PK/PD modeling : Clinical Implications

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with many things borrowed from

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http://www.isap.org
The problems ...

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>
</tr>
</thead>
<tbody>
<tr>
<td>First Generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0.5-1 g q6-8h</td>
<td>2 g q6-8h</td>
<td>12.5-33 mg/kg q6-8h</td>
<td></td>
</tr>
<tr>
<td>Cephalothin</td>
<td>0.5-1 g q8h</td>
<td>2 g q4-6h</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>10-20 mg/kg q6h</td>
<td></td>
</tr>
</tbody>
</table>
The problems ...

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

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**CEFTAZIDIME**

Les concentrations critiques séparent les souches sensibles des souches de sensibilité intermédiaire et ces dernières, des résistantes:

S ≤ 4 mg/l et R > 32 mg/l
The problem as seen from a question of the FDA...

Breakpoints tend to set up quantic limits in what is fundamentally a **continuous** distribution ...
So, you need to know the enemy ...

\[ \text{MIC} = .016 \text{ mg/L} \quad \text{Susceptible} \]

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

- $\text{AUC}_{24h} / \text{MIC}$
- $C_{\text{max}} / \text{MIC}$
- Time above MIC

Exercice with
- the fluoroquinolones
- the $\beta$-lactams
The saga of the AUC / MIC vs $C_{\text{max}} / \text{MIC}$ ratio for fluoroquinolones ...
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)
1st Example:
You want to control antibiotic dosing at the level of the patient

- Patient 60 yr, pneumonia and suspected bacteraemia/sepsis
- Ixacin 400 mg IV q8h $\rightarrow$ AUC = 30
- Gram negative rod, E-test MIC=0.01 mg/L
- $30/0.01 \rightarrow 3000$!
- You can quietly adjust dose to 100 mg/day

Mouton & Vinks, PW 134:816
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

**Poorly functioning PMNs**
- Aplastic anemia
- 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
So, let us accept values with some degree of precaution

If you follow Drusano and wish to prevent resistance

peak / MIC > 10

If you believe your patient is not a healthy mouse …

AUC\textsubscript{24h} / MIC > 100
### Breakpoint issues ...

<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>

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</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit of sensitivity (μg/ml) for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>$C_{\text{max}}$ in mg/L total/free: 1.4/1.1 (400 mg PO)</td>
<td>Efficacy: 0.1–0.4</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>$C_{\text{max}}$ in mg/L total/free: 2.5/1.75 (500 mg PO)</td>
<td>Efficacy: 0.2–0.8</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>$C_{\text{max}}$ in mg/L total/free: 4/3 (400 mg PO)</td>
<td>Efficacy: 0.3–0.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>$C_{\text{max}}$ in mg/L total/free: 4/2.8 (500 mg PO)</td>
<td>Efficacy: 0.3–0.9</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>$C_{\text{max}}$ in mg/L total/free: 3.1/1.8 (400 mg PO)</td>
<td>Efficacy: 0.2–0.7</td>
</tr>
</tbody>
</table>

2\textsuperscript{d} example: you want to control antibiotic dosing at the level of the hospital

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

**Levofloxacin** 500 mg 1x/d
- AUC [(mg/l)xh] 47
- peak [mg/l] 5

⇒ MIC$_{max}$ < 0.5
⇒ EUCAST bkpt: 1-2 *

The S/I-breakpoint from 1.0 to 2.0 avoids dividing the wild type MIC distribution. The breakpoint of 2 relates to high dose (750-1,000 mg) therapy.

**Moxifloxacin** 400 mg 1x/d
- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5

⇒ MIC$_{max}$ < 0.5
⇒ EUCAST bkpt: 1

MIC data: J. Verhaegen et al., ECCMID 2003
Is France like Belgium?

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

PK/PD breakpoint for a dose of 400 / 500 mg/day

- moxifloxacin
- levofloxacin
\[ \beta\text{-lactams} : T > \text{MIC} \ldots \]
but how much, how long, etc... ??

- Static dose vs maximum effect ?
- Free fractions of the drug \((Fu)\) ?
- The same for all micro-organisms ?
- The same for all beta-lactams ?
- The same for all infections ?
- Variance of PK in population ?
- Value in combination therapy ?
How much time above MIC?

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

100% - Maximal effect?
Here is a proposal ...

