MACROLIDES: pharmacokinetics and pharmacodynamics

P. M. Tulkens, MD, PhD

Unité de Pharmacologie Cellulaire et Moléculaire
Université Catholique de Louvain, Brussels, Belgium

International Society of Anti-infective Pharmacology

www.md.ucl.ac.be/facm www.isap.org
Pharmacokinetics / pharmacodynamics as a step towards therapy...

- the ideal molecule
- brilliant and clear solutions
- the big black box
- patient’s cure

- chemistry
- microbiology
- PK/PD
- therapy
PK/PD parameters: a first sight

- Peak
- Trough
- Area under the curve

Serum Concentration varying with time
What does the clinician (and the patient) want?

Dosage

Serum Concentration varying over time

Max

therapeutic effects

Min

toxic effects

freely adapted from W.A. Craig
Pharmacokinetics ...

- Dosage → Serum Concentration varying over time
- Concentration in non-target tissues
- Concentration at the site of infection
- Max
- Min
toxic effects
therapeutic effects

adapted from W.A. Craig
Pharmacodynamics...

- **Dosage** → Serum Concentration varying over time

  - Concentration in non-target tissues → min → toxic effects
  - Concentration at the site of infection → Max → therapeutic effects

adapted from W.A. Craig
The combination of

- in vitro modelling,
- proper design of animal model experiments,
- pharmacokinetic information on patients in clinical trials

allows an in depth understanding of which aspects of drug exposure are most closely linked to

- therapeutic outcomes (successes as well as failures !!)
- quantifiable / predictable toxicity hazards
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

July 1998
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.

ISAP / FDA workshop, March 1st, 1999

Pharmacokinetic/ Pharmacodynamics and antibiotic resistance...

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 to produce such a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP working parties...

EMEA discussion paper on Antimicrobial resistance, January 3, 1999
EMEA/9880/99
PK/PD and drug development

A view from EMEA

Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation

Who should take these points in consideration?

1. Industry: surely!
   (for sake of efficacy both short and long term)
   but what do they do with that?

2. Clinicians: more and more (to optimize therapy)
   but they often feel alone or insufficiently informed

3. Regulatory bodies (to better appraise new drugs)
   but they wish to be certain that this is the correct way!
Pharmacokinetic / Pharmacodynamic parameters: a 2d sight

Peak / trough
AUC / Time

> Minimal inhibitory concentration

peak
area under the curve
time above the MIC
MIC
trough
## PK/PD: role of concentration

<table>
<thead>
<tr>
<th>Marked effect</th>
<th>Weak effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>important concentration</td>
<td>little or no concentration</td>
</tr>
<tr>
<td>dependency</td>
<td>dependency</td>
</tr>
</tbody>
</table>

- aminoglycosides
- fluoroquinolones
- metronidazole
- daptomycin
- ketolides
- amphotericin
- β-lactams (all)
- glycopeptides
- macrolides
- clindamycine
- tétracyclines

Optimize the concentration
PK/PD: role of concentration

an example with Listeria monocytogenes

PK/PD: role of time

Kill quickly

- aminoglycosides
- fluoroquinolones

Kill more slowly

- β-lactams (all)
- glycopeptides
- macrolides
- oxazolidinones
- clindamycine
- tetracyclines
- flucytosine

Optimize the time
PK/PD: prolonged effects

- Post antibiotic effect (PAE) delay in regrowth upon antibiotic removal
- Sub-MIC activity (SME) tests the distribution of antibiotic susceptibility in the bacterial population
- Post antibiotic leucocyte enhanced effect (PLAE) pre-treatment makes bacteria more susceptible to phagocytosis and killing
### PK/PD: role of prolonged effects

<table>
<thead>
<tr>
<th>Marked influence</th>
<th>Weak of no influence</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminoglycosides</td>
<td>β-lactams (all)</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td>macrolides</td>
</tr>
<tr>
<td>azithromycin</td>
<td>clindamycine</td>
</tr>
<tr>
<td>glycopeptides</td>
<td></td>
</tr>
<tr>
<td>tertracyclines</td>
<td></td>
</tr>
<tr>
<td>streptogramins</td>
<td></td>
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<tr>
<td>fluconazole</td>
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</table>

Optimize the amount of drug
Neutropenic Murine Thigh and Lung Infection Models

- Cyclophosphamide 150 and 100 mg/kg at 4 and 1 day before infection
- Thigh infection produced by injection of 0.1 ml of $10^7$ CFU/ml 2 hrs before treatment
- Lung infection produced by 45 min aerosol of $10^9$ CFU/ml 14 hrs before treatment
- $10^{7-8}$ CFU/g in thigh or lung at start of therapy

W.A. Craig et al.
### PK/PD Parameters Correlating with Efficacy in Murine Thigh and Lung Infections

<table>
<thead>
<tr>
<th>Time Above MIC</th>
<th>AUC (Peak)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Monobactams</td>
<td>Daptomycin</td>
</tr>
<tr>
<td>Tribactams</td>
<td>Ketolides</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Streptogramins</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Glycopeptides</td>
</tr>
<tr>
<td>Glycylcyclines</td>
<td>Tetracyclines</td>
</tr>
</tbody>
</table>

*W.A. Craig et al.*
How do you get a given 24h-AUC?

1. Importance of the dose (a)

The 24h-AUC is the integral of the serum concentration over the 24h interval, proportional to the total daily dose and the bioavailability.

Thus...

Adjust the total daily dose by...
How do you get a given 24h-AUC?

1. administer the right dose...

the 24h-AUC is the integral of the serum concentration over the 24h interval...

proport. to the total daily dose and the bioavailability

Thus...

adjust the total daily dose by ...

performing single dose increases ...

- 600 mg
- 200 mg
the 24h-AUC is the integral of the serum concentration over the 24h interval…
proport. to the total daily dose and the bioavailability

Thus...

or, by repeating single doses over 24h

adjust the total daily dose…
How do you get a given 24h-AUC?

3. get a low clearance

the 24h-AUC is inversely proportional to the clearance.

24h-AUC = \[
\frac{(24h\text{-Dose} \times B_{av})}{Cl}
\]

Thus...

Use a drug with a long half-life.
But isn’t anything more?

A bacteria which does not get killed is a collection of genes that can mutate!!
How to predict efficacy in the intracellular milieu?

Where are bacteria?

- Cytosol: *Listeria hly+*, *Shigella*
- Phagolysosomes: *S. aureus*, *Salmonella*, *M. leprae*, ...
- Endosomes: *Legionella*, *Chlamydia*, ...

Exemplification of bacterial location in host cells.
Pharmacokinetic modulation of intracellular activity: drug trapping

[Chemical structures and graphs showing cellular accumulation and chemical modifications]
How to predict efficacy in the intracellular milieu?

Both serum and cellular concentration fluctuate!

(Azithromycin; 500 mg qd)

Van Bambeke et al, JAC, 1998, 42:761-767
And we may have a very bright future...