Pharmacodynamic indices in targeting therapy of critical infections

P.M. Tulkens
Cellular and Molecular Pharmacology,
Catholic University of Louvain,
Brussels, Belgium

&

International Society of Anti-infective Pharmacology
What are "Pharmacodynamic indices"?

- all drugs have pharmacokinetic properties that describe the way the body handles them
  - antibiotics are no exception …
  - you need to consider the $C_{\text{max}}$ and the clairance (that will result in a given half-life) to describe the drug exposure

- a drug needs to bind to its target to act …
  - antibiotics are again no exception, but the target is the bacteria …
  - the antibiotics can be studied in vitro to look at the extent of their action at increasing concentrations (like the binding of a ligand to its receptor in conventional pharmacology)
Pharmacokinetics + Pharmacodynamics...

Pharmacokinetics
conc vs time

Pharmacodynamics
conc vs effect

PK/PD
effect vs time
Example of a pharmacodynamic relationship

- **Emin**
- **Emax**
- **MIC**

And what if we put pharmacokinetics?

![Graph showing pharmacokinetic parameters with labels for Emin, Emax, Cmin-Cmax, and MIC.](image)

- Emin
- Emax
- Cmin-Cmax
- MIC
And what if we put pharmacokinetics?

\[ \Delta \log \text{CFU (24 h - 0 h)} \]

- **Oxacillin**
  - Low concentration dependency

- **Gentamicin**
  - High concentration dependency

\[ C_{\text{min}} - C_{\text{max}} \]
More dynamic models …

Drug Conc. = Inflow = Clearance

\[ T_{1/2} = 0.693 \times \frac{V}{Cl} \]

Adapted from M.N. Dudley, ISAP / FDA Workshop, March 1st, 1999
Pharmacodynamics: the basic question?

Which antibiotics are time-dependent or concentration-dependent in clinically meaningful conditions?
Pharmacodynamics: the practical question?

How shall we dose antibiotics in the clinics?

time-dependent

concentration-dependent
from pharmacokinetics to pharmacodynamics...

- $C_{\text{max}}$
- $\text{Cmax} / \text{CMI}$
- $\text{AUC} / \text{CMI}$
- $\text{Time} \sim \text{conc} > \text{MIC}$
- $\text{AUC} > \text{MIC}$
- $t > \text{MIC}$
- $\text{MIC}$
Main PK/PD properties of antibiotics

Available antibiotics can be divided in 3 groups:

- time-dependent ($T > \text{MIC}$)
- $\text{AUC} / \text{MIC}$ dependent
- both $\text{AUC} / \text{MIC}$ and peak / MIC-dependent
Antibiotics Group # 1
(after W.A. Craig, 2000; revised 2002)

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</td>
</tr>
<tr>
<td>clindamycin</td>
<td></td>
<td>time</td>
</tr>
<tr>
<td>oxazolidinones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>flucytosine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
How long should you stay above the MIC?

- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- lung infection
More experimental data with penicillins, cephalosporins and carbapenems ... 

Fig. 7. Relationship between the change in log_{10} CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○) and carbapenems (□).

- different pathogens
  - same shape of dose response
  - diff. In $T > MIC$ for a static effect (penicill. > carbap.)
  - diff $E_{max}$ (penicill. < carbap.)

How to optimize $T > \text{MIC}$?

1. Increase the unitary dose?
How to optimize \( T > MIC \) ?

1. Increase the unitary dose?

[Diagram showing concentration over time with two dosage levels (dosis = 1 and dosis = 2) and a remark about a useless peak.]

But useless peak!!

dosis = 2

dosis = 1

gain...
How to optimize T > MIC?

2. Increase the number of administrations?

Seems more logical…
## 2. Antibiotics with **time-dependent effects**, no or little influence of concentration, but marked persistent effects

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycopeptides</td>
<td>AUC / MIC</td>
<td>optimize the amount of antibiotic</td>
</tr>
<tr>
<td>tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrolides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>streptogramins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluconazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. **Antibiotics with concentration-dependent bactericidal activity and prolonged persistent effects (post-antibiotic effects)**

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminoglycosides</td>
<td>Peak and AUC / CMI</td>
<td>optimize the peak and the amount of antibiotic</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>daptomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ketolides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>amphotericin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aminoglycosides: get a peak!

1. Appropriate mode of administration
   - IV route

2. Calculation of the necessary peak value
   - minimal peak: \( \frac{MIC}{8} \)

3. Calculation of the adequate dosage
   - peak = \( \frac{dosis}{Vd} \)
   - dosis = peak \( \times \) Vd
   - dosis = \( MIC \times 8 \times Vd \)
Aminoglycosides are concentration-dependent drugs in the clinically meaningful concentration range ...
Aminoglycosides: why a peak?

Clinical efficacy is linked to peak/MIC ratio

Relationship between the maximal peak level/MIC ratio and the rate of clinical response. Vertical bars represent SE values.

