Pharmacokinetic/ Pharmacodynamics in Drug Discovery, Development and Evaluation

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International Society of Anti-infective Pharmacology

www.md.ucl.ac.be/facm

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April 9, 2001

www.isap.org
Pharmacokinetic/ Pharmacodynamics in Drug Discovery, Development and Evaluation
Personnal presentation

- **Scientific activities**
  - toxicology of aminoglycosides
  - intracellular infection
  - introducing new modes of AB administration to the clinics

- **Regulatory activities**
  - Adviser to the Registration Commission (for AB)
  - Member of the National “Transparency Commission”
  - Member of the National Committee for the Coordination of the Antibiotic Policy

- The once-a-day concept (1985-1990)
  - present AB
  - new derivatives

- β-lactams by continuous infusion
Personnal presentation

- International activities
  - Member of the Editorial Boards and regular reviewer for Scientific Journals
  - Advisory Boards in Industry
Registering a new antibiotic: the issues

molecule → man

"Scientist" by Ben Shahn
New Jersey State Museum,
Trenton, N.J.
The ideal antibiotic ...

- the molecule
- brilliant and clear solutions
- patient’s cure

chemistry
microbiology
therapy
Will it always be ideal?

the ideal molecule

brilliant and clear solutions

chemistry microbiology

patient’s cure

therapy
Main causes of antibiotic failures...

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

- **Failures related to the patient**
  - compliance failure (broadly speaking)
  - inappropriate administration route (broadly speaking)
  - immunodepressed hosts

- **Pharmacological failures**
  - insufficient amount or drug
    - inappropriately administered
  - insufficient attention paid to pharmacodynamic parameters
    - in situ inactivation or lack of drainage

- **Failures related to the microorganism**
  - wrong pathogen
    - resistance acquired during treatment
  - insufficient bactericidal activity, bacterial persistence
    - inoculum effect

Adapted from J.C. Pechère (In Schorderet et coll., 1988, 1993, 1998)
Microbiological evaluation is (classically) static

identification

sensitivity

MIC

Breakpoints

by static techniques
Static techniques are (partly) inappropriate for \textit{in vivo} projections of sensitivities.
Breakpoints introduce artificial (and not always scientific) discontinuities in what is essentially a continuous distribution.

Figure 2. TROVAFLOXACIN vs Staphylococcus aureus (N = 458)

Same dose ??

And what about this one?
PK / PD ...

- **Pharmacokinetics**
  What the body does to the drug ...
  - absorption
  - metabolism
  - elimination
  \[ C_{\text{max}} \]
  \[ \text{AUC} \]
  \[ \text{half-life} \]

- **Pharmacodynamics**
  What the drug does to the body ...
  - direct effects
  - post-drug effects
  - selection effects
  \[ E_{\text{max}}, \text{rate of killing, ...} \]
  \[ \text{PAE, PASME, ...} \]
  \[ \text{resistance} \]

Adapted from H. Derendorf, 2d ISAP Educational Workshop, 2000
From PK to PD ...

Pharmacokinetics
conc. vs time

Pharmacodynamics
conc. vs effect

PK/PD
effect vs time

Adapted from H. Derendorf, 2d ISAP Educational Workshop, 2000
Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation of Efficacy

The combination of

- **in vitro modeling**,  
- 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

1st ISAP Discussion Workshop with Regulatory Authorities, Rockville, MD, March 1st, 1999 (http://www.isap.org)
Are PK/PD important for efficacy / toxicity?

- Medline search on March 25th, 2001 for:
  - pharmacodynamics, \textit{and}
  - pharmacokinetics, \textit{and}
  - efficacy or toxicity, \textit{and}
  - antibiotic*

534 references...
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

http://www.fda.gov/cder/present/anti-infective798/biopharm/sld008.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 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

Are PK / PD important in resistance?

- PubMed search on March 25th, 2001 for:
  - pharmacodynamics, *and*
  - pharmacokinetics, *and*
  - resistance, *and*
  - antibiotic*

1756 references...
Just a few of them…

  Pharmacokinetics and pharmacodynamics of fluoroquinolones in the respiratory tract.
  Wise R, Honeybourne D: “Pharmacokinetic and pharmacodynamic features are important predictors of the therapeutic efficacy of an antibiotic”.

