PK/PD: from theory to applications in the real world...

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International Society of Anti-infective Pharmacology
Antibiotic treatment: What does the clinician want?

- Best therapeutic effects
- No or minimal toxic effect
- “The” drug

Diagram:
- Happy face leading to “Best therapeutic effects”
- Stop sign leading to “No or minimal toxic effect”
The ideal antibiotic ...

the molecule

brilliant and clear solutions

microbiology

chemistry

therapy

cure
Is the molecule always ideal?

the ideal molecule

brilliant and clear solutions

patient’s cure

chemistry microbiology therapy
Main causes of antibiotic failures...
Adapted from Pechère J.C., 1988, 1993, 1998

- False failures
  - erroneous diagnosis
  - underlying disease uninfluenced by antibiotics
  - unjustified lack of patience
  - inactivation of the antibiotic

- Patient related failures
  - compliance failure (broadly speaking)
  - inappropriate administration route (broadly speaking)
  - immunodepressed hosts

- Pharmacological failures
  - insufficient amount or drug inappropriately administered
  - no attention paid to pharmacodynamic parameters
  - in situ inactivation or lack of drainage

- Micro-organism related failures
  - wrong pathogen
  - resistance acquired during treatment
  - insufficient bactericidal activity
  - inoculum effect
Farmacokinetiek

Dosering → Serumconcentratie variërend in de tijd

Concentratie op de infectiehaard

Concentratie in de andere weefsels
Farmacodynamie

Dosering

Serumconcentratie variërend in de tijd

Concentratie op de infectiehaard

Therapeutische effecten

Concentratie in de andere weefsels

Toxische effecten
Microbiology

identification

sensitivity

by static techniques

drug concentration stays constant

18-03-06 Milan - PK/PD

drug concentration stays constant
What did the textbooks say about antibiotic dosages and schedules in the 70’s?

1. Stay above the MIC… but how much?
2. Remain around for a while… but how long?
3. Hope it works… against everything?
4. Hope it is not toxic… can’t do much…
Les méthodes statiques sont (souvent) inadaptées pour définir les conditions de sensibilité \textit{in vivo}.

Où doit se situer le point critique ?

Première difficulté: les points critiques ignorent le caractère dynamique des taux sériques de médicament.

\textbullet \; \textit{Pic}

\textbullet \; \textit{Aire sous la courbe}

\textbullet \; \textit{Vallée}
Pharmacocinétique ➔ Pharmacodynamie
Les antibiotiques actuellement disponibles peuvent être regroupés en 3 groupes montrant, une dépendance prédominante vis-à-vis soit :

- du temps ("T > MIC")
- du rapport AUC / MIC (AUC\textsubscript{24h}/MIC)
- du rapport Pic / MIC (C\textsubscript{max}/MIC)
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>

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig, et al. ICAAC 2002; Craig 2003
## Antibiotics Group # 2

*(after W.A. Craig, 2000; revised 2003)*

### 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</td>
<td>Optimize the quantity of AB administered</td>
</tr>
<tr>
<td>tétracyclines</td>
<td>ratio</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>

*2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig et al., ICAAC 2002; Craig, 2003*
Antibiotics Group # 3  
(after W.A. Craig, 2000; revised 2003)

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

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminoglycosides</td>
<td>$C_{\text{max}} / \text{MIC}$ and $24h \text{ AUC} / \text{MIC}$ 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>
<tr>
<td>ketolides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>amphotericin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig et al., ICAAC 2002; Craig, 2003
Relationship between peak/MIC and efficacy of cefotaxime towards *Klebsiella pneumoniae* in murine pneumonia (after W.A. Craig *)

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
Relationship between time above MIC (T>MIC) and efficacy of cefotaxime towards *Klebsiella pneumoniae* in murine pneumonia (after W.A. Craig *)
Pharmacokinetics / Pharmacodynamics in action ... 

What can (and must) the clinician know?
How much time above MIC?

- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- pulmonary infection

100% - Maximal effect?

Static dose?

40% $R^2 = 94%$
Here is a proposal ...

- 40% Moderately severe infection in a non-immunospressed patient
- 100% Severe infection in an immunosuppressed patient
Typical pharmacokinetics of a model $\beta$-lactam *

<table>
<thead>
<tr>
<th>time</th>
<th>serum concentration (mg/L) for 0.5 g</th>
<th>1 g</th>
<th>2 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>25</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>12.5</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
<td>1.5</td>
<td>3</td>
</tr>
</tbody>
</table>

* single administration; 2h half-life; $V_d = 0.2$ l/kg

How much do you want at 8h?
Pharmacokinetics / Pharmacodynamics in action ...