Response rate (%)

Maximum peak/mic ratio

Aminoglycosides: why a peak?

- 141 predominantly elderly patients with severe bacterial infections.
- All patients received once-daily doses of 2 g ceftriaxone, in addition to netilmicin.

"Netilmicin-induced toxicity may be reduced by using once-daily dosing regimens and limiting the duration of treatment."

Aminoglycosides: why a peak?


National survey of extended-interval aminoglycoside dosing (EIAD).
Chuck SK, Raber SR, Rodvold KA, Areff D.

- 500 acute care hospitals in the United States
- EIAD adopted in 3 of every 4 acute care hospitals
  - 4-fold increase since 1993
  - written guidelines for EIAD in 64% of all hospitals
- rationale
  - 87.1% : equal or less toxicity (),
  - 76.9% : equal efficacy
  - 65.6% : cost-savings
- dose: > 5 mg/Kg
- 47% used extended interval in case of decline in renal function (38% with Hartford nomogram)
### Aminoglycosides: which dosage for which MIC?

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Peak (mg/L) for $V_d = 0.25 \text{ l/kg}$</th>
<th>peak/MIC if MIC =</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>1 2 4 8</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>2 4 8 16</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>3 6 12 24</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>4 8 16 32</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>6 12 24 48</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>8 16 32 64</td>
</tr>
</tbody>
</table>
Fluoroquinolones: get a peak and an AUC!

Increase the amount administered, in order to optimize AUC/MIC should be > 125 *
and peak/MIC should be > 10

Get both a peak and a AUC!!

* we will discuss this figure tomorrow...
How to optimize the AUC / MIC ratio?

AUC = dosis / CI

Adjust the daily dose
~ target AUC

Adapt the number of administrations
~ pharmacokinetics of the drug
AUC and peak after one dose are directly related to the dose

A "theoretical" example...
24h-AUC is inversely related to the drug clearance (BUT so is NOT the peak ...)

AUC = 24 \( \approx \) 5

AUC = 48

AUC = 24

AUC = 12

a “theoretical” example...
24h-AUC is correlated to the number of unit doses (BUT, again, so is NOT the peak …)

A “theoretical” example…

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g</td>
<td>120</td>
</tr>
<tr>
<td>2 x 1g</td>
<td>120</td>
</tr>
</tbody>
</table>

AUC = 48

AUC = 24
PK/PD of fluoroquinolones in a nutshell

Remember:

• 24h-AUC is proportional to the daily dose
• peak is proportional to the unit dose...

- get a \( \frac{24\text{h-AUC}}{\text{MIC}} > 125 \), and
- get a \( \frac{\text{peak}}{\text{MIC ratio}} > 8 \)

efficacy and resistance

• get this with the total daily dose and the appropriate unit dose ...
### Defining PK/PD breakpoints for fluoroquinolones

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>AUC/MIC (24h)</th>
<th>peak / MIC</th>
<th>PK/PD Bkpts (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin</td>
<td>800</td>
<td>0.1</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>0.1</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>0.2-0.4</td>
<td>0.3-0.4</td>
<td></td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>0.4</td>
<td>0.4-0.5</td>
<td></td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>0.4</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>
Adjust the dosage to the MIC

<table>
<thead>
<tr>
<th>Daily dosage of levofloxacin</th>
<th>AUC *</th>
<th>MIC for an AUC$_{24h}$/MIC = 125</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>28</td>
<td>0.2</td>
</tr>
<tr>
<td>500</td>
<td>56</td>
<td>0.4</td>
</tr>
<tr>
<td>1000</td>
<td>112</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* based on normal half-lifes; CL ~ 100 mg/dl; doses for an adult of 65 kg
But keep the unitary dose in the allowed limit ...

Peak-related side effects:

SNC toxicity

Inhibition of CYP 450 activity
chondrotoxicity
phototoxicity
Choose the most active molecule

<table>
<thead>
<tr>
<th>drug</th>
<th>Dosage (mg/24h)</th>
<th>AUC *</th>
<th>MIC for AUC/MIC = 125</th>
<th>MIC S. pneumo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>66</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>lévofloxacin</td>
<td>500</td>
<td>73</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>1000</td>
<td>40</td>
<td>0.3</td>
<td>0.5-2</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>48</td>
<td>0.4</td>
<td>0.01-0.5</td>
</tr>
</tbody>
</table>
PK/PD: take home message

1. For each drug, choose on a PK/PD basis the appropriate
   • scheme of administration
   • daily dosis

2. Adapt the dosage to the susceptibility of the target organism,
   • based on MIC data for the individual patient
   • based on local epidemiology
PK/PD : from today to tomorrow

today : applying these concepts can help us to reach an optimized efficacy

but let's prepare tomorrow:

how can we use this science to really help clinicians?