Towards clinical Applications of PK-PD in specific situations

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with many things borrowed from

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http://www.isap.org

50th Interscience Conference on Antimicrobial Agents and Chemotherapy
Boston, Mass.
The problem ... #1 of many ...

1. Infections are (most often) treated with the same dosing regimen irrespective of the absolute susceptibility of the micro-organism ...

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>Usual Dose</th>
<th>Adults</th>
<th>Severe Disease</th>
<th>Children</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0.5-1 g q6-12h</td>
<td>2 g q6-8h</td>
<td></td>
<td>12.5-33 mg/kg q6-8h</td>
<td></td>
</tr>
<tr>
<td>Cephalothin</td>
<td>0.5-1 g q6h</td>
<td>2 g q4-6h</td>
<td></td>
<td>20-25 mg/kg q6h</td>
<td></td>
</tr>
<tr>
<td>Cephapirin</td>
<td>0.5-1 g q6h</td>
<td>2 g q4-6h</td>
<td></td>
<td>10-20 mg/kg q6h</td>
<td></td>
</tr>
</tbody>
</table>

What is a "severe disease?"
The problem ... #2 (of many)

2. Clinicians tend to ask only (and clinical microbiologists to provide only) "S – I – R" answers based on accepted breakpoints …

But, what is a breakpoint?
The problem as seen from a question of the FDA...

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

Breakpoints tend to set up quantic limits in what is fundamentally a continuous distribution ...

Same dose ?? And what about those ones ?
So, you need to know the enemy ...

For a fluoroquinolone....

\[
\text{MIC} = 0.016 \text{ mg/L} \quad \text{Susceptible}
\]

\[
\text{MIC} = 2.0 \text{ mg/L} \quad \text{Susceptible ?}
\]
Which parameter are you going to use in your hospital?

- $AUC_{24h} / MIC$
- $C_{max} / MIC$
- Time above MIC

Exercise with

- the fluoroquinolones
- the $\beta$-lactams
The saga of the AUC / MIC vs $C_{\text{max}} / \text{MIC}$ ratio for fluoroquinolones ...

AUC / MIC is the parameter ...

Forrest et al., AAC, 1993
AUC/MIC_{24h} = 125 : a magical number??

125 was the limit below which failure rates became unacceptable because of either
- a large MIC
- or a too low dosage (AUC is proportional to the dosage)
- was derived from studies on Gram-negative infections
Is 125 good for all ??

The saga of *S. pneumoniae* ...
Conditions That Predispose to Pneumococcal Infection

**Defective antibody formation**
- Primary Congenital agammaglobulinemia

**Common variable (acquired) hypogammaglobulinemia**
- Selective IgG subclass deficiency
- Secondary Multiple myeloma
- Chronic lymphocytic leukemia Lymphoma
- HIV infection

**Defective complement (primary or secondary)**
- Decreased or absent C1, C2, C3, C4

**Insufficient numbers of PMNs**
- Primary Cyclic neutropenia

**Secondary Drug-induced neutropenia**
- Aplastic anemia

**Poorly functioning PMNs**
- Alcoholism
- Cirrhosis of the liver
Conditions That Predispose to Pneumococcal Infection

**Glucocorticosteroid treatment**
Renal insufficiency?

**Poorly avid receptors for FCγII (R131 allele)**

**Defective clearance of pneumococcal bacteremia**

**Primary Congenital asplenia, hyposplenia**

**Secondary Splenectomy**

Sickle cell disease (autosplenectomy)

Multifactorial

**Infancy and aging**

Malnutrition

Diabetes mellitus

Prior respiratory infection

Influenza

Cigarette smoking

Asthma

COPD
Quinolones: to peak or not to peak?

- Three studies have shown AUC/MIC predictive for outcome
- One prospective study showed Peak/MIC to be more predictive

Modelling studies show that:

- **Survival linked to Peak/MIC when ratio > 10/1**
- **Survival linked to AUC/MIC when ratio < 10/1**
- the risk of resistance is minimized if the peak/MIC > 10

![Graph showing probability vs. peak/MIC ratio]
So, let us accept values with some degree of precaution with fluoroquinolones

If you wish to get a faster eradication and reduce emergence of resistant

- peak / MIC > 10

If you are interested in global effect …

- $AUC_{24h} / MIC: 30 \text{ to } 125$
1st Example:
You want to control fluoroquinolone dosing at the level of the patient

- Patient 60 yr, pneumonia and suspected bacteraemia/sepsis
- Ixacin 400 mg IV q8h ➔ AUC = 30
- Gram negative rod ...