- J Chemother 1999 Dec;11(6):426-39
  Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUIC to improve efficacy and avoid resistance.
  Schentag JJ: “Resistance is also predictable from these parameters, fostering a rational means of using dosing adjustments to avoid or minimize the development of resistant organisms”.

  Clinical efficacy and antimicrobial pharmacodynamics.
  Wise R: “Changes in the susceptibility of bacterial pathogens and the availability of new antimicrobial drugs mean that physicians need to understand the underlying pharmacodynamics of each antimicrobial therapy”.

Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation

Who should take these points in consideration?

1. Industry: surely!
   ➔ efficacy both in short (efficacy) and long (emergence of resistance) terms
   this is what they already do at the research level ...

2. Clinicians: more and more
   ➔ optimizing therapy now and protect the future
   but they often feel alone or insufficiently informed ...

3. Regulatory bodies
   ➔ to better appraise new drugs and set guidelines
   but they wish to be certain that this is the correct way!
Pharmacokinetic/ Pharmacodynamics: What are the goals?

- **Effectiveness**: defining prospectively
  - the daily dose(s) that will be effective;
  - the optimal schedule;
  - the risk of emergence of resistance

- **Lack or minimization of adverse effects**: drug uptake characteristics at the target organs
  - influence of schedule and of repair between drug administration

- **Prevention of resistance**: evaluating prospectively
  - the risk of low doses and/or to high bkpts
  - the importance of the rate of bacterial killing
  - the potential for synergy
  - the doses needed for the resistant organisms

**Drugs mentioned**
- teicoplanine
- aminoglycosides
- fluoroquinolones
- β-lactams
- linezolid
- ampicillin x AG
- VISA strains
PK / PD of antibiotics in 2001?

- Much Basic Science is already available
  - review articles
    Craig, Drusano, Schentag, Dalhoff, Zinner, Carbon, …¹
  - chapters of books
    Mandell, Armstrong, …

- New drugs are being developed and registered with strong PK/PD bases
  - moxifloxacin (fluoroquinolone)
  - télithromycine (ketolide)
  - …

- We need to apply the PK/PD principles to the existing drugs and/or to those which have introduced recently without sound PK/PD bases
Parameters controlling efficacy

- concentration (peak / MIC)
- time above the MIC
- AUC / MIC ratio
- post-antibiotic and other persistent effects
  - sub-MIC effects;
  - post-exposure sub-MIC effects;
  - post-antibiotic (leukocyte enhancement effects)
Pharmacokinetics → Pharmacodynamics

- Area under the curve
- Time above MIC
- Peak / MIC
- MIC
The rest of the talk ...

- Methods use to determine which are the pertinent PK/PD parameters
- PK/PD parameters of existing antibiotics
- What does Industry do?
- What can Regulatory Bodies require?
Methods use to determine which are the pertinent PK/PD parameters

- In vitro dynamic models
- Animal models
- Clinical trials
- Population pharmacokinetics
Methods

- In vitro dynamic models
- Animal models
- Clinical trials
- Population pharmacokinetics
In vitro dynamic models

- Dilution models
- Diffusion models
- Hybrid models
- ‘Physiologic models’
- Intracellular models

Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001
Dilution models

- **Stepwise**
  - simple dilution
  - sedimentation & resuspension
- **Continuous, pump**
  - without outflow
  - with outflow, retaining equal volume (filters)

Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001
Dilution models: a simple, useful system ...

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

Adapted from M.N. Dudley, ISAP / FDA Workshop, March 1st, 1999
Dilution models: more sophisticated ones...

Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001
Diffusion models

- Membranes (hollow fibers)
- dialyzers (artificial kidneys)

Adapted from M.N. Dudley, ISAP / FDA Workshop, 1999
The goal is to mimic potentially useful and achievable serum concentration variations.

Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001.
Why *in vitro* dynamic models ...

- The goal is to establish **basic** relationships between drug exposure (PK) and effect (PD)
  - PK:PD parameters for efficacy to apply across species, models, for combinations, etc...
  - Basis of dosage in phase II trials

- **Limitations:**
  - Experimental conditions (laboursome; contamination; …)
  - Usually only 1 or 2 days (effects ‘fade’ after 12-24 h)
  - Haag factor (biofilm…)
  - Absence of host factors (incl. protein binding and metabolism)
  - …

Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001
Methods

- In vitro dynamic models
- Animal models
- Clinical trials
- Population pharmacokinetics
Animal models

- Neutropenic mouse
- rabbit (endocarditis)
- rat, guinea pig, ...