β-lactams: if you have reached the limits ...

• increase the frequency of administration to get enough time > MIC

  efficacy

• high peaks are unnecessary and may cause toxicity
Pharmacokinetics / Pharmacodynamics in action ... 

β-lactams: what can you really do?

I guess 10 µg/ml is the limit if you use it optimally (2 to 3 x / day and up to a total of 4 to 6 g/day...)

PK / PD breakpoints for β-lactams:

8 µg/ml
Reducing $\beta$-lactams interval: where can we go?

- Same daily dose (4 g)
- Divided in $x$ administrations
- $\mu g / ml$ at 66% of time between administrations

![Graph showing the relationship between 66% MIC coverage and the number of administrations per day.](image)
β-lactams by continuous infusion

\[ C_{ss} = \frac{K_o}{Cl} \]

Serum concentration

rate of infusion

clearance

stability of the molecule ...

specific applications ...

Servais & Tulkens, AAC, September 2001

Nosocomial pneumonia, cystic fibrosis, ... in progress
Problems with continuous infusion ...

- Clearance estimates
- Variations in clearance (ICU)
- Non-linear clearance
- Drug instability
Ceftazidime concentrations (ICU patients)

concentration (mg/L) vs. time (h)

Mouton, unpublished
Ceftazidime concentrations in ICU patients (successive determinations)

Laterre et al., ICAAC 2002
What about meropenem?

The stability of meropenem is more limited than for other β-lactams... Infusion must be limited to 3h

Viaene et al., AAC 2002; 46:2327-2332
Use a long infusion of meropenem vs. \textit{P. aeruginosa}

2g meropenem

![Graph showing % kill vs. MIC (mg/L) for different infusion times: 0.5 h infusion, 1 h infusion, 2 h infusion, 3 h infusion.](image)

**Meropenem with prolonged infusion ...**

<table>
<thead>
<tr>
<th>MIC</th>
<th>1 g q8h (3 h)</th>
<th>1 g q8h (1 h)</th>
<th>500 mg q8h (3 h)</th>
<th>500 mg q8h (1 h)</th>
<th>500 mg q6h (1 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.008</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>99.95</td>
<td>100</td>
</tr>
<tr>
<td>0.016</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>99.8</td>
<td>100</td>
</tr>
<tr>
<td>0.125</td>
<td>100</td>
<td>99.99</td>
<td>100</td>
<td>99.45</td>
<td>100</td>
</tr>
<tr>
<td>0.25</td>
<td>100</td>
<td>99.97</td>
<td>100</td>
<td>98.65</td>
<td>99.84</td>
</tr>
<tr>
<td>0.5</td>
<td>100</td>
<td>99.82</td>
<td>100</td>
<td>95.4</td>
<td>99.36</td>
</tr>
<tr>
<td>1.0</td>
<td>100</td>
<td>99.28</td>
<td>100</td>
<td>89.65</td>
<td>97.04</td>
</tr>
<tr>
<td>2.0</td>
<td>100</td>
<td>96.21</td>
<td>99.25</td>
<td>65.45</td>
<td>88.04</td>
</tr>
<tr>
<td>4.0</td>
<td>99.1</td>
<td>81.08</td>
<td>79.6</td>
<td>31.9</td>
<td>63.02</td>
</tr>
<tr>
<td>8.0</td>
<td>79.6</td>
<td>23.12</td>
<td>14.2</td>
<td>4.4</td>
<td>19.08</td>
</tr>
<tr>
<td>16.0</td>
<td>14.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>32.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Target attainment</td>
<td>86.4</td>
<td>79.5</td>
<td>79.3</td>
<td>67.5</td>
<td>76.4</td>
</tr>
</tbody>
</table>

*Values in parentheses are infusion times.

A clinical algorithm ...

Pathology and epidemiology

Knowledge or our "educated" suspicion of the causative agent

Local MIC data

Is the organism probably highly susceptible?

yes

Use common dosage but with attention to PK/PD

no

Obtain an MIC

S / I / R is insufficient!!

Adjust the dosage on a full PK/PD basis
Success?

- re-evaluate
  - the dosage
  - the therapeutic scheme
  - the antibiotic class based on PK/PD properties

no

Consider step-down therapy if acceptable on a microbiological point of view

yes

Use these pieces of information to establish recommendations based on local epidemiology and on the knowledge of the PK/PD properties and of the risk for resistance
It’s a brilliant idea…

But don’t let you fool your self…