- E-test MIC = 0.01 mg/L
  - 30/0.01 ➔ 3000!
  - 100 mg/day is plenty!
- E-test MIC = 1 mg/L
  - 30/2 ➔ 30!
  - 400 mg q8h may fail

Mouton & Vinks, PW 134:816
## Breakpoint issues ...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>AUC/MIC* (mg/24h)</th>
<th>peak / MIC** (24h)</th>
<th>NCCLS &quot;S&quot; 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</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>0.4</td>
<td>0.4 - 0</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>

*Based on US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN®, and AVELOX®

* AUC/MIC = 125
** peak / MIC = 10
A proposal for PK/PD based-breakpoints for fluoroquinolones...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage(^a)</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit of sensitivity (μg/ml) for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(C_{\text{max}}) in mg/L total/free (dose)</td>
<td>(AUC_{24,\text{h}}) (mg × h/L) total/free</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1</td>
<td>14/11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(400 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75</td>
<td>24/18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(500 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3</td>
<td>40/30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(400 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8</td>
<td>40/28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(500 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8</td>
<td>35/21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(400 mg PO)</td>
<td></td>
</tr>
</tbody>
</table>

2\textsuperscript{d} example: you want to control fluoroquinolone choice and dosing for patients with CAP

- You have two Ixacins: L-xacin and M-xacin
- They have essentially the same pharmacokinetics and tolerance
- Which one will you recommend in YOUR set-up for CAP?
Application to pneumococci in Belgium

**Moxifloxacin** 400 mg 1x/d
- AUC [(mg/l)xh]: 48
  - MIC max: 0.5-1.5
- peak [mg/l]: 4.5
  - $\text{MIC}_{\text{max}} \sim 0.5$

**Levofloxacin** 500 mg 1x/d
- AUC [(mg/l)xh]: 47
  - MIC max: 0.5-1.5
- peak [mg/l]: 5
  - $\text{MIC}_{\text{max}} \sim 0.5$

MIC data: J. Verhaegen et al., ECCMID 2003
Similar values in 2009 (Vanhoof, ECCMID 2009)
Can you do that in another country?

Fig. 1. Distribution of fluoroquinolone MICs for *S. pneumoniae* blood isolates.
EUCAST

• formed in 1997
• convened by the main ad-hoc scientific and breakpoints committees in Europe
• sets common breakpoints for surveillance of antimicrobial resistance and harmonise clinical breakpoints for existing drugs
• sets breakpoints for all newly registered antimicrobials for inclusion in the labeling (SPC) through ongoing agreement with the European Medicines Agency (EMEA)
• all breakpoints are based on a combination of
  • PK/PD data (in vitro, animals, …)
  • PK in humans with Monte-Carlo simulations and target attainment rates with dose simulations
  • Clinical data
### Enterobacteriaceae

<table>
<thead>
<tr>
<th>Fluoroquinolones</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin¹</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.5</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

All EUCAST data are freely available at http://www.eucast.org
2d example: $\beta$-lactams : $T > MIC$ …

You know it is "time above MIC", but…

- How much / How frequent ?
  (Static dose vs maximum effect ?)
- The same for all beta-lactams ?
  (Free fractions of the drug ($Fu$) ?)
- The same for all micro-organisms ?
- The same for all infections ?
- Can you apply to all patients ?
How much time above MIC?

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

100% - Maximal effect?

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

- Moderately severe infection in a non-immunospressed patient
- Severe infection in an immunosuppressed patient

- 40%
- 100%?
The same for all β-lactams?

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 (□).

Andes & Craig Int.
J. Antimicrob. Agents
2002, 19: 261-268
The same for all microorganisms?

T> MIC for static effect

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enterobacteriaceae</th>
<th>S. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone (free)</td>
<td>38 (34-42)</td>
<td>39 (37-41)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>38 (36-40)</td>
<td>38 (36-40)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>36 (27-42)</td>
<td>39 (35-42)</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>35 (29-40)</td>
<td>37 (33-39)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>22 (18-28)</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>24 (17-28)</td>
<td></td>
</tr>
</tbody>
</table>
How do you adjust the dose for a given "Time > MIC"?