The main advantage is the possibility to explore a VERY large array of dosing regimens so as
• dissociate PK covariables ($C_{\text{max}}$ vs AUC ...)
• explore the PK “conditions of failure”
Dissociating PK covariables

Adapted from F. O. Ajayi, ISAP-FDA Workshop, 1999
A typical animal model to establish which PK parameters is associated with efficacy

- Use neutropenic murine thigh-and lung-infection models
- Evaluate 20-30 different dosing regimens (5 different total doses given at 4-6 different dosing intervals)
- Measure efficacy from change in $\log_{10}$ CFU per thigh or lung at the end of 24 hours of therapy
- Correlate efficacy with various pharmacodynamic parameters (Time above MIC, peak/MIC, 24-Hr AUC/MIC)

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000
Relationship Between Peak/MIC Ratio and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
Relationship Between 24-Hr AUC/MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
Relationship Between Time Above MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)

\[ R^2 = 94\% \]

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
End-points of animal models

- Bacterial counts
  - static dose
  - 50 % effect
  - $E_{\text{max}}$

- Mortality

- Recovery of resistant bacteria

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
Relationship Between 24 Hr AUC/MIC and Mortality for FQs in immunocompromised Animal Models with Gram (-) bacilli infection (Craig, 2000) *

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
Relationship Between 24 Hr AUC/MIC and Mortality for FQs in Immunocompetent Animal Models with *Str. pneumoniae* infection (Craig, 2000) *

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
Known PK problems (with solutions) linked with animal models

- Serum clearance of most antimicrobials is faster in animals than in man
- Serum protein binding is usually less in animals than in man
- The higher doses required for studies in animal models may result in non-linear kinetics
- Sensitive drug assays should be used to identify deep tissue compartments that could prolong activity against very susceptible organisms

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000
Known PD problems with animal models

- short term, acute infections
- necessity to make the animal receptive to the infection
- difficulties to eradicate (subpopulations not dealt with by impaired host defenses)
- growth of bacteria influenced by local (artificial) conditions
- disagreements concerning the end points to consider (static dose, $E_{\text{max}}$, etc…)

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000
Demonstrated advantages of animal models

- Is the magnitude of the parameter required for efficacy the same in different animal species?  
  YES

- Does the magnitude of the parameter vary with:
  1. the dosing regimen?  NO  
  2. different drugs within the same class?  NO  
  3. different organisms ?  Minimal  
  4. different sites of infection (e.g. blood, lung, peritoneum, soft tissue)?  NO, but ...

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000
Methods

- In vitro dynamic models
- Animal models
- Clinical trials
- Population pharmacokinetics
PK/PD of fluoroquinolones in clinics

Demonstration of the role of the 24h-AUC / MIC ratio

Forrest et al., AAC, 1993
24h AUC / MIC: what were the data?

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<td>28</td>
<td>82</td>
<td>79</td>
</tr>
<tr>
<td>0.125-0.25</td>
<td>13</td>
<td>75</td>
<td>69</td>
</tr>
<tr>
<td>0.5</td>
<td>14</td>
<td>54</td>
<td>success 79</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>33</td>
<td>failures 44</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0</td>
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Forrest et al., AAC, 1993
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<tr>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24h AUC / MIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-125</td>
<td>19</td>
<td>32</td>
<td>42</td>
</tr>
<tr>
<td>125-250</td>
<td>16</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>250-1000</td>
<td>14</td>
<td>79</td>
<td>71</td>
</tr>
<tr>
<td>1000-5541</td>
<td>15</td>
<td>87</td>
<td>80</td>
</tr>
</tbody>
</table>

Forrest et al., AAC, 1993
What is the 24h-AUC / MIC ratio (AUIC)?

\[
\text{AUC}_{24h} = \frac{\text{dose}_{24h}}{\text{clearance}}
\]
What is the 24h-AUC / MIC ratio (AUIC) ?

