Basic Concepts of PK/PD
-pharmacodynamic indices-

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This patient needs antibiotics. But which ones?
Intensive care patient

Ceftazidime, *P. aeruginosa* infection

Which of the following dosing regimens is best?

A. 1000 mg q12h

B. 500 mg q6h

C. 2000 mg q12h

D. 1000 mg q8h
Dosing should be such that the level of antimicrobial activity is associated with a high likelihood of therapeutic success.
Dose Finding - The Past
Efficacy of the drug

Potency of a drug (MIC)

Exposure to the bug

In vivo

(PK)
ANTIMICROBIAL EFFICACY

(Microbiological Cure)

ACTIVITY

in vitro (MIC)

CONCENTRATIONS

in vivo (PK)

DOSING regimen

Other factors

CLINICAL EFFICACY

(Clinical Cure)

Mouton et al., Drug Resistance Updates 2011
Lowest concentration with no visible growth after 18 hour incubation

\[ \text{MIC} = 2 \text{ mg/L} \]

PK

X-acin 500 mg

\[
\begin{array}{ccccccc}
.25 & .5 & 1 & 2 & 4 & 8 \\
\bullet & \bullet & \bullet & \bullet & \circ & \circ & \circ \\
\end{array}
\]
Thus, we have to:

- Establish a relationship between the MIC in vitro and concentrations in vivo (thus, dosing regimens)
- Determine which dosing regimens are optimal for Treatment in relation to the MIC
Any idea where we are today?

No idea… may be a mouse?

Might be a human, though…
An elephant....
Today it is an elephant!
Neutropenic Mouse Thigh-Infection Model

1. Neutropenia induced by 2 injections of cyclophosphamide on days -4 and -1

2. Bacteria injected into thighs on day 0 ($10^{4-7}$)

3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days

4. Mortality or dcfu
PK/PD dose fractionation studies

- Neutropenic mouse thigh model

- Various doses and dosing regimens (q1 to q24)

- Outcome parameter: cfu counts after 24 h

- Plot PK parameter and/or PK/PD index (AUC, Peak, %fT>MIC) to effect
Pharmacokinetic parameters: Measures of Exposure

Area under the concentration-time curve
Integrated concentration over time

AUC
Pharmacokinetic parameters: Measures of Exposure

AUC is usually linearly related to Dose.
Pharmacokinetic parameters: Measures of Exposure

AUC is usually linearly related to Dose

Dose x 2 = AUC x 2

Dose x 4 = AUC x 4
**K. pneumoniae, imipenem**

Every point = one mouse thigh

\[
d\text{logcfu} = \log\text{cfu (t=24h)} - \log\text{cfu (t=0h in controls)} = \text{net effect of treatment}
\]

Based on data from Craig WA
For *K. pneumoniae*, there is no clear relation between AUC (or total daily dose) of imipenem and efficacy in an in vivo model of infection.
AUC and Peak are usually linearly related to Dose.
Time > MIC dependent on dose frequency

- 12.5 q6
- 25 q12
- 50 q24

Total length of bars corresponds to Time > MIC

Concentration mg/L

Time (h)

MIC 2 mg/L
Based on data from Craig WA
For beta-lactams, there is a direct relation between

Time > MIC and efficacy
Levofoxacin in *S. pneumoniae* infection in mice

Relationship between T>MIC, Peak, AUC

Each dot represents one mouse / dosingregimen.

Based on data from Scaglione & Mouton, 2001, 2003
PK/PD relationship is Class Dependent

- **levofloxacin**
- **ceftazidim**

(Andes IJAA 2002)
# Relationship PkPd and Effect

<table>
<thead>
<tr>
<th><strong>T&gt;MIC</strong></th>
<th><strong>AUC</strong></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>Lipopeptides</td>
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<tr>
<td>Tribactams</td>
<td>Ketolides</td>
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<td></td>
<td>Macrolides</td>
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<td></td>
<td>Clindamycin</td>
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<td></td>
<td>Streptogramins</td>
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<td>Glycopeptides</td>
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<tr>
<td></td>
<td>Glycylcyclines</td>
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<tr>
<td></td>
<td>Oxazolidinones</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
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<tr>
<td></td>
<td>Azoles</td>
</tr>
</tbody>
</table>
Relationship AUC and effect

- What has the MIC to do with this?
Fluconazole efficacy in mice
Dose vs MIC
Pharmacokinetic parameters: Measures of Exposure

AUC and Peak are usually linearly related to Dose

Mouton et al. 2007 21-44
In Antimicrobial Pharmacodynamics in Theory and Clinical Practice
'Normalizing pk/pd relationships'

Pharmacokinetic parameter

MIC

Pharmacodynamic index

(AUC/MIC, Peak/MIC, T>MIC)
Fluconazole Pharmacodynamics Against Isogenic Strain Pairs of Susceptible and Resistant C. albicans

Andes et al ISHAM 2003
In vitro effect at fixed concentrations

In vivo CT profile dynamic concentrations

Response Curve

MIC

2log fluconazole mg/L

time h

conc mg/L

extinction

2log fluconazole mg/L

fluconazole (auc/mic)

prob cure
Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis  n=132

• Prob cure correlates with AUC/MIC
• POSITIVE correlation with EXPOSURE
• INVERSE correlation with MIC

Pharmacodynamic index (AUC/MIC)

Rodriguez- Tudela et al, AAC 2007
Why is the term pk/pd index used instead of pk/pd parameter?