- "out of the package insert" PK data
- Monte-Carlo simulations and target attainment approaches
Typical pharmacokinetics of an IV β-lactam

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

* Single administration unique; half-life 2h; \( V_d = 0.2 \) l/kg
### Reading the labeling (package insert)

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

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

*Where would you like to be?*
Simple optimisation of IV β-lactams for "difficult" organisms

- 2 g every 12 h
  \[ T > \text{MIC} = 100 \% \]
  if \( \text{MIC} \leq 3 \text{ mg/L} \)

- 2 g every 8 h
  \[ T > \text{MIC} = 100 \% \]
  if \( \text{MIC} \leq 12 \text{ mg/L} \)

More frequent administrations is the best way to increase the activity of β-lactams in difficult-to-treat infections...

\[ \text{PK / PD breakpoint for IV β-lactams} : \text{MIC} < 8 \mu g/ml \]
### Cephalosporins

<table>
<thead>
<tr>
<th></th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R ≥</td>
<td>S ≥</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1</td>
<td>2</td>
<td>30</td>
</tr>
</tbody>
</table>

1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL, plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.

Why so low? To exclude ESBL..
But there are variation of PK in individuals...

Concentration-time profile of a beta-lactam in volunteers

$V_d = 20 \text{ L}$, $k_a = 1.2 \text{ h}^{-1}$, $k_e = 0.3 \text{ h}^{-1}$
Variation of PK in individuals...

Concentration-time profile of a beta-lactam in patients with a simulation with a coefficient var. of 20 %
Monte Carlo Simulations in pk/pd

• Have estimates of PK parameter values and a measure of their dispersion (usually SD)
• Simulate PK curves
• use MIC distribution values in the target population
• calculate a probability of attaining the desired target
• examine if this is feasible in clinical practice…
Target Concentration for β-lactams: continuous infusion

- Maximum effect time-kill at 4 x MIC
- Maximum effect in vitro model 4 x MIC
- Effect in endocarditis model 4 x MIC (Xiong et al 1994)
- Effect in pneumonia model dependent on severity of infection

Dose Calculations for continuous infusion

- Total Clearance estimate
- Elimination rate constant

$$C_{ss} = \frac{K_o}{Cl}$$

- Serum concentration
- Clearance

- Volume of distribution for the initial loading dose (loading dose = \(C_{target} / Vd\))
Continuous infusion of β-lactams: an overview...

• The exact role of continuous infusion of β-lactam antibiotics in the treatment of severe infections remains unclear...

• However, increasing evidence is emerging that suggests potential benefits
  – better attainment of pharmacodynamic targets for these drugs
  – More reliable pharmacokinetic parameters in seriously ill patients
  – when the MIC of the pathogen is ≥4 mg/L (empirical therapy where the susceptibility of the pathogen is unknown)

• Clinical data supporting continuous administration are less convincing, but
  – Some studies have shown improved clinical outcomes from continuous infusion
  – none have shown adverse outcomes.
  – clinical and bacteriological advantage are visible in seriously ill patients requiring at least 4 days of antibiotic therapy.

• Seriously ill patients with severe infections requiring significant antibiotic courses (≥4 days) may be the subgroup that will achieve better outcomes with continuous infusion.

Problems with continuous infusion ...

- Clearance estimates
- Variations in clearance (ICU)
- Volume of distribution (ICU, burned patients, ...)
- Non-linear clearance
- Drug instability
Problems with continuous infusion ...

- Clearance estimates
- Variations in clearance (ICU)
- Volume of distribution (ICU, burned patients, ...)
- Non-linear clearance
- Drug instability

you may like to monitor the serum levels if MICs $\geq 4$
(also for discontinuous administration)

temocillin > piperacillin > ceftazidime > cefepime ...

!! carbapenems are unstable (3-4h max.)
Continuous infusion with vancomycin?