AUC\textsubscript{24h} / MIC = 125 \rightarrow 5 \times \text{MIC for 24h}
Modeling of the clinical data

Associating successes and failures to PK parameters

- **Logistic Regression**
  - for evaluating the effects of covariates on outcome where the outcome measure is binary
- **Generalized Linear Modeling (GLM)**
  - multiple linear regression approach
- **Generalized Additive Modeling (GAM)**
  - models the dependence of outcome on the predictor variables
- **Tree based modeling**
  - An approach for understanding the predictive power of PD variables (clinical outcome, microbiological outcome)

F. O. Ajayi, ISAP-FDA Workshop, 1999
Application to 24h AUC /MIC

clinical outcome

F. O. Ajayi, ISAP-FDA Workshop, 1999
AUC - - AUC /MIC - - Cmax/MIC - - T > MIC ?

F. O. Ajayi, ISAP-FDA Workshop, 1999
Why are the conclusions of the clinical trials apparently (sometimes and apparently) contradictory?

- **insufficient separation of covariates**
  - only one or a few dosage regimens
- **not enough true failures**
  - self-limiting diseases
  - study design
- **intercurrent variables influencing outcome and not recognized as such**
- **unsufficient or inappropriate collection of PK data**
  - only “peaks” or troughs...
Methods

- In vitro dynamic models
- Animal models
- Clinical trials
- Population pharmacokinetics
Doctor or Regulator?

- In clinical therapy, we would like to give optimal dose to each individual patient for the particular disease
  
  **Individualized therapy**

- In new drug assessment/development, we would like to know the overall probability for a population of an appropriate response to a given drug and proposed regimen
  
  **Population-based recommendations**

H. Sun, ISAP-FDA Workshop, 1999
PK/PD and population-based recommendations: the issues

- PK parameters are variable among patients.
- If PK/PD parameters predict outcome, then PK variabilities will have a significant impact on the overall rate of clinical responses.
- Then, you need to estimate what are the chances of reaching an appropriate level of the pertinent PK/PD parameter in a sufficiently high proportion of patients...
Examples of variations

**$C_{\text{max}}$**

**$T > MIC$**

H. Sun, ISAP-FDA Workshop, 1999
Obtaining population cumulative frequencies

Quantal drug concentration effects

Quantal T>MIC plots

H. Sun, ISAP-FDA Workshop, 1999
The rest of the talk ...

- Methods to derive pertinent PK/PD parameters
- Data with selected existing antibiotics
- What does Industry do?
- What can Regulatory Bodies require?
PK/PD patterns of antimicrobial activity

The existing antibiotics consistently show 3 type of dominant pattern:

– Time-dependency
– AUC / MIC - dependency
– AUC / MIC- and Peak / MIC -dependency
1. Antibiotics with time-dependent killing, no or little effect of concentration, and minimal to moderate persistent effects

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Key PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta-lactams</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clindamycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxazolidinones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrolides</td>
<td>Time above MIC</td>
<td>Optimize the duration of exposure to drug</td>
</tr>
<tr>
<td>flucytosine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Relationship between time above MIC and efficacy
For β-lactams, macrolides and TMP/SFX in otitis media

Fig. 1. Relationship between the percentage of time that serum levels exceed the MIC\textsubscript{90} and the bacteriologic cure in otitis media caused by \textit{S. pneumoniae} (open symbols) and beta-lactamase-positive and -negative \textit{H. influenzae} (closed symbols). Data available for 10 beta-lactams, 2 macrolides and trimethoprim-sulfamethoxazole. The coefficient of determination was 0.57.

T > MIC must reach 50 %
**β-lactams**: at least 50% of the time above the MIC...

---

You must calculate the interval

\[ C_t = C_0 \times e^{-kt} \]

Time between 2 administrations:

- **dir.** proportionnal to the dose
- **inv.** proportionnal to the half-life

Most betalactams have an half-life of approx. 2 h or less.
PK / PD in action: what can you do with a model β-lactam *

<table>
<thead>
<tr>
<th>time (hours)</th>
<th>concentr. (mg/L) for a dose of 0.5 g</th>
<th>1 g</th>
<th>2 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>25</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>12.5</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>12</td>
<td>25</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>

if given every 12h

- 50 % coverage
- 66 % coverage
- 100 % coverage

* adult 50 kg; single administration; 2h half-life; V_d = 0.2 l/kg; free fraction !!
Improving β-lactam efficacy by reducing the interval

<table>
<thead>
<tr>
<th>time (hours)</th>
<th>concentration for</th>
<th>if given every 8 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 g</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td></td>
</tr>
<tr>
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* single administration; 2h half-life; V_d = 0.2 l/kg; **free fraction** !!
β-lactams PK / PD and resistance