-a ratio (e.g.) of two independent parameters, not a parameter by itself

Thus, 2 factors influence the value of the pk/pd index:

MIC and its Errors/variation
Pharmacokinetics and its variation
Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST

Kahlmeter et al, JAC 2003
Growth and/or kill rate dependent:
- strain, species
- medium composition, brand
  - MH, supplements, ISO
- number of bacteria
- inoculum
  - $5.10^5$ (CLSI) vs $10^5$ (BSAC)
- temperature ($35^\circ$ vs $37^\circ$)
- growth phase
- CO$_2$
- etc.
The reference method

2003  20 June DIN Berlin
      CEN TC140/WG10

2004  22 April DIN Berlijn
      Combined meeting with
      ISO ISO/TC 212 WG4
      Vienna Agreement

2005  Vote on first draft and comments
      by all Member Countries

2006  Final version 27 October 2006,
      8th CEN, 6th ISO meeting
      ISO 20776-1

2007  Final version validation ISO 20776-2.
The reference method - Microdilution

- Microdilution, 0.1 ml
- Mueller Hinton (1941, Corn starch)
- Inoculum 5 (2-8) \( \cdot 10^5 \) cfu/ml
- \( 36 \pm 1 \) °C
- \( 18 \pm 2 \) h incubation
The reproducibility of the MIC test is within 2 2fold dilutions. The variation introduced in the AUC/MIC and Peak/MIC values by the MIC is there for at least 0.5 tot 2 x the pk/pd index value!
Why is outcome of beta-lactams \( \% f T > \text{MIC} \) related? And aminoglycosides AUC related?
In vitro activity of ceftazidime – exposure-response relationship

- Incubate inoculum at increasing concentrations
- Sample every two h

- Time h
- log10 cfu

- 0 mg/l
- 0,125 mg/l
- 0,5 mg/l
- 1 mg/l
- 2 mg/l
- 4 mg/l
- 16 mg/l
- 64 mg/l

Mouton et al. AAC 2007 51:3449
Modelling Kill Kinetics

\[ E = E_{max} \cdot \frac{C^\gamma}{(C^\gamma + E C^\gamma)} \]

Mouton et al. AAC 2007 51:3449
Patterns of activity: Kill curves of P. aeruginosa

ceftazidime

tobramycin

- + controle
- △ 32 * MIC
- ○ 16 * MIC
- ⋅ 8 * MIC
- ⌂ 2 * MIC
- ⋇ 1 * MIC
- ⋆ 0.5 * MIC
- ⋆ 0.25 * MIC
Figure 44

1a

γ high: steep slope
'concentration independent'

1b

γ low: shallow slope
'concentration dependent'

Steep
Shallow

3.59 h⁻¹
13.4 h⁻¹
The overall effect of antimicrobial therapy is dependent on exposure AND MIC

The effect differs by antibiotic class
  - Beta-lactams: %$fT>MIC$ related
  - Most others: AUC related

Exposure response relationship can be explained by the pd characteristics
  - Fast vs slow kill (speed of killing)
  - Maximum kill rate (extend of killing)
  - Concentration effect (hill slope)

Adjust dosing regimens based on pkpd!
  - For beta-lactams: adjust dose: frequency matters!
  - For most others: adjust frequency
PHARMACOKINETIC parameters
**AUC**

*Definition*: The Area under the Concentration-time curve over 24 hours.

*Note*: ..... It should be stated how the AUC is determined: based on (log) linear trapezoidal rule, based on clearance, or based on microconstants.

*Dimensions*: concentration × time e.g. mg.h/L or µg.h/mL

AUC 0-24 = 3033
AUC inf = 5100
AUC 0-24 sd = 1361
AUC inf sd = 1700
WHICH AUC?

• $AUC_{0-24h}$ or $AUC_{\infty}$
• Steady State?
• (log) trapezoidal rule?
• Derived? ($A/\alpha + B/\beta$ or other)
**AUC/MIC**

**Definition**: The area under the concentration-time curve over 24 hours in steady state divided by the MIC. 

**Note**: For unbound fraction of the drug, use \( f_{AUC/MIC} \)

**Dimensions**: no dimensions

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Mouton et al, J Antimicrob Chemother 2005
Available from ISAP site

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AUIC

Definition: The Area under the inhibitory curve over 24 hours.

Note: the AUIC should be reserved for those cases where actual inhibitory titers have been measured and used in the calculations. The AUIC is not equal to the AUC/MIC. See also Flaherty et al, AAC 1988;32(12):1825-29; Hyatt JM et al AAC 1994;38(12):2730-7; Occhipinti DJ et al, AAC 1997;41(11):2511-7.

Dimensions: none

Mouton et al, J Antimicrob Chemother 2005
Available from ISAP site
**Peak/MIC**

*Definition*: the peak level divided by the MIC.

*Dimensions*: no dimensions.

Mouton et al, J Antimicrob Chemother 2005
Available from ISAP site
WHICH PEAKLEVEL?

- After the 1st, 2nd or later dose?
- If more than one compartment, the peak level in compartment 1, 2 or even 3?

Scaglione et al, AAC 2003
Scaglione et al., AAC 2003
Time > MIC

Definition: the % of time above the MIC over a period of 24 hours.

Note: if the period is other than 24 h, this should be stated explicitly.

Dimensions: %.
Variation in *methods, definitions*

Variation in *estimation*

Variation in *population*
For all indices:

- how are they determined
- how are they calculated
- what is the error?

Only when these questions have been answered do we know the true impact and value of the index.