2. Time-dependent antibiotics with weak concentration effect but with post-antibiotic effect

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD Parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycopeptides *</td>
<td>AUC_{24h} / MIC</td>
<td>Daily dose optimization</td>
</tr>
<tr>
<td>tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrolides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>linezolid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>streptogramins</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What can YOU do…?
Continuous infusion of vancomycin

Infusion will push music to its limits

- Will maximise antibiotic effects…
- Will allow for an easier administration scheme

<table>
<thead>
<tr>
<th>Studies *</th>
<th>indications</th>
<th>conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. controlled studies with clinical endpoints</td>
<td>VAP, Gram + osteomyelitis, other serious infections (ICU, open heart surgery)</td>
<td>equivalence (6) superiority (3)</td>
</tr>
</tbody>
</table>

* Only papers in ‘peer-reviewed’ journals

A typical example...

Continuous versus Intermittent Infusion of Vancomycin in Severe Staphylococcal Infections: Prospective Multicenter Randomized Study

Marc Wysocki,1* Frederique Delatour,2 François Faurisson,2 Alain Rauss, Yves Pean,4 Benoit Misset,3 Frank Thomas,6 Jean-François Timsit,7 Thomas Similowski,8 Hervé Mentecl,9 Laurence Mier,10 Didier Dreyfuss,10 and The Study Group†

Medico-Surgical Intensive Care Unit1 and Microbiology,2 Institut Mutualiste Montsouris, Medico-Surgical Intensive Care Unit, Hôpital Saint-Joseph,3 Medico-Surgical Intensive Care Unit, Hôpital de Diaconesses,6 INSERM U132 and Infectious Diseases Critical Care Unit,7 Hôpital Bichat-Claude Bernard, and Respiratory Intensive Care Unit, Hôpital de la Pitié-Salpêtrière,8 Paris, Medico-Surgical Intensive Care Unit, Hôpital V. Dupuy, Argenteuil,9 and Medical Intensive Care Unit, Hôpital Louis Mourier, Colombes,10 France

Received 28 June 2000/Returned for modification 2 January 2001/Accepted 5 June 2001

• 119 critical care patients with multi-resistant organisms (bacteriemia, 35%; pneumonia, 45%).
• Microbiological and clinical outcomes,
• Safety, pharmacokinetics, ease of administration, cost …

- clinical outcome and safety: equivalence
- target concentrations (20-25 mg/L) reached faster
- less samples needed for blood levels follow up
- AUC_{24h} less variable
- costs: 23% less!
Continuous infusion of vancomycine in daily practice …

- **Loading dose**

\[
C_t = \frac{\text{Dose}}{V_d}
\]

\[
\text{Dose} = C_t \times V_d
\]

<table>
<thead>
<tr>
<th>Vd (L/kg)</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7 *</th>
<th>0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>dose (mg/kg)</td>
<td>12.5</td>
<td>15.0</td>
<td>17.5</td>
<td>20.0</td>
</tr>
</tbody>
</table>

* Vdss of vancomycin: 0.39 to 0.97 L/kg

Results

The target concentration was reached after 48 h with the help of the clinical pharmacist...

There was, however, a large inter- and intra-individual variability in vancomycin serum concentrations...

Ampe et al., in preparation
Results: efficacy

Correlation between AUC$_{24h}$/MIC (E-Test) and clinical efficacy (n=19)

Clinical outcome: cure / failure

- CURE
- FAILURE

AUIC $< 450$

<table>
<thead>
<tr>
<th>AUIC $&lt; 450$</th>
<th>cure</th>
<th>failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$5/9$</td>
<td>$4/9$</td>
</tr>
</tbody>
</table>

$P < 0.05$

Ampe et al., in preparation
Conclusions … or what do you need with any antibiotic for "difficult to treat patients" or environments where susceptibility is no longer to its best… ?

- Obtain MIC distributions in YOUR clinical environment

- On this basis, construct nomograms to examine which doses (AUC *, peak *) and/or frequency of administration (time *) are necessary for the MIC you are interested in …

- Examine whether this is feasible for YOUR patients… with the drug you want to use

- The situation may be critical for "new" antibiotics (telavancin, doripenem, …) for which the EUCAST/FDA breakpoints are close to the upper limit of the wild type distribution…

* get this information from your pharmacist, the literature, and/or the Industry …
A clinical algorithm or a path to success...

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
A clinical algorithm (follow.) ...

Success?

- no
  - re-evaluate
    - the dosage
    - the therapeutic scheme
    - the antibiotic class based on PK/PD properties

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

Use these pieces of information to establish recommendations based on local epidemiology, knowledge of PK/PD properties and awareness of the risk for resistance, and SHARE YOUR EXPERIENCE.