- too low doses
- too long intervals
- too high breakpoints

lead to suboptimal effects

- delay in eradication
- selection of subpopulations with reduced susceptibility
2. Antibiotics with **time-dependent killing**, but also **prolonged persistent effects**

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<tr>
<th>Drugs</th>
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<tr>
<td>glycopeptides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tetracyclines</td>
<td>24 h AUC / MIC ratio</td>
<td>Optimize the amount of drug administered</td>
</tr>
<tr>
<td>azithromycin</td>
<td></td>
<td></td>
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<tr>
<td>streptogramins</td>
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</tr>
<tr>
<td>fluconazole</td>
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</tbody>
</table>

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000*
Evidence is mounting that resistance to 
  • macrolides 
  • glycopeptides 
  • tetracyclines 

can be linked to 
  • their slow and uncomplete bactericidal activity; 
  • the too low doses; 
  • their use in situations in which eradication is impossible to achieve.
AUC / MIC - dependent antibiotics and resistance

Examples:

- **glycopeptides**
  - eradication of MRSA colonization
  - selective decontamination of the digestive tract
  - primary treatment of antibiotic associated colitis (AAC)
  - topical application or irrigation

- **macrolides**
  - otitis media
  - “good for all respiratory tract infections” promotion

- **tetracyclines**
  - low doses for fear of toxicity
  - treatment of acne
### 3. Antibiotics with concentration-dependent killing and prolonged persistent effects (post-antibiotic effects)

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<tr>
<td>aminoglycosides</td>
<td>Peak and 24 h</td>
<td>Optimize concentrations and drug amount</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>daptomycin</td>
<td>AUC / MIC ratio</td>
<td></td>
</tr>
<tr>
<td>ketolides</td>
<td></td>
<td></td>
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<tr>
<td>amphotericin B</td>
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* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000*
Aminoglycosides: obtain a peak!

1. Adequate mode of administration
   - i.v. administration

2. Calculate the peak you need
   - Minimal peak = MIC / 8

3. Calculate the dose you need
   - \[ \text{dose} = \text{peak} \times V_d \]
PK / PD in action ...

Aminoglycosides:

increase the unit dose to get the appropriate peak!

$\text{MIC} = 1 \text{ mg/L} \Rightarrow C_{\text{max}} = 8 \text{ mg/L} \Rightarrow 3 \text{ mg/kg}$

$\text{MIC} = 2 \text{ mg/L} \Rightarrow C_{\text{max}} = 16 \text{ mg/L} \Rightarrow 6 \text{ mg/kg}$

$\text{MIC} = 4 \text{ mg/L} \Rightarrow C_{\text{max}} = 32 \text{ mg/L} \Rightarrow 15 \text{ mg/kg}$

limit for $G, T, N$

limit for $A, I$
PK /PD in action ...

Aminoglycosides 1st rule of tumb...

- anything with an MIC < 1 (within the indications...) will be treatable

- efficacy will become a problem for organisms with MIC’s
  - > 2 for G, T, N (up to 6 mg/kg)
  - > 4 for A, I (up to 15 mg/kg)

PK / PD “safe” breakpoints for AG
- G, N, T : 2 µg / ml
- A / I : 4 µg / ml
PK PD in action...

Aminoglycosides 2d rule of thumb...

- give them once-a-day to reduce toxicity
  - 1h peaks of 12-18 mg/L for G, T, N
  - 1h peaks of 20-30 mg/L for A, I

Increase interval (⇒ 36h, ⇒ 48h)
in case of renal failure
before reducing the unit dose...

Once-daily dosing of aminoglycoside antibiotics

Fisman, DN; Beth Israel Deaconess Med Ctr; Div Infect Dis; Harvard Univ, Sch Publ Hlth, Infectious-Disease-Clinics-of-North-America. Jun 2000
Fluoroquinolones: get both a peak and an AUC!

\[
\begin{align*}
24\text{h-AUC} / \text{MIC} & \geq 125 \quad \text{(Schentag)} \\
24\text{h-AUC} \text{ is proportional to the daily dose} & \quad \Rightarrow \text{adjust the daily dose} \\
\text{peak} & \geq 10 \quad \text{(Drusano)} \\
\text{peak is proportional to the unit dose} & \quad \Rightarrow \text{adjust the unit dose} \\
\end{align*}
\]

* you may like to consider only the free fraction!!
24h-AUC / MIC as a tool to determine acceptable sensitivities to standard doses of FQ

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>24h-AUC (mg/L x h)</th>
<th>PK/PD Bkpt [AUC/MIC = 125]</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin</td>
<td>800</td>
<td>14 * , #</td>
<td>0.1</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>12 *</td>
<td>0.1</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>31 to 66 * , +</td>
<td>0.2 - 0.4</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>47 *</td>
<td>0.4</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>400</td>
<td>35 *</td>
<td>0.3</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>48 *</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®; # litterature data; + first dose to equilibrium
Peak concentrations as a tool to determine acceptable sensitivities to standard doses of FQ

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>PK/PD Bkpt $[C_{\text{max}} / 12]$ (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin</td>
<td>800</td>
<td>2.4 *</td>
<td>0.2</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>2.4 *</td>
<td>0.2</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>3-4.5 *, +</td>
<td>0.3 - 0.4</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>5-6 *, +</td>
<td>0.4 - 0.5</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>400</td>
<td>4.2 *</td>
<td>0.4</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>4.5 *</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, TEQUIN®, LEVAQUIN®, and AVELOX®
+ first dose to equilibrium
Combining it all ...(Peak and 24h-AUC / MIC) as predictors of efficacy standard doses of FQ ...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>AUC/MIC (24h)</th>
<th>peak / MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin</td>
<td>800</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>0.2-0.4</td>
<td>0.3 - 0.4</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>0.4</td>
<td>0.4 - 0.5</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>400</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®
Combining it all …(Peak and 24h-AUC / MIC) as predictors of efficacy standard doses of FQ ...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>AUC/MIC (24h)</th>
<th>peak / MIC</th>
<th>NCCLS Bkpts*</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin</td>
<td>800</td>
<td>0.1</td>
<td>0.2</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>0.1</td>
<td>0.2</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>0.2-0.4</td>
<td>0.3 - 0.4</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>0.4</td>
<td>0.4 - 0.5</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>400</td>
<td>0.3</td>
<td>0.4</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>0.4</td>
<td>0.4</td>
<td>&lt; 2</td>
</tr>
</tbody>
</table>

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®
Which value of AUC / MIC?

An example with levofloxacin 500 mg qD

<table>
<thead>
<tr>
<th>creatinine clearance (mg/l)</th>
<th>AUC (mg/L X h)</th>
<th>PK/PD Bkpt (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>0.8</td>
</tr>
<tr>
<td>But the peak remains unchanged at ~ 5 mg/L</td>
<td>AUC / MIC = 125</td>
<td>AUC / MIC = 25</td>
</tr>
</tbody>
</table>
To increase efficacy of FQ, you need to increase both the AUC and the peak …

An example with levofloxacin (qD)

<table>
<thead>
<tr>
<th>Dosage (qD)</th>
<th>AUC * (mg*h/L)</th>
<th>PK/PD Bkpt**</th>
<th>Peak * (mg /L)</th>
<th>PK/PD Bkpt***</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>28</td>
<td>1</td>
<td>2.5</td>
<td>0.25</td>
</tr>
<tr>
<td>500</td>
<td>56</td>
<td>2</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>1000</td>
<td>112</td>
<td>4</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

* based on normal half-lifes; CL ~ 100 mg/dl; doses for an adult of 65 kg
** for a 24h AUC / MIC = 25
*** for a peak / MIC = 10

MIC for S. pneumoniae ~ 1-2 mg/L
Classical breakpoints of older FQs and of levofloxacin are probably set too high and correspond to AUC / MIC-based PK/PD breakpoints only if

- clearance is lower than in normal subjects
- accepting an AUC / MIC ratio of 25 as being sufficient...
- considering total concentrations

Classical FQ breakpoints almost never correspond to a peak / MIC ratio $\geq 10$!
The rest of the talk ...

- Methods to derive pertinent PK/PD parameters
- Data with selected existing antibiotics
- What does Industry do?
  (but they may not tell you…)
- What can Regulatory Bodies require?
What does Industry do?

• Preclinical studies examine the PK/PD parameters related to efficacy (in vitro and animal models), to help in selecting lead candidates.

