meaningful" concentration window only …
Clinically-meaningful concentration window …

All antibiotics are concentration-dependent, but it all dependent as how you look at them …

S. aureus; 24 h

Barcia-Macay et al, submitted; Lemaire et al (2005) JAC
Antibiotics Group # 1
(after W.A. Craig, 2000; revised 2003)

1. Antibiotics with **time-dependent effects**
and no or little persistent effects

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>Time above MIC</td>
<td>Maximize the exposure time</td>
</tr>
</tbody>
</table>

2. **Antibiotics with time-dependent effects, with little or no influence of the concentration BUT with persistent effects**

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycopeptides</td>
<td>24h AUC / MIC ratio</td>
<td>Optimize the quantity of AB administered</td>
</tr>
<tr>
<td>tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrolides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>streptogramines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluconazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Antibiotics with concentration-dependent activity and with persistent effects (PAE)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>PK/PD Parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminoglycosides</td>
<td>$C_{\text{max}} / \text{MIC}$ and $24\text{h AUC} / \text{MIC}$ ratios</td>
<td>Optimize both the peak and the quantity of drug</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>daptomycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PK / PD in action for the clinics

Some achievements:

• once-daily dosing of aminoglycosides introduced in many countries
  • amikacin, netilmicin (from bid to qd)
  • isepamicin (registered essentially for qd dosing)

• 24h AUC / MIC and $C_{max}$ / MIC ratios used as guides for phase II / III trials, for treatment optimization and for registration of new antimicrobials
  • moxifloxacin
  • telithromycin

• dosage of beta-lactams adjusted to cover $T > MIC$ in relation with the expected pathogen...
PK/PD and resistance ...
Mutant Prevention Concentration ...

Bactericidal effect of a FQ towards *Mycobacterium bovis*

\[
\text{MIC}_{99} = 0.8
\]

"Classic" bactericidal effect

\[
\text{MPC}_{10} = 9
\]

Elimination of first mutants

Dong et al; AAC 43:1756-1758
Mutant Prevention Concentration …

MIC\textsubscript{99} = 0.8

Concentration which will inhibit the majority of the organisms

MPC\textsubscript{10} = 9

Concentration necessary to prevent the selection of the first mutants

Dong et al; AAC 43:1756-1758
"Window" where selection of mutants takes place …

"Window" where selection of mutants takes place …

- Eradication of the first mutants
- Selection of the first mutants
- No therapeutic effect

Time after administration

Concentration

MPC
MSC
MIC

Therefore, new breakpoints for FQ ...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit of sensitivity (µg/ml) for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$C_{\text{max}}$ in mg/L total/free (dose)</td>
<td>$\text{AUC}_{24\text{h}}$ (mg × h/L) total/free</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1 (400 mg PO)</td>
<td>14/11</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75 (500 mg PO)</td>
<td>24/18</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3 (400 mg PO)</td>
<td>40/30</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8 (500 mg PO)</td>
<td>40/28</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8 (400 mg PO)</td>
<td>35/21</td>
</tr>
</tbody>
</table>

Or, correct assessment of telithromycin…

PK/PD limit of sensitivity (0.25 mg/L)

MIC\textsubscript{90} for Ery-s strains: < 0.06 ...

But MIC\textsubscript{90} for Ery-r strains: 0.25-0.5 ...

PK/PD in 2005 …

• Use if for efficacy …

• Consider it for avoiding resistance