Moderately severe infection in a non-immunospressed patient

Severe infection in an immunosuppressed patient

100 % ?
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>MK-0826</td>
<td>32 (20-39)</td>
<td></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>
<tr>
<td>Linezolid</td>
<td></td>
<td>40 (33-59)</td>
</tr>
</tbody>
</table>
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 ($\triangle$), cephalosporins ($\bigcirc$) and carbapenems ($\square$). 

Andes & Craig Int.  
J. Antimicrob. Agents  
2002, 19: 261-268
How do you adjust the dose for 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
Typical pharmacokinetics of an IV β-lactam

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<tr>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Where would you like to be?

* Single administration unique; half-life 2h; $V_d = 0.2$ l/kg
Simple optimisation of IV $\beta$-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 $\beta$-lactams in difficult-to-treat infections...

PK / PD breakpoint for

IV $\beta$-lactams: MIC < 8 μg/ml
But there are variation of PK in individuals...

Concentration-time profile of a beta-lactam in volunteers

$V_d = 20$ L, $k_a = 1.2$ h$^{-1}$, $k_e = 0.3$ 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 %

4h

10h
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…
Example: target Attainment Rates of piperacillin

The response to piperacillin may be largely unpredictable.

Variation of PK in individuals...
Collaboration between EUCAST and the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS) about penicillins, cephalosporins and carbapenems

Ongoing …

• EUCAST Cephalosporin breakpoints for *Enterobacteriaceae* are now $S \leq 1 - R \geq 8$ (will be posted on EUCAST web site soon) …

• Carbapenems and Monobactams may follow …
Target Concentration:
continuous infusion

- Maximum effect time-kill at 4 x MIC
- Maximum effect in vitro model 4 x MIC (Mouton et al 1994)
- Effect in endocarditis model 4 x MIC (Xiong et al 1994)
- Effect in pneumonia model dependent on severity of infection (Roosendaal et al 1985, 1986)
Continuous Infusion
Pharmacokinetic Considerations

- Protein binding
- Linear relationship between clearance and dose
- Linear relationship between protein binding and dose
- Third compartment effects (CNS)
Dose Calculations for continuous infusion

- Total Clearance estimate
- Elimination rate constant

\[ \text{CSS} = \frac{K_o}{Cl} \]

- Volume of distribution for the initial loading dose (loading dose = \( \frac{C_{\text{target}}}{Vd} \))
Normogram Continuous Infusion (rate of infusion)

Mouton & Vinks, JAC 1996
Example Target Controlled Dosing for Cefticostix

- Patient 60 yr, UTI and suspected bacteraemia/sepsis
- Cefticostix 1 g IV q8h
- Gram negative rod, E-test MIC=0.12 mg/L
- Adjust dose to 30 mg/day CI based on patient clearance

Mouton & Vinks, PW 134:816
Cost comparisons:
vs 4 g by continuous infusion (CI) vs 2 g q8h (CA)
for 51 patients in an European ICU for empiric therapy

<table>
<thead>
<tr>
<th>criteria</th>
<th>C.I.</th>
<th>C.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean duration of treatment</td>
<td>7.8</td>
<td>7</td>
</tr>
<tr>
<td>total amount of ceftizidine used (g)</td>
<td>703.2</td>
<td>945</td>
</tr>
<tr>
<td>mean amount per patient (g)</td>
<td>27.05</td>
<td>39.37</td>
</tr>
<tr>
<td>total ceftazidime expenses (euros)</td>
<td>16,208.76</td>
<td>21,797.23</td>
</tr>
<tr>
<td>mean ceftazidime expense per patient (euros)</td>
<td>643.41</td>
<td>908.21</td>
</tr>
<tr>
<td>mean difference per patient (euros)</td>
<td></td>
<td>264.81</td>
</tr>
</tbody>
</table>

Laterre et al., ICAAC 2002
Problems with continuous infusion ...

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

Variation in $V_d$?
Ceftazidime concentrations in ICU patients (successive determinations) during continuous infusion (4 g/day)

Laterre et al., ICAAC 2002
A clinical algorithm ...

Pathology and epidemiology

Knowledge or ou “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?

- 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 and on the knowledge of the PK/PD properties and of the risk for resistance.
Conclusions … or what do you need with fluoroquinolones, \( \beta \)-lactams, for "difficult to treat patients" etc…?

- Obtain MIC distributions in YOUR clinical environment

- On this basis, construct normograms 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

* get these informations from your pharmacist and/or the Industry, or see in the next presentation …