• Phase I studies examine if the human PK properties of the drug candidate are compatible with sufficient activity.

• Phase II trials are designed with an optimized dosage.
And look at the FDA registration dossier * of a new fluoroquinolone...

* Avelox® (moxifloxacin)
FDA hearing committee 1999

PK/PD Parameters that best correlate with Quinolone Efficacy*

- $C_{max} / MIC_{90} > 8-10$
- $AUC / MIC_{90} > 100$
- Post Antibiotic Effect (PAE)

*Craig, 1998

**AUC/MIC**$_{90}$* Data for Selected Quinolones

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>MXF</th>
<th>LEV</th>
<th>CIP</th>
<th>SPFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>192</td>
<td>47.5</td>
<td>11.6</td>
<td>17.0</td>
</tr>
<tr>
<td>H. influenza</td>
<td>1600</td>
<td>1583</td>
<td>387</td>
<td>17.0</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>800</td>
<td>1583</td>
<td>193</td>
<td>623</td>
</tr>
</tbody>
</table>

For optimal antimicrobial effect and to minimize resistance, AUC/\(MIC_{90}\) should be > 125 (Craig 1998)

400 mg qD
The end of the talk ...

- Methods to derive pertinent PK/PD parameters
- Data with selected existing antibiotics
- What does Industry do?
  (but they may not tell you...)
- What can Regulatory Bodies require?
What can Regulatory Bodies require?
1. Preclinical data

• Knowing the microorganisms:
  ➔ Recent, local sensibility data
    • MIC distributions
    • population analysis
  Where are the MIC_{50, 90, 99}?
  Subpopulations of R+ org.?

• Knowing the intrinsic properties of the drug
  ➔ PK / PD parameters associated with
    • efficacy
    • resistance
    • toxicity
  • In vitro dynamic models
  • PK/PD-finding animal studies
  • Resistance studies
What can Regulatory Bodies require?

2. Clinical data

- Knowing what the drug can realistically make to the bugs in the patients
  - PK parameters at both the individual and at the population level *
    - Monte-Carlo simulations for efficacy based on population pharmacokinetics
    - appropriate design of the phase II trials (human dose finding)
    - justification of the dosage adopted for the phase III trials
    - prospective definition of conditions that may lead to predictable failures
    - minimization of toxicity

* free fractions !!
What can Regulatory Bodies require?

3. Package insert

- Defining correctly the drug true potential
  - PK/PD based “breakpoints” (which should be upper limits of MIC’s above which the prescriber needs to be warned that failures and selection of resistant strains are likely…)
  - MIC-based posologies for serious infections (forget the notion of “mild” and “severe” infections”-based posologies)
  - PK/PD-based recommendations for minimization of dose-related toxicities
Do you do that in your own country?

“The prescriber needs to inform him/her-self about the posologies that, at the present time, are recommended for this class of antibiotics. Studies … show indeed very clearly that a ratio "24-h Area Under the Curve / Minimal Inhibitory Concentration" (24h-AUC/MIC) is one of the main parameters predicting efficacy for XXX in serious infections (nosocomial pneumonia). This ratio must be 125 or higher.”

Free translation of an Official statement (“Definitive Opinion”) of the Belgian “Transparency Commission” made on April 17th 2000, concerning antibiotic XXX, for which the Manufacturer was seeking reimbursement by the Social Security

<table>
<thead>
<tr>
<th>daily dose (mg)</th>
<th>max. MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>0.060</td>
</tr>
<tr>
<td>400</td>
<td>0.125</td>
</tr>
<tr>
<td>600</td>
<td>1.180</td>
</tr>
<tr>
<td>800</td>
<td>0.250</td>
</tr>
<tr>
<td>1200</td>
<td>0.400</td>
</tr>
</tbody>
</table>
Better approaches in antibiotic approval ...

Perhaps sooner and easier than you thought...

W.A. Craig
G.L. Drusano
J.J. Schentag
A. McGowan
X. Zao
V. Firsov
S. Zinner
A. Dalhoff
...

http://www.isap.org

"Scientist" by Ben Shahn
New Jersey State Museum, Trenton, N.J.
And remember: we are not so far away from one another ...

Self-portrait of P.P. Rubens (Antwerp) on display at the National Gallery of Arts, Canberra, ACT (with authorization of the